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Electroörganic Preparations

XIII. Reduction of Isonicotinic Amide and Related Compounds

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Isonicotinic amide is reduced to pyridine-4-aldehyde in mineral acid solution; in acetate buffer the reduction yields γ-pyridyl carbinol. Aliphatic, hydroaromatic and benzyl substituted isonicotinic amides behave similarly. Aromatic substituted isonicotinic amides form some pyridine-4-aldehyde on reduction in very strongly acid solution, but at pH > 0 no traces of aldehyde are found. Isonicotinic anilide is reduced in N HCl to γ-pyridyl carbinol and 4-anilinomethylpyridine. The latter compound is reduced in acid solution to aniline and γ-picoline. In alkaline solution isonicotinic anilide is reduced to 1,4-dihydroisonicotinic anilide.

Isonicotinic thiamide is reduced in mineral acid solution to a rather stable intermediate with a sulfhydryl group and an amino group at the same carbon atom. At a more negative potential this intermediate is reduced to aminomethylpyridine and hydrogen sulfide. In the anodic reaction of isonicotinic thiamide in alkaline solution 4-cyanopyridine is formed. The reduction of 4-cyanopyridine in alkaline solution involves a reductive splitting of the carbon-carbon bond between the pyridine nucleus and the cyanide group.

Picolinic and nicotinic amide are reduced in mineral acid solution in a similar way as isonicotinic amide.

Isonicotinic amide has previously been investigated polarographically,[1] but the nature of the electrode reactions has not been proved. The purpose of the present investigation is to throw light on the electrode reactions in the polarography of isonicotinic amide and derivatives of and compounds related to isonicotinic amide.

POLAROGRAPHIC INVESTIGATION

The results from the polarographic investigation of isonicotinic amide and 1-ethyl-4-carbamoyl-pyridinium bromide are shown in Fig. 1. In Fig. 1 the wave height in alkaline solution of the latter compound is shown as the sum of the heights of the two rather poorly separated one-electron waves found in this medium.

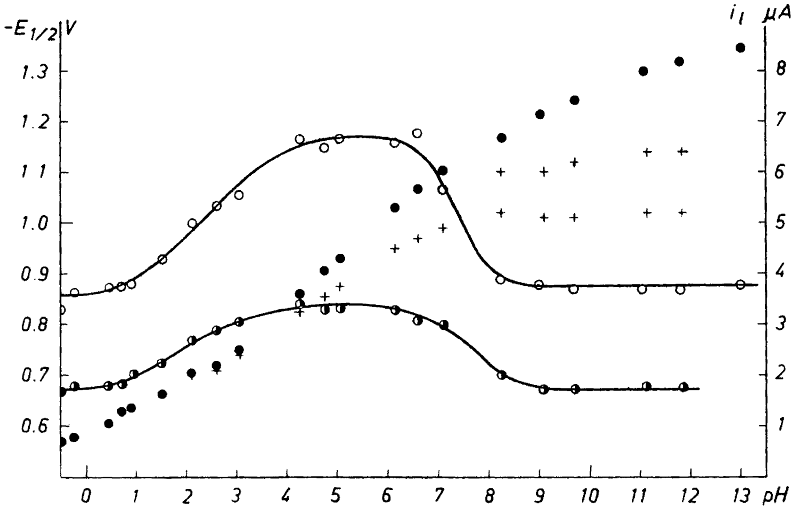

Fig. 1. Dependence on pH of limiting currents in µA (i_l) and half-wave potentials *vs* S. C. E. ($E_{1/2}$). Concentration 40 mg/l. Isonicotinic amide: O i_l, ● $E_{1/2}$. 1-Ethyl-4-carbamoylpyridinium bromide: ◑ i_l, + $E_{1/2}$.

In Fig. 2 is depicted the polarographic behaviour of N-methyl isonicotinic amide and N-butyl isonicotinic amide. The N-benzyl- and N-cyclohexyl isonicotinic amides behave polarographically very much like N-butyl isonicotinic

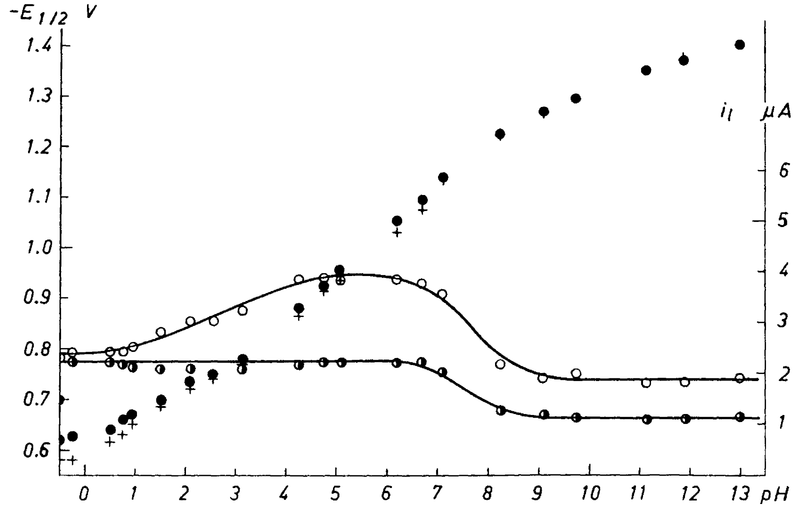

Fig. 2. Dependence on pH of limiting currents in µA (i_l) and half-wave potentials *vs* S. C. E. ($E_{1/2}$). Concentration 40 mg/l. N-methyl isonicotinic amide: O i_l, ● $E_{1/2}$. N-butyl isonicotinic amide: ◑ i_l, + $E_{1/2}$.

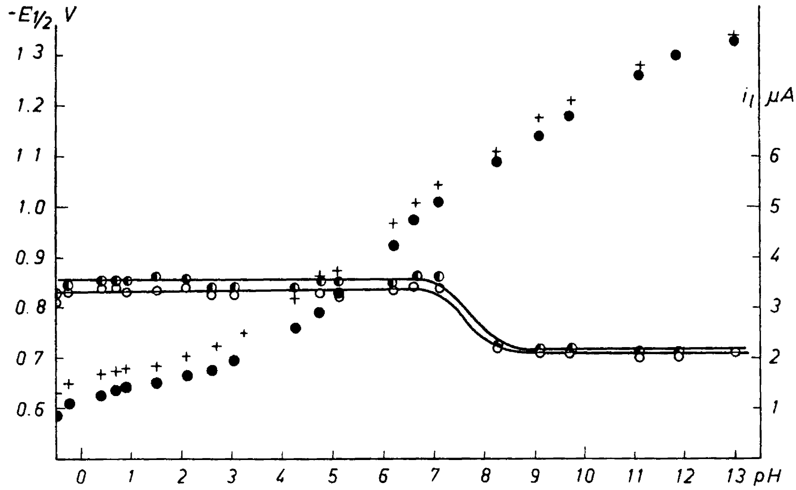

Fig. 3. Dependence on pH of limiting currents in µA (i_l) and half-wave potentials *vs* S. C. E. ($E_{½}$). Concentration 40 mg/l. Isonicotinic anilide: ◑ i_l, + $E_{½}$. N-methyl-N-phenyl isonicotinic amide: ○ i_l, ● $E_{½}$.

amide, whereas the behaviour of N,N-dimethyl isonicotinic amide is more like that of N-methyl isonicotinic amide.

