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Original Scientific Paper

Electrochemical Reduction of Intermediates in the Vitamin B₆ Production. I. Reduction of 2-Methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine*

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2-Methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I) was reduced on a mercury-pool cathode in an electrolytic cell fitted with a diaphragm. The catholyte consisted of a mixture of acetic acid and hydrochloric acid and the anolyte was dilute hydrochloric acid. At a potential of -0.5 V vs. SCE. compound I was reduced to 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine (II). Compound II was reduced at a potential of -1.1 V vs. SCE. to give 2,4-dimethyl-3-amino-5-cyanopyridine (III). Compound III was reduced at constant current density to 2,4-dimethyl-3-amino-5-aminomethylpyridine (IV).

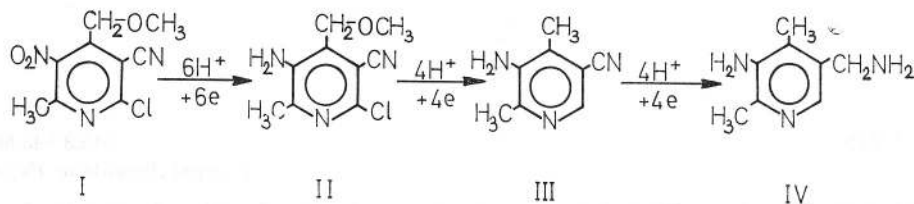
The influence of several factors (depolarizer concentration, electrolyte concentration and temperature) on yield of products was examined in each step. Polarograms were recorded with compounds I, II and III, and the character of limiting currents was assessed using the usual criteria.

The possibility of selective electrode reduction (or oxidation) of individual functional groups in a molecule is one of the most important advantages of electrochemical over chemical methods in reducing or oxidizing organic compounds. During the last fifteen years several review articles have been published on this subject, involving both methods of electrolysis at controlled potential¹⁻⁶, and with constant current density^{3,4,7}. Also several procedures for selective electrochemical reduction in polyfunctional molecules with one or more reducible centers have recently been reported^{2,8-10}.

However, there have been no specific reports, so far, concerning selectively reducing functional groups bound to a pyridine nucleus. One of these compounds, 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I) — an intermediate product of industrial vitamin B₆ synthesis — has been under study in our laboratory, and we found it readily underwent selective reduction during electrolysis. Four of its five functional groups, *viz.* the $-\text{NO}_2$, $-\text{CH}_2\text{OCH}_3$, $-\text{Cl}$, and $-\text{CN}$ groups, are reduced in turn, following the scheme:**

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** Assignment of polarographic waves, *e.g.* reduction steps proposed in some papers (Refs. 14 and 15), quite differs from our suggested reaction scheme, because the authors, investigating polarographic behaviour of I, for analytical purposes only, have neglected the identification of each reduction step product.



Compounds III and IV, arising in the course of electrochemical reduction of I, appear as intermediate products in the synthesis of antivitamin B₆¹¹, which has been recognised as an antitumor agent¹².

EXPERIMENTAL

All cathode potentials were measured *vs.* S.C.E. All melting points are uncorrected.

Apparatus and Procedure

Electrolyses were performed in a cell provided with a diaphragm, a mercury-pool cathode, and a platinum-wire anode, as previously described¹³. The catholyte was made up of 105 ml glacial acetic acid and 45 ml 10% aqueous HCl. However, in a series of experiments intended to test the influence of HCl concentration, the concentration of aqueous hydrochloric acid used to make up the catholyte was varied from 5 to 25 %. In all experiments, however, 10% HCl was used as the anolyte.

The cell was thermostated in a water bath and kept within limits of $\pm 2^\circ\text{C}$ of the specified temperature.

Conditions for electrolysis at controlled potential were selected from data shown by the curve in Fig. 1. This curve represents the change of cathode potential with time, as obtained in electrolysis of I at constant current density. The value of the latter was calculated according to M. J. Allen¹. The curve in Fig. 1 indicates that