The polarographic results from the investigation of isonicotinic anilide and N-methyl-N-phenyl isonicotinic amide are found in Fig. 3. In acid solution the anilide shows a pronounced maximum at the potential where 4-anilinomethylpyridine is reduced. The maximum can be suppressed with, *e.g.*, Triton X-100.

The shape of the $E_{½}$—pH curves is similar for these amides and will be discussed below. The i_l—pH curves are similar at higher pH but in mineral acid solution differences exist. The amides with small substituents in the amide group show a two-electron wave in this pH-region, whereas the amides with larger substituents in the amide group yield a four electron wave. The borderline between a "small" and a "large" substituent is dependent on the concentration as shown in Table 1, from which it is seen, that the limiting current for N-butyl isonicotinic amide at pH 1 deviates from a linear concentration dependence at lower concentrations than does the limiting current of N-benzyl isonicotinic amide.

1-Ethyl-4-(phenylcarbamoyl)-pyridinium bromide behaves polarographically like isonicotinic anilide below pH 8. At higher pH two or more waves are found whose shape depends on concentration and pH. At pH 13 two one-electron waves are found.

The $E_{½}$—pH and i_l—pH curves of 4-anilinomethylpyridine are shown in Fig. 4. The curves are similar to those of 4-aminomethylpyridine; the half-wave potentials of the former are, however, less negative than those of the latter, and the wave is thus visible in mineral acid solution. At low pH a pronounced maximum is found which can be suppressed by, *e.g.*, Triton X-100.

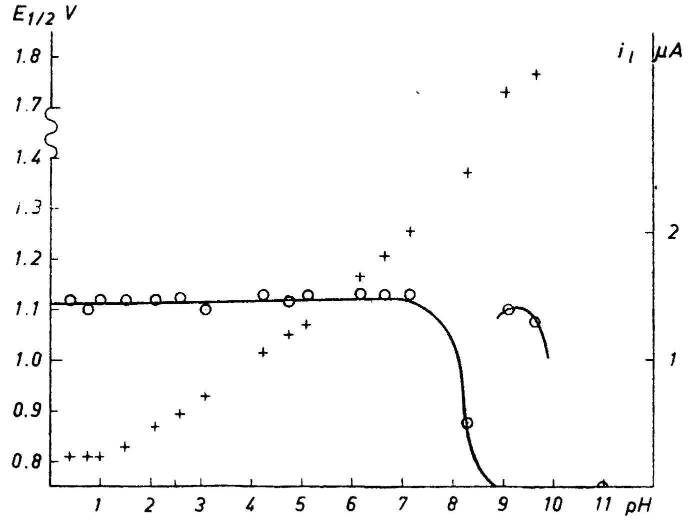

Fig. 4. Dependence on pH of limiting currents in μA (i_l) and half-wave potentials *vs* S. C. E. ($E_{1/2}$) for 4-anilinomethylpyridine. Concentration 40 mg/l. ○ i_l, + $E_{1/2}$.

The results from the polarographic investigation of isonicotinic thiamide are shown in Fig. 5. They resemble those obtained by Kane[2] in the investigation of 2-ethyl-4-thiocarbamoylpyridine (ethionamide). The limiting current

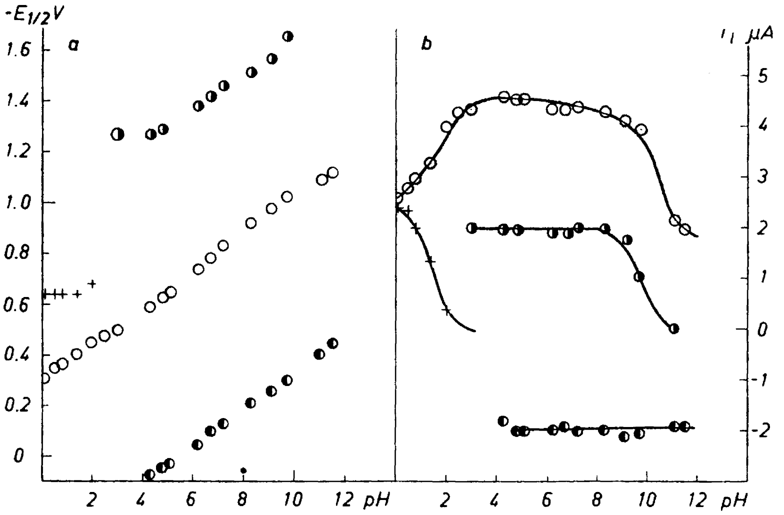

Fig. 5. Dependence on pH of (a) half-wave potentials *vs* S. C. E. and (b) limiting currents in μA of isonicotinic thiamide. Concentration 40 mg/l. ○ Reduction wave I, + reduction wave II, ◑ reduction wave III, ◐ anodic wave.

of the main reduction wave (wave I, Fig. 5b) depends on pH in the same way as does the limiting current of isonicotinic amide. Besides the main reduction wave two other reduction waves II and III are found. Wave II is found only in acid solution, and the wave height diminishes with decreasing acidity. The sum of the wave heights of I and II corresponds to a four electron wave. The reduction wave III is a two-electron wave, and its half-wave potentials are found at the potentials where aminomethylpyridine is reduced. The height of the anodic wave IV corresponds to the consumption of two electrons per molecule.

4-Mercaptomethylpyridine and its disulfide are polarographically reducible. The polarography of these compounds will be described in a later communication.

PREPARATIVE REACTIONS

In mineral acid solution isonicotinic amide is reduced to pyridine-4-aldehyde, and if the reduction is stopped after a consumption of two electrons per molecule this compound can be isolated. Pyridine-4-aldehyde is reducible at the potential necessary for the reduction of isonicotinic amide. It is, however, partly protected against further reduction by formation of a rather stable, non-reducible hydrate. The reduction of isonicotinic amide can be formulated as:

$$\begin{aligned} \mathrm{HN^+C_5H_4CONH_2} + \mathrm{H^+} &\rightleftharpoons \mathrm{HN^+C_5H_4CONH_3^+} \\ + 2\,e^- + \mathrm{H^+} &\rightarrow \mathrm{HN^+C_5H_4{-}CO^-} + \mathrm{NH_4^+} \\ + \mathrm{H^+} &\rightarrow \left\{ \begin{array}{l} \mathrm{HN^+C_5H_4{-}CHO} \\ + \mathrm{H_2O} \downarrow \quad \uparrow -\mathrm{H_2O} \\ \mathrm{HN^+C_5H_4{-}CH(OH)_2} \end{array} \right. \end{aligned}$$

If the reduction is continued at the potential necessary for the reduction of the amide, the free aldehyde is reduced further to γ-pyridyl carbinol:

$$\mathrm{HN^+C_5H_4{-}CHO} + 2\,e^- + 2\,\mathrm{H^+} \rightarrow \mathrm{HN^+C_5H_4{-}CH_2OH}$$

During a reduction of isonicotinic amide in an acetate buffer (pH 4.5) no polarographic evidence was obtained of the formation of pyridine-4-aldehyde as an intermediate in the 4-electron reduction. The reduction can be formulated as:

$$\begin{aligned} \mathrm{NC_5H_4{-}CONH_2} + \mathrm{H^+} &\rightleftharpoons \mathrm{HN^+C_5H_4{-}CONH_2} \\ + 2\,e^- + 2\,\mathrm{H^+} &\rightarrow (\mathrm{HN^+C_5H_4{-}CH(OH)NH_2}) \\ + 2\,e^- + 2\,\mathrm{H^+} &\rightarrow \mathrm{NC_5H_4{-}CH_2OH} + \mathrm{NH_4^+} \end{aligned}$$

The intermediate is hypothetical. Arguments discussed below make is reasonable to assume that the reduction passes through such an intermediate which, however, does not diffuse away from the electrode, before it is reduced further.

The quaternary isonicotinic amide, 1-ethyl-4-carbamoyl-pyridinium bromide, is reduced in acid and neutral solution in the same manner as isonicotinic amide, and substitution at the amide group with one or two alkyl groups, with a hydroaromatic or a benzyl group does not alter the main reduction route. The electron consumption is, however, slightly higher for N-benzyl- and N-cyclohexyl isonicotinic amide than for the parent amide. In mineral acid solution the main reduction route passes through the aldehyde, whereas the alcohol is the main product at pH 5. In the reduction of 1-ethyl-4-carbamoyl-pyridinium bromide in acetate buffer pH 4.5, however, traces of a compound which might be 1-ethyl-4-formyl-pyridinium bromide could be detected polarographically.

α-Picolinic amide is reduced in a similar manner as isonicotinic amide; nicotinic amide forms pyridine-3-aldehyde by reduction in N hydrochloric acid, but the aldehyde is protected against further reduction to a lesser degree than pyridine-4-aldehyde. The yield of aldehyde after the consumption of two electrons per molecule is thus lower in the reduction of the nicotinic amide than in the reduction of isonicotinic amide.

Substitution of a hydrogen atom in the amide group with a phenyl group alters the picture somewhat. At pH 5 the reduction proceeds in the same manner as that of isonicotinic amide; *γ*-pyridine carbinol is formed. However, in solutions as acid as N HCl no pyridine-4-aldehyde can be detected during the reduction of neither isonicotinic anilide nor N-methyl-N-phenyl-isonicotinic amide. The reduction of the latter proceeds in this medium according to:

$$\mathrm{HN^+C_5H_4CON(CH_3)C_6H_5} + 4\,e^- + 5\,\mathrm{H^+} \rightarrow \mathrm{HN^+C_5H_4CH_2OH} + \mathrm{H_2N^+(CH_3)C_6H_5}$$

By reduction of the two above mentioned compounds in 4 N HCl small amounts of pyridine-4-aldehyde can be detected polarographically during the reduction. In this medium, however, the protection of the aldehyde in its hydrated form is less effective than at, say, pH 1, and the small amounts of pyridine-4-aldehyde are, therefore, reduced to *γ*-pyridyl carbinol. The main part of, *e.g.*, N-methyl-N-phenyl-isonicotinic amide is reduced to *γ*-pyridyl carbinol without passing through the free pyridine-4-aldehyde.

Isonicotinic anilide is reduced in acid solution partly to *γ*-pyridyl carbinol and partly to anilinomethylpyridine. The yields of anilinomethylpyridine is lower at higher pH. In 4 N HCl the yield is 45 %, in N HCl it is 30 %, and in citric acid buffer pH 2.5 no anilinomethylpyridine is formed. In 4 N HCl the reduction of isonicotinic anilide can be formulated as:

$$\mathrm{HN^+C_5H_4{-}CONH_2^+C_6H_5} + 2\,e^- + \mathrm{H^+} \rightarrow \mathrm{H_3N^+C_6H_5} + \mathrm{HN^+C_5H_4{-}CO^-} \xrightarrow{\mathrm{H^+}} \mathrm{HN^+C_5H_4CHO}$$

$$+\,\mathrm{H^+}\ \Big\uparrow\!\Big\downarrow\ -\mathrm{H^+}$$

$$\mathrm{HN^+C_5H_4CONHC_6H_5} + 2\,e^- + 2\,\mathrm{H^+} \rightarrow (\mathrm{HN^+C_5H_4CH(OH)NHC_6H_5})$$

$$+\,2\,e^- + 3\,\mathrm{H^+} \rightarrow \begin{cases} \mathrm{HN^+C_5H_4{-}CH_2NH_2^+{-}C_6H_5} & (45\ \%) \\ \mathrm{HN^+C_5H_4CH_2OH} + \mathrm{H_3N^+C_6H_5} & \end{cases}$$

In acid solution the anilinomethylpyridine can be reduced at a potential about 0.5 V more negative than the half-wave potential of isonicotinic anilide. The electrode reaction consumes two electrons per molecule and aniline can be isolated. The reaction thus is:

$$HN^+C_5H_4CH_2NH_2^+-C_6H_5 + 2\,e^- + 2\,H^+ \rightarrow HN^+C_5H_4-CH_3 + H_3N^+-C_6H_5$$

The quaternary isonicotinic anilide, 1-ethyl-4-phenylcarbamoylpyridinium bromide, behaves very much like isonicotinic anilide in acid solution. In mineral acid solution it is reduced to an amine and a carbinol as is the parent compound. 1-Ethyl-4-anilinomethyl pyridinium bromide is reduced as anilinomethylpyridine. 1-Ethyl-4-hydroxymethyl-pyridinium bromide is polarographically reducible in alkaline solution.