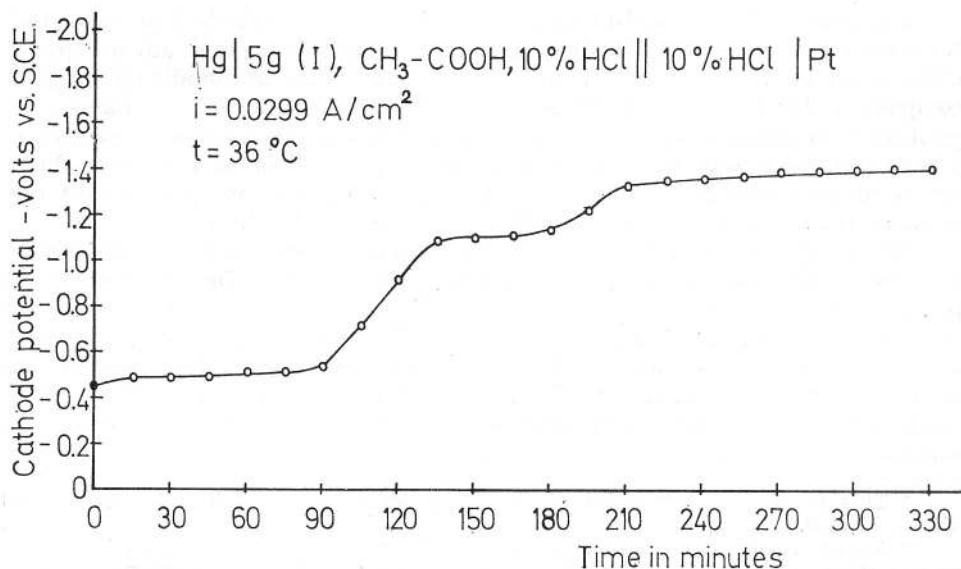


Fig. 1. Cathode potential *vs.* time curve for reduction of 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I) at constant current density.

three separate processes take place during reduction of I: the first (a) occurs between -0.5 and -0.55 V, the second (b) between -1.1 and -1.15 V, and the third (c) between -1.35 and -1.4 V. In several typical experiments with I and II as depolarizers the solution of these compounds were subjected to reduction at potentials corresponding to the first and the second steps, respectively, of the potential-time curve (Fig. 1). Depolarizer concentrations were varied from 0.033 to 0.2 M in these experiments. As the experiment proceeded, the current dropped exponentially to practically zero. Graphical integration of the area under the current-time curve (corrected for residual current) gave the amount of current consumed, and this value was used to calculate the number of electrons participating in the reduction.

Electrolysis at constant current density was started by adjusting the current until a potential of -0.5 or -1.1 V, respectively, was obtained, and then left to proceed for the theoretically required time.

Reduction I \rightarrow II was carried out both at controlled potential (-0.5 ± 0.02 V) and with constant current density. When the reduction has been completed, the content of the cathode compartment was removed and concentrated to a volume of about 20 ml, under reduced pressure. The remaining solution was neutralized with aqueous sodium hydroxide (50%), and left standing for one hour. The resulting precipitate of crude II was filtered off, dried over CaCl_2 for 24 hours and weighed*. To identify the resulting compound product, it was recrystallized from 80% aqueous ethanol to give bright-yellow crystals, m. p. $117-118^\circ\text{C}$. This substance had an IR spectrum identical with that from an authentic sample of 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine (II).

Reduction II \rightarrow III was performed at controlled potential of -1.1 ± 0.02 V and at constant current density. The crude product was isolated as described above, and recrystallized from 70% aqueous ethanol. Colorless needles, $164-166^\circ\text{C}$, of 2,4-dimethyl-3-amino-5-cyanopyridine, were obtained (anal.: C 65.33%, H 6.40%, N 28.33%; calcd. for $\text{C}_8\text{H}_9\text{N}_3$ C 65.28%, H 6.16%, N 28.55%). The IR spectrum of this substance indicated the presence of a cyano group (ν_{CN} 2220 cm^{-1}). NMR spectrum: CDCl_3 ; $\delta = 2.35$ singlet (4- CH_3); 2.48 singlet (2- CH_3); broad signal centred at 3.83 ($-\text{NH}_2$); 8.2 singlet (6-H).

Reduction III \rightarrow IV: 1.257 g (0.00787 mole) of compound III was dissolved in 150 ml catholyte and reduced at a constant current density of 0.0431 A/cm^2 ; during the electrolysis the cathode potential varied between -1.35 and -1.40 V. Samples were withdrawn every half-hour and subjected to thin-layer chromatography (adsorbent: HF-silicagel, solvent system: n-butanol — acetic acid — water, 4 : 1 : 5, R_F — values: III, 0.728 — IV, 0.032). After 7 hours the reduction went to completeness as indicated by the absence of the R_F 0.728 spot. The electrolysis was thereupon interrupted, the contents of the cathode compartment evaporated to dryness under reduced pressure, and the residue taken up in a small amount of methanol. Addition of benzene precipitated 1.58 g of white crystals of IV-hydrochloride monohydrate, m. p. 307°C (decomp.) reported¹¹ m. p. 310°C (decomp.). This compound showed no CN-band (2220 cm^{-1}) in the IR spectrum.

Reaction of compound IV with nitrous acid resulted in the replacement of the two amino groups by hydroxy groups according to described procedure¹¹. White crystals were obtained, m. p. $260-264^\circ\text{C}$. This substance gave an IR spectrum identical with that from an authentic sample of 4-desoxyadhermine hydrochloride.