In strongly alkaline solution, *e.g.* 0.5 N KOH, isonicotinic anilide is reduced in a two-electron reduction. The product is only slightly soluble in this medium and can be filtered off. The elementary analysis is consistent with $(C_{12}H_{12}N_2O)_n$. When dissolved in ethanol and precipitated with water some of the compound is reoxidized to isonicotinic anilide, if the alcohol and water are not deaerated with nitrogen. The UV-spectrum of the compound has maximum at 243 mμ with $\varepsilon = 1.2 \times 10^4$ and no maxima at longer wave-length. The IR-spectrum is shown in Fig. 6. The compound gives an anodic wave in slightly and strongly alkaline solution. On heating, the crystals (needles) become crackled about 80° and soften to a viscous, yellowish oil around 110°. On standing in the reaction medium overnight the product, which remains in solution, turns yellow, and the UV-spectrum of the solution contains a broad shoulder around 400 mμ. The product is assumed to be a 1,4-dihydropyridine, and the reduction thus is

$$NC_5H_4-CONHC_6H_5 + 2\ e^- + 2\ H_2O \rightarrow HNC_5H_5-CONHC_6H_5 + 2\ OH^-$$

In alkaline solution the quaternary isonicotinic amide, 1-ethyl-4-carbamoyl-pyridinium bromide, and the quaternary isonicotinic anilide, 1-ethyl-4-(phenylcarbamoyl)-pyridinium bromide, are reduced in two steps. During an electrolysis of the amide in 0.2 N potassium hydroxide at a potential corre-

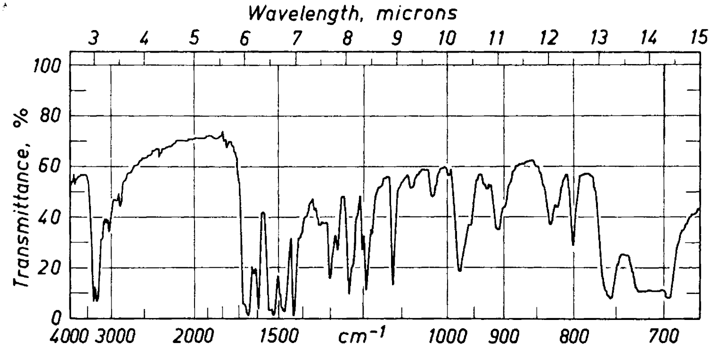

Fig. 6. IR-spectrum (1/2 % in KBr) of the product from the reduction of isonicotinic anilide in alkaline solution, presumably 1,4-dihydroisonicotinic anilide.

sponding to the first wave the solution turned greenish; when the current was stopped the green colour faded and disappeared in the course of a minute. The quaternary anilide yielded under similar conditions a green precipitate, which was stable for at least two days, when oxygen was excluded. The green precipitate was shown to be a radical by its paramagnetic properties. It was, however, too insoluble in the medium in which it was prepared to yield a resolved e.s.r.-spectrum. The radical was soluble in tetrahydrofuran yielding a red solution, which faded in the course of a few minutes. An e.s.r.-spectrum could thus not be obtained in tetrahydrofuran solution, and a technique as that used by Geske and Maki[3] would be preferable.

Reduction of the quaternary isonicotinic anilide at a more negative potential in an alkaline solution containing 20 % alcohol yields a dihydrocompound. The IR-spectrum of the reduction product closely resembles that of the dihydroisonicotinic anilide mentioned above, but only one N—H stretching frequency about 3 μ is found. Also the UV-spectrum with a maximum at 245 mμ resembles that of the above mentioned dihydroisonicotinic compound. The product from the reduction of the quaternary isonicotinic anilide is thus assumed to be 1,4-dihydro-1-ethyl-4-phenylcarbamoyl pyridinium bromide.

The reduction of 1-ethyl-4-phenylcarbamoyl pyridinium bromide in alkaline solution can be formulated as:

$$C_2H_5N^+C_5H_4-CONHC_6H_5 + e^- \rightarrow (C_2H_5NC_5H_4-CONHC_6H_5)\cdot \qquad \text{(1. wave)}$$

$$+ e^- + H_2O \rightarrow C_2H_5NC_5H_5-CONHC_6H_5 + OH^- \qquad \text{(2. wave)}$$

In mineral acid solution isonicotinic thiamide is reduced in two two-electron waves. The product of the electrode reaction corresponding to the first wave is stable in acid solution, but it has not been isolated. At higher pH it is rapidly hydrolyzed. At the same potential as that of the second wave of isonicotinic thiamide, the product is reduced to aminomethylpyridine. This shows that the carbon-nitrogen bond is intact in the product. The compound gives an anodic wave in acid solution in the same way as hydrogen sulfide and other sulfhydryl compounds do. The anodic wave attributed to the reduction product is not caused by hydrogen sulfide, as the wave did not diminish after nitrogen had bubbled through the acid solution for 2 h. After hydrolysis, the compound reacts with phenylhydrazine, and the phenylhydrazone of pyridine-4-aldehyde is formed. Isolation of the compound was attempted by evaporation of the solution *in vacuo*, but although the residue contained a sulfhydryl compound most of it consisted of pyridine-4-aldehyde hydrochloride. On these grounds the product has been assumed to have the formula $HN^+C_5H_4-CH(SH)NH_2$ and the reduction of isonicotinic thiamide in mineral acid solution to proceed according to:

$$HN^+C_5H_4-CSNH_2 + 2\ e^- + 3\ H^+ \rightarrow NH^+C_5H_4-CH(SH)NH_3^+$$

At a more negative potential this compound is reduced further according to:

$$HN^+C_5H_4-CH(SH)NH_3^+ + 2\ e^- + 2\,H^+ \rightarrow HN^+C_5H_4-CH_2-NH_3^+ + H_2S$$

About pH 3 the two waves merge, and in slightly acid and neutral solution the polarographic reduction of isonicotinic thiamide consumes four electrons per molecule, as the intermediate two-electron reduction product is not stable at higher pH. The products formed in a reduction in an acetate buffer pH 4.8 were 4-aminomethylpyridine and 4-mercaptomethylpyridine. The latter was isolated as the disulfide. 4-Hydroxymethylpyridine was not isolated, but its presence in the reduction mixture can not be excluded. The reduction can be formulated as:

$$NC_5H_4CSNH_2 + H^+ \rightleftharpoons HN^+C_5H_4CSNH_2$$

$$+ 2\,e^- + 2\,H^+ \rightarrow HN^+C_5H_4{-}CH(SH)NH_2$$

$$+ 2\,e^- + 3\,H^+ \rightarrow \begin{cases} NC_5H_4{-}CH_2NH_3^+ + H_2S \\ NC_5H_4{-}CH_2SH + NH_4^+ \end{cases}$$

The sulfur-containing reduction product is regarded as 4-mercaptomethylpyridine and the isolated compound as its disulfide on the following evidence: The analysis of the isolated sulfur-containing compound corresponded to $C_{12}H_{12}N_2S_2$. The compound was polarographically reducible and gave a one-electron wave followed by a two-electron wave at a more negative potential. The two-electron wave was found at the same potential as that of the reduction product from which it was formed by air-oxidation. The reduction product gave an anodic wave as do all sulfhydryl compounds.

The electrode reactions of 4-mercaptomethylpyridine will be discussed in a later communication.

The anodic wave of isonicotinic thiamide is caused by a two-electron oxidation. A preparative oxidation in alkaline solution at a macro mercury electrode yielded mercury sulfide and 4-cyanopyridine. The reaction in this medium thus is:

$$NC_5H_4{-}CSNH_2 + Hg + 2\ OH^- \rightarrow 2\ e^- + NC_5H_4{-}CN + HgS + 2\ H_2O$$

The resulting 4-cyanopyridine is reducible[4] and the reduction product in mineral acid solution is aminomethylpyridine. In alkaline solution the electrode reaction consumes two electrons per molecule, and cyanide ions and pyridine is formed in high yield. The electrode reaction thus is:

$$NC_5H_4{-}CN + 2\ e^- + H_2O \rightarrow NC_5H_5 + CN^- + OH^-$$

DISCUSSION

The polarography of isonicotinic amide has been discussed previously,[1] and it has been shown that at pH < 8 the reduced species carry a proton at the ring nitrogen. In the pH region 4 to 8 the protonated molecule is formed in a recombination reaction with a proton at the electrode surface just prior to the reduction.

A prominent feature in the polarography of the isonicotinic amides is, that the slope of the $E_{1/2}$ *vs.* pH curve (Figs. 1, 2, 3) changes around pH 3.5. The pK_A of the protonated ring nitrogen in isonicotinic amides is about 3.5. The change in the slope can be explained by the fact that at pH $<$ pK_A the majority of the molecules carry a proton at the ring nitrogen, when they arrive at the electrode surface, whereas only a minority do at pH $> \mathrm{p}K$. One hydrogen ion more per molecule is required at the electrode surface before the potential determining step in the latter case than in the former.

The slope of the $E_{1/2}$ *vs* pH curve for isonicotinic amide is about 0.059 V/pH at pH < 3 and about 0.089 V/pH at pH 4 to 7. These values suggest that at pH < 3 two hydrogen ions are required before and including the potential determining step and three hydrogen ions at pH 4 to 7.

In support of the explanation given above can be mentioned that the quaternary isonicotinic amides do not show a change in the slope of the $E_{1/2}$ *vs* pH curve up to pH about 8, and for 1-ethyl-4-carbamoylpyridinium bromide (Fig. 1) the slope is about 0.059 V/pH. The quaternary isonicotinic amides carry at all pH-values a positive charge on the ring nitrogen when arriving at the electrode surface. The change in the slope of the $E_{1/2}$ *vs* pH curve around pH 8 is caused by a change in the course of the electrode reaction.

Another feature in the polarography of isonicotinic amides is worth mentioning. As noted above N-butyl- and N-benzyl-isonicotinic amide have a wave height at pH 1 corresponding to a four electron reduction. The preparative reduction, however, was found to yield pyridine-4-aldehyde as the main product just as the parent amide does. At higher concentrations of the said substituted amides the wave height corresponds to less than a four electron reduction at pH 1 compared to the wave height at pH 4.5, which is assumed to represent a four electron reduction (Table 1). The fall in limiting current is noticeable at lower concentrations for N-butyl- than for N-benzyl-isonicotinic amide. Other similar substituted isonicotinic amides show the same phenomenon to varying degrees. Those with small substituents resemble the parent amide, whereas those with bulky substituents are more like the N-benzylisonicotinic amide.

The explanation of the phenomenon is not clear. Addition of tetrabutylammonium bromide or ammonium chloride also lowers the wave height at pH 1. If the proposed reduction scheme for the isonicotinic amides is essentially correct it might be suggested that the adsorption of a protonated nitrogen compound (or quaternary ammonium compound) to the electrode surface modifies the electrical double layer in such a way that it facilitates the reductive splitting of the carbon-nitrogen bond in the amide group. However, the phenomenon is being investigated in similar compounds containing other heterocyclic nuclei and will be discussed when more data are available.

The shape of the $E_{1/2}$ $-$pH curve of the main reduction wave (I) of isonicotinic thiamide (Fig. 5a) is similar to that of isonicotinic amide. It is thus

Table 1. Limiting currents (μA) of N-benzylisonicotinic amide (I) and N-butylisonicotinic amide (II) in 0.1 N HCl and in acetate buffer at different concentrations.

	Conc. mg/l	40	200	800
Compound	pH			
I	1.0	2.2	9.6	34
I	4.5	2.2	10.6	42
II	1.0	2.3	8.1	30
II	4.5	2.3	11.3	42

reasonable to assume that the protonation of the pyridine ring is similar to that of isonicotinic amide discussed above.

The results of the polarographic and macro-scale reductions of isonicotinic amides can be explained by the following assumptions. Pyridine-4-aldehyde is formed during the reduction when both the ring nitrogen and the amide nitrogen carry a positive charge, *e.g.* by protonation. The amide nitrogen of isonicotinic amide is unprotonated in the bulk of the solution at pH > 0, and the protonation of the amide group is assumed to take place at the electrode surface immediately before the reduction of the molecule. When only the ring nitrogen is protonated γ-pyridyl carbinol is the main product and pyridine-4-aldehyde can not be detected polarographically during the reduction. If none of the nitrogens carry a positive charge the reduction can take place in the pyridine nucleus or a reductive splitting of a carbon-carbon bond can occur.