Polarography

The polarograms were recorded with a Polariter PO-4 polarograph (Radiometer, Copenhagen) using a standard H-shaped cell. Capillary characteristics were as follows: $m = 2.10\text{ mg/sec}$, $t = 3.92\text{ sec}$ in 0.1 N KCl at 25°C , $h = 50\text{ cm}$, and $E = 0\text{ V}$. During polarography the temperature was kept constant by means of a VEB-Prüfgerätewerk type NBE thermostat.

* The values used in the diagrams on Fig. 2 are average yields from three electrolyses, each having a relative precision of $\pm 3\%$.

RESULTS AND DISCUSSION

The result of chemical analysis, as well as the coulometrically determined number of electrons participating in the process corresponding to the first step of the potential-time curve in Fig. 1 ($n = 5.8$) suggests this step, *i. e.* the reduction at -0.5 V, to be a six-electron reduction converting the nitro group of I into an amino group. Under various conditions this process yielded between 40 and 75% of the theoretical amount of 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine. The effects of varying depolarizer concentration, temperature and HCl concentration are shown on Fig. 2. The curves in this Figure demonstrate that both depolarizer concentration and temperature quite markedly affect the yield of the product of reduction, while the change of HCl concentration in the catholyte from 0.5 to 2.5 M exerted no significant influence.

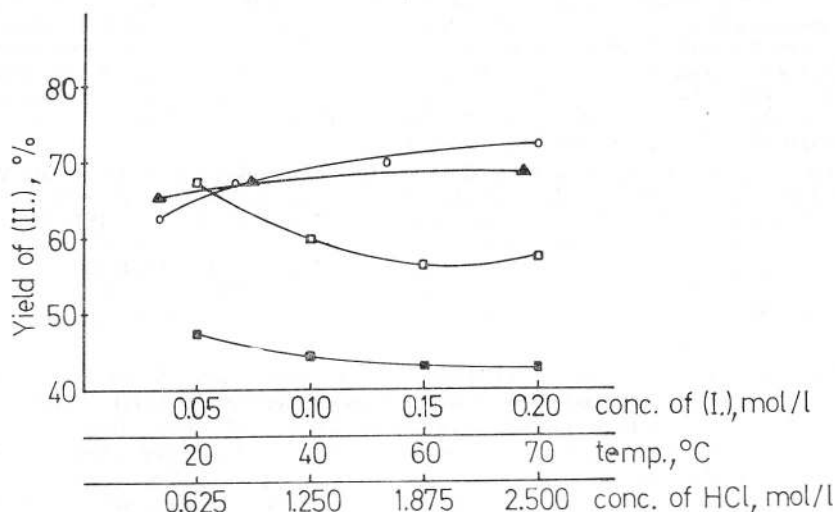


Fig. 2. Influence of various factors on yield of 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine (II)

○ influence of concn. of depolarizer (I), temp. = 20° C, concn. of HCl = 0.88 M

□ influence of temperature at controlled potential, concn. of (I) = 0.066 M, concn. of HCl = 0.88 M

■ influence of temperature at uncontrolled potential, concn. of (I) = 0.066 M, concn. of HCl = 0.088 M

▲ influence of concn. of HCl in catholyte, temp. = 20°, concn. of (I) = 0.066 M

Reduction step II \rightarrow III at -1.1 V must involve the breaking of two bonds in two different functional groups, *i. e.* the C—Cl bond in position 6 and a C—O bond in the methoxymethyl group, since the structure of the resulting compound, III, could be recognized as 2,4-dimethyl-3-amino-5-cyanopyridine. The coulometrically determined number of participating electrons (3.7) is well in keeping with the assumption that two two-electron reductions have taken place in this step.

The yields of III varied from 55 to 80%, depending on experimental conditions, as shown on Fig. 3. In the reduction II \rightarrow III all the examined factors considerably affected the yields. Depolarizer concentration affects the reaction rate, therefore increasing depolarizer concentration raised the yield.