In support of the assumptions can be mentioned: (1) The formation of pyridine-4-aldehyde in the reduction of isonicotinic amide is restricted to solutions with pH lower than about 3. This is also the pH-region where the pyridine-4-aldehyde is partly protected against further reduction by the formation of a non-reducible hydrate.[5] (2) 1-Ethyl-4-carbamoyl-pyridinium bromide is reduced to 1-ethyl-4-formyl-pyridinium bromide in the same pH-region. This aldehyde, however, is protected against reduction as the hydrate up to pH about 7.[6] There thus exists a pH-region where the aldehyde would be protected against reduction if it were formed. The fact that only traces of aldehyde has been detected during the reduction of 1-ethyl-4-carbamoyl-pyridinium bromide in an acetate buffer pH 4.5 shows that the hydrate formation is essential for the protection of the aldehyde, when it is formed, but it is not the factor which determines, whether the aldehyde is formed or not. (3) The isonicotinic amides of amines which has a base strength comparable to that of ammonia form pyridine-4-aldehyde on reduction in solutions more acid than pH about 3. Isonicotinic amides of aromatic amines form no pyridine-4-aldehyde on reduction in solutions with pH > 0. In 4 N HCl, however, some pyridine-4-aldehyde is formed in the reduction of such amides. (4) The reductive splitting of the C—N bond in the reduction of $HN^+C_5H_4-CO-NH_3^+$ is similar to that in the reduction of $Ar-CO-CH_2-NR_3^+$ [7] and $HN^+C_5H_4-CH_2-NH_2^+-C_6H_5$.

The reduction in acid solution of an amide to an aldehyde occurs in other compounds than the pyridine carboxamides. Carbamoyl groups in activated positions in other heterocyclic nuclei containing a basic nitrogen have been found to be reduced similarly. Reports on the reduction of these compounds will be published later.

The reduction in an acetate buffer of isonicotinic amide is formulated with a hypothetical intermediate, $HN^+C_5H_4CH(OH)NH_2$. A similar intermediate is formed in the reduction of isonicotinic thiamide in acid solution. In the reduction of isonicotinic amide in an acetate buffer the amide nitrogen is unprotonated, and the carbon-nitrogen bond is thus not apt to be cleaved reductively. The carbon-oxygen double bond is then the vulnerable point, and the reduction is assumed to take place here. The amide nitrogen is then no longer influenced by a carbonyl group and it accepts easier a proton, and when the nitrogen is protonated a reductive splitting of the carbon-nitrogen bond can occur. The results are, however, also consistent with the assumption that a hydrolysis of the intermediate takes place before the further reduction.

Isonicotinic anilide and N-(1-naphthyl) isonicotinic amide are remarkable as they are the only substituted pyridine carboxamides which have been found to yield some amine in the electrolytic reduction. Neither from the reduction of N-methyl-N-phenyl isonicotinic amide nor from picolinic anilide was any amine found, although the polarographic behaviour of the latter closely resembles that of isonicotinic anilide.

The polarographic reduction of isonicotinic amide resembles that of benzthiamide; this compound and thiobenzoylmorpholine yield on electrolytic reduction the same products as benzaldehyde does on reduction. However, from the reduction of thiobenzanilide in mineral acid solution was isolated about 25 % benzylaniline together with reduction products of benzaldehyde.[8] It thus seems that primary aromatic amines possess special properties which promote amine formation.

The yield of amine in the reduction of isonicotinic anilide is higher in more acid solution, which seems to indicate that a protonation at some time during the reduction is responsible for the formation of the amine. The phenyl group makes the amide nitrogen less basic than that in isonicotinic amide, and it seems possible that the protonation of the assumed intermediate, $HN^+C_5H_4-CH(OH)NHC_6H_5$, could partly take place at the oxygen. Such a protonation would make the cleavage of the carbon-oxygen bond easy, and the amine would be formed either by direct reduction of the carbon-oxygen bond or by loss of water followed by a reduction of the formed azomethine compound. The latter possibility would explain why N-methyl-N-phenyl-isonicotinic amide does not form an amine in the electrolytic reduction in acid solution.

In alkaline solution the reduction of isonicotinic anilide takes place in the pyridine nucleus, and this is probably also the case in the reduction of isonicotinic amide and substituted isonicotinic amides under similar conditions. The isolated dihydroisonicotinic anilide has tentatively been formulated as 1,4-dihydroisonicotinic anilide on the grounds mentioned below.

The compound is considered to be a dihydropyridine on the folloving grounds: the electrode reaction consumes two electrons per molecule, the elementary analysis corresponds to $C_{12}H_{12}N_2O$, it forms isonicotinic anilide by oxidation with air in alkaline solution, and it gives an anodic wave in alkaline solution. The IR-spectrum (Fig. 6) contains two bands in the 3 μ region, which may be caused by two N—H bondings, one in the amide group and one in the hetero ring. If this interpretation is correct the IR-spectrum excludes a 2,3-dihydropyridine.

The UV-spectrum of the dihydrocompound contains a maximum at 243 mμ and no absorption above 280 mμ. This suggests a 1,4-dihydropyridine, where the double bonds are not conjugated with the carbonyl group of the amide. A 1,2-dihydroisonicotinic anilide would not be expected to have maximum of absorption at shorter wave length than croton anilide, which has $\lambda_{\max} = 271$ mμ and log $\varepsilon = 4.15$.[9]

A comparison of the UV-spectrum with the spectra of known 1,2- and 1,4-dihydropyridines is of limited value, as the known compounds contain at least one carbethoxy or carbamoyl group in the 3-position.

The N.M.R.-spectrum is also best interpreted on the assumption that the compound is a 1,4-dihydropyridine. Besides bands caused by nitrogen and phenyl protons the N.M.R-spectrum contains two bands each with an intensity of two protons at 370 c.p.s. and 270 c.p.s. and a band with an intensity of one proton at 235 c.p.s. These bands are interpreted as being caused by the protons in the α, β, and γ positions, respectively.

On standing in alkaline solution the compound is transformed into a yellow compound, which has absorption above 400 mμ. The double bonds of the dihydropyridine ring is believed to move into conjugation with the anilide group. A yellow compound is rapidly formed in acid solution.

The formation of 1,4-dihydroisonicotinic anilide in the reduction of isonicotinic anilide in alkaline solution thus seems to be analogous to the reduction of α-naphthoic amide in alkaline solution, where 1,4-dihydronaphthoic amide-1 is the isolated product.[10]

The quaternary isonicotinic anilide forms a radical on reduction in alkaline solution, and this radical is at a slightly more negative potential reduced to a dihydropyridine compound with an IR- and UV-spectrum similar to that of the above mentioned dihydropyridine. The formation of a radical in the reduction of quaternary isonicotinic amides has previously been found in the reduction of 1-ethyl-4-carbamoyl-pyridinium bromide in acetonitrile.[11] The radical was, however, too unstable to yield a good e.s.r.-spectrum. This is similar to the finding that the solution in tetrahydrofuran of the radical from the reduction of 1-ethyl-4-phenylcarbamoylpyridinium bromide was too unstable to obtain an e.s.r.-spectrum by the conventional technique.

The polarography of isonicotinic thiamide resembles that of thiobenzamide.[8] The former is, however, in acid solution reduced in two steps and the latter in one, but the waveheight-pH dependence of the first wave of isonicotinic thiamide is very similar to that of thiobenzamide. The two-electron reduction product formed in acid solution from isonicotinic thiamide is much more stable than the intermediate formed in the reduction of thiobenzamide, which is hydrolyzed and reduced further during the reduction.

The intermediate contains a mercapto and an amino group at the same carbon atom and shows in mineral acid a remarkable stability for such a compound. At higher pH the compound is rapidly hydrolyzed, and such a hydrolysis might be the explanation for the raise of the limiting current of the main reduction wave with pH in slightly acid solution.

The formation of both 4-aminomethylpyridine, which in mineral acid solution is formed by reduction of the above mentioned aminomercapto intermediate, and 4-mercaptomethylpyridine in the reduction in neutral and slightly acid solution might be explained by the loss of hydrogen sulfide or ammonia before the further reduction, but a direct reduction of the carbon-sulfur or carbon-nitrogen bond can not be excluded.

The anodic reaction of isonicotinic thiamide in alkaline solution is similar to that of thiobenzamide, in both cases the nitrile is formed. The observed electrode reaction is thus not an oxidation of the thiamide, but of the mercury electrode.

4-Anilinomethylpyridine and 4-aminomethylpyridine are reduced to γ-picoline and aniline or ammonia, respectively. This reduction is similar to that of certain substituted 2-aminoacetophenones.[7] The methyl group in the 2 and 4 position of pyridine is known to be activated similarly as the methyl group of acetophenone. In accordance with that 4-acetoxymethylpyridine is reduced to γ-picoline similarly to the reduction of 2-acetoxyacetophenone to acetophenone.[12] The reduction of picolines containing other substituents in the methyl group is being investigated.

The reduction of 4-cyanopyridine in alkaline solution to cyanide ion and pyridine is similar to the reduction of the 1-ethyl-4-cyanopyridinium ion, where the first of the two one-electron reductions produces cyanide ions and a reducible, dimerized compound.[11] The reduction of a carbon-carbon bond is not common and is probably promoted by the stability of the cyanide ion.

EXPERIMENTAL

The apparatus was the same as that used previously.[13]

The compounds were prepared by standard methods. Compounds not described in the literature or with somewhat different m.p. were: N-Butylisonicotinic amide hydrochloride, m.p. 140°; isonicotinic anilide, m.p. 176°–177° (170°–172°)[14]; 1-ethyl-4-phenylcarbamoyl pyridinium bromide, m.p. 205°; 1-ethyl-4-(N-methyl-N-phenylcarbamoyl) pyridinium bromide, m.p. 302°; aminomethylpyridinium dihydrochloride (prepared by electrolytic reduction of 4-cyanopyridine in N HCl), m.p. 255°. (Found: C 39.73; H 5.47; N 15.36. Calc. for $C_6H_{10}N_2Cl_2$: C 39.79; H 5.57; N 15.47); pyridine-4-aldehyde hydrochloride, m.p. 108°.

Reduction of isonicotinic amide (I). 0.50 g of isonicotinic amide was reduced in 160 ml 0.8 N HCl at a cathode potential of –0.80 V *vs* S. C. E. The temperature was kept at 5°C. After the consumption of two electrons per molecule the reduction was stopped and the yield of pyridine-4-aldehyde determined polarographically in a phosphate buffer pH 6.6. Yield 87 %. To the remaining solution were added 3 g of phenylhydrazine. It was boiled for a minute and the volume reduced to 50 ml *in vacuo*. The acid was neutralized with solid sodium carbonate and the precipitate (650 mg) filtered off. It was identified as pyridine-4-aldehyde phenylhydrazone from the m.p. 178° and the IR-spectrum.

Reduction of isonicotinic amide (II). 1.00 g of isonicotinic amide was reduced in a citric acid buffer pH 3.5 containing 30 % alcohol. The reduction consumed four electrons per molecule. After reduction the solution was made alkaline with solid sodium carbonate and extracted continuously overnight with a mixture of chloroform-isopropanol(3:1). Most of this solvent was distilled off through a column, hydrogen chloride was added to the remnant, and the hydrochloride precipitated with ether. The precipitate, 1.0 g, was extracted in a Soxhlet apparatus with alcohol; on addition of ether a precipitate, 625 mg, was formed, m.p. 170°–172°, which was identified as γ-pyridine carbinol hydrochloride from the m.p. (167°–172°),[15] the IR-spectrum, and the analysis. (Found: C 49.32; H 5.65; N 9.64; Cl^- 24.24. Calc. for C_6H_8NClO: C 49.50; H 5.54; N 9.62; Cl^- 24.36).

Reduction of isonicotinic anilide (I). 0.50 g of isonicotinic anilide was reduced in 170 ml 2 N HCl at –0.75 V *vs* S. C. E. The reduction consumed four electrons per molecule. The polarogram of the reduced solution showed the presence of anilinomethylpyridine (yield 40 %). The solution was neutralized with solid sodium carbonate and extracted twice with 75 ml of ether and twice with 75 ml of butanol. The ether was extracted with N HCl, which was neutralized with solid sodium carbonate. The precipitate, 170 mg, was filtered off and identified as anilinomethylpyridine from the m.p. 102°–103° (102°).[16] The filtrate contained γ-pyridine carbinol and some anilinomethylpyridine; both were identified through the IR-spectra of their hydrochlorides.

The butanol layer was extracted with N HCl; on evaporation of the solvent *in vacuo* a residue remained which was identified as γ-pyridyl carbinol hydrochloride through its IR-spectrum.

Reduction of isonicotinic anilide (II). 1.00 g of isonicotinic anilide was suspended in 160 ml of 0.4 N KOH containing 10 % alcohol and reduced at −1.40 V *vs* S. C. E. During the reduction which consumed two electrons per molecule the isonicotinic anilide gradually dissolved and another precipitate was formed. After completion of the reduction the solution was cooled to 0°, partly neutralized with carbon dioxide and filtered. The precipitate was washed with water and quickly dried in an exsiccator. Yield 0.70 g. The crystals had no well-defined m.p., they "crackled" about 80°, turned yellow and softened at 110−115°. On further heating small needle-shaped crystals appeared which had m.p. 163°. (Found: C 71.79; H 6.04; N 14.10. Calc. for $C_{12}H_{12}N_2O$: C 71.98; H 6.04; N 13.99). The IR-spectrum (KBr) contained the following bands (cm^{-1}): 3385 (s), 3315 (s), 3050 (m), 2856 (w), 1676 (s), 1649 (s), 1615 (m), 1595 (s), 1530 (s), 1480 (s), 1437 (s), 1302 (m), 1277 (w), 1239 (m), 1200 (w), 1187 (m), 1171 (w), 1120 (m), 1078 (w), 1029 (w), 972 (m), 905 (m) 825 (m), 795 (m), 750 (ms), 720−680 (ms). The UV-spectrum contained a maximum (alcohol) at 243 mμ ($\varepsilon = 1.2 \times 10^4$) and no maxima at longer wave-length. The N.M.R. -spectrum was obtained in $CDCl_3$ with $(CH_3)_4Si$ as standard. It contained the following bands (c.p.s.): 126 (1 H) very broad, 235 (1 H), 270 (2 H), 335 (1 H) broad, 370 (2 H), 415-475 (5 H).

Reduction of isonicotinic thiamide (I). 0.50 g of isonicotinic thiamide was reduced at the plateau of the first wave in N HCl. The temperature was kept at 5°. The reduction consumed two electrons per molecule; the second wave of isonicotinic thiamide was not affected by the reduction. The product yielded an anodic wave which did not disappear on bubbling nitrogen through the solution for two hours. The product was unstable in neutral and alkaline solution, where it lost hydrogen sulfide. Part of the solution was evaporated *in vacuo* (1 mm) at a bath-temperature not exceeding 25°. Although the residue still contained some sulfide most of it consisted of pyridine-4-aldehyde hydrochloride, identified through its IR-spectrum. — To the rest of the solution was added phenylhydrazine and sodium carbonate. A precipitate of pyridine-4-aldehyde phenylhydrazone, m.p. 176°−178°, was obtained.

Reduction of isonicotinic thiamide (II). 0.50 g of isonicotinic thiamide was reduced in N HCl as described above. The potential was then adjusted to the plateau of the second wave. This reduction also consumed two electrons per molecule, and hydrogen sulfide was evolved. When the reduction was completed a sample was polarographed at pH 9; the polarogram showed the presence of aminomethylpyridine. The solution was evaporated, the residue dissolved in conc. hydrochloric acid to which alcohol was added. A precipitate, m.p. 255°, was identified as aminomethylpyridine dihydrochloride from the m.p. and the IR-spectrum.

Reduction of isonicotinic thiamide (III). 0.50 g of isonicotinic thiamide was reduced in an acetate buffer pH 4.8 at −0.85 V *vs* S. C. E. The reduction consumed four electrons per molecule. The polarogram of the reduced solution showed the presence of 4-mercaptomethylpyridine and 4-aminomethylpyridine. The solution was made slightly alkaline with sodium carbonate and left in an open flask overnight. The precipitate formed was filtered off, dissolved in a small volume alcohol and reprecipitated with water, 95 mg, m.p. 160°−162°. (Found: C 58.10; H 4.92; S 24.06. Calc. for $C_{12}H_{12}N_2S_2$: C 58.04; H 4.87; S 25.82). The IR-spectrum (in KBr) contained bands at (cm^{-1}): 3050 (w), 3028 (w), 2975 (w), 1931 (w), 1596, (s) 1553 (m), 1490 (m), 1406 (s), 1240 (w), 1216 (s), 1203 (w), 1129 (m), 1071 (w), 988 (s), 978 (w), 875 (m), 863 (m), 831 (s), 822 (m), 809 (s), 742 (w). The UV-spectrum (in alcohol) contained a broad maximum at 255−260 mμ. A polarogram in a borate buffer pH 9.0 consisted of a one-electron wave at −0.67 V *vs* S. C. E. and a two-electron wave at −1.45 *vs* S. C. E. Hydrochloride, m.p. 211°, picrate m.p. 177°−179°. — The filtrate was extracted with butanol, which was in turn extracted with N HCl. The solution was evaporated to dryness, and a polarogram and an IR-spectrum of the residue showed the presence of 4-aminomethylpyridine and some 4-mercaptomethylpyridine and its disulfide.

Oxidation of isonicotinic thiamide. 0.50 g of isonicotinic thiamide was dissolved in 0.05 N potassium hydroxide containing 0.5 M potassium chloride and oxidized at an anode potential of −0.2 V *vs* S. C. E. The temperature was kept at 5°. The reaction was completed after the consumption of two electrons per molecule. A black precipitate was formed during the reaction. The anodic and cathodic waves of isonicotinic thiamide disappeared gradually during the oxidation and another wave with a half-wave potential about −1.29 V *vs* S. C. E. appeared. 4-Cyanopyridine yields a wave at this potential in the medium used. When the oxidation was completed the black precipitate was filtered off, pH was lowered to 1 with HCl, and the solution evaporated *in vacuo*. The residue was extracted with alcohol which was evaporated. The IR-spectrum and polarographic behaviour of the residue proved that the main reaction product was 4-cyanopyridine.

Reduction of 4-cyanopyridine. 0.50 g of 4-cyanopyridine was reduced in 0.1 N potassium hydroxide at a cathode potential of −1.40 V *vs* S. C. E. The temperature was kept at 5°. The reduction consumed 2 electrons per molecule. After reduction, cyanide ions were determined photometrically after reaction with picric acid, yield of cyanide ions, 90−95 %. The remaining solution was made strongly alkaline and most of the solution distilled into a receiver containing hydrochloric acid. This solution was evaporated *in vacuo*, dissolved in a few ml of water, and on addition of sodium perchlorate a precipitate was obtained. It was identified as pyridinium perchlorate from the m.p. 285°−288° (288°)[17] and the IR-spectrum.

Reduction of anilinomethylpyridine. 0.400 g of anilinomethylpyridine was reduced in 0.20 N HCl at a cathode potential of −0.85 V *vs* S. C. E. Near the completion of the reduction some side reaction took place and the reduction was stopped after the consumption of 2 electrons per molecule. The polarograms showed that about 10 % of anilinomethylpyridine remained unreduced. In the reduced solution aniline was determined colorimetrically after diazotization and coupling. Yield of aniline 85 %, about 95 % of the reduced anilinomethylpyridine. No attempts were made to determine the γ-picoline in the solution.

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