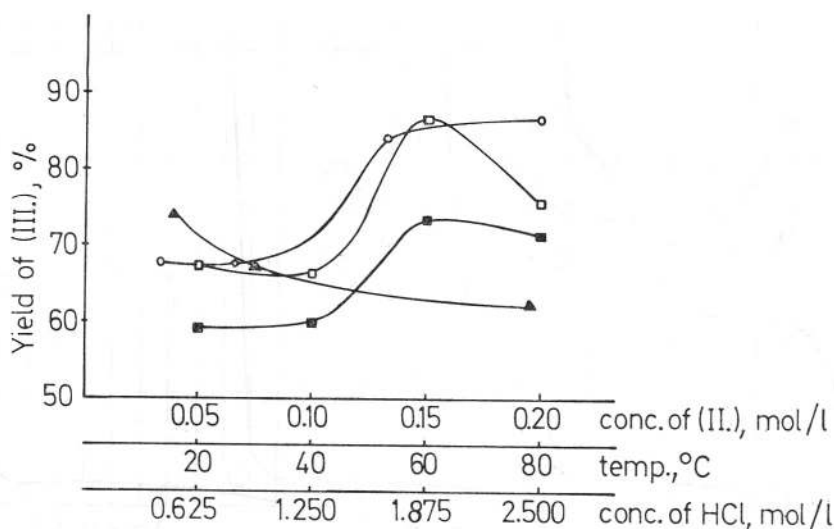


Fig. 3. Influence of various factors on yield of 2,4-dimethyl-3-amino-5-cyanopyridine (III)

- influence of concn. of depolarizer (II), temp. = 20° C, concn. of HCl = 0.88 M
- influence of temperature at controlled potential, concn. of (II) = 0.066 M, concn. of HCl = 0.88 M
- influence of temperature at uncontrolled potential, concn. of (II) = 0.066 M, concn. of HCl = 0.88 M
- ▲ influence of concn. of HCl in catholyte, temp. = 20° C, concn. of (II) = 0.066 M

In considering the influence of temperature and of the HCl concentration in the catholyte, one must take into consideration that these factors might affect side reactions giving rise to by-products other than III, say the hydrolysis or hydration of the cyano group. Higher HCl concentration and elevated temperature probably favor side reactions, but the increase in yield of III obtained on raising the temperature from 20 to 60° C may be explained by the relatively lower rates of side reactions in this interval.

Generally the yields of electrolysis at controlled potential were higher than those obtained at constant current density — as was to be expected.

Polarography. — Polarograms of 0.5×10^{-4} M solutions of compounds I, II, and III in a mixture of 105 ml CH₃COOH and 45 ml 10% HCl (pH = 0.2) are shown on Fig. 4. Compound I exhibits three polarographic waves with $E_{1/2}$ -values of -0.20, -0.85, and -0.95, respectively. The Ilkovič equation permits to calculate the number of electrons involved in the corresponding electrode processes: that related to the first wave involves $n_1 = 5.73$ electrons; these related to the second and third waves involve the sum $n_{2+3} = 3.40$ electrons*, assuming that the diffusion coefficient of compound I comes near that of the benzoate ion.

The magnitude of the temperature coefficient, as well as the fact that for all three waves the limiting currents depend on the square root of the

* Because of the shape of the polarographic waves the determination of the sum of the second and third waves gives more accurate values than the determination of each of the two waves separately.

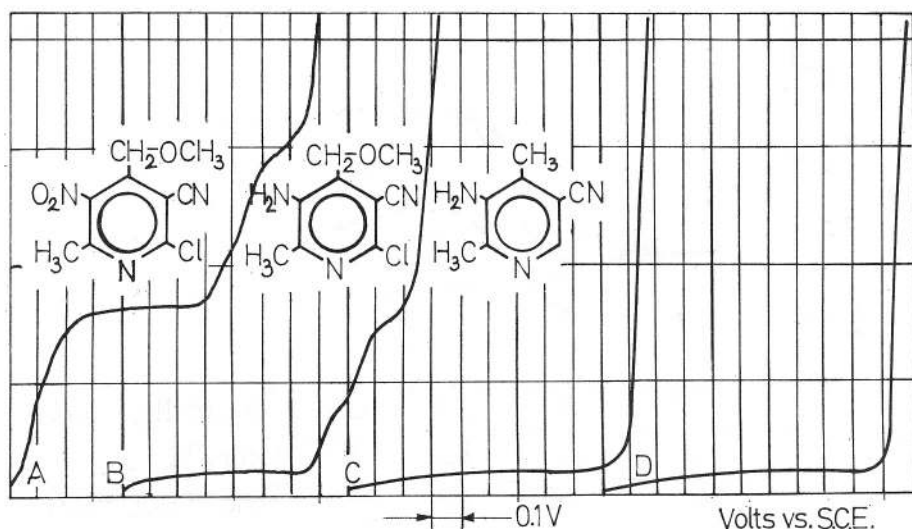


Fig. 4. Polarographic curves of 0.5×10^{-4} M solutions (starting with -0.1 V vs. S.C.E.)
 A. 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine;
 B. 2-methyl-3-amino-4-methoxymethyl-5-cyano-6-chloropyridine;
 C. 2,4-dimethyl-3-amino-5-cyanopyridine;
 D. Supporting electrolyte (10% CH_3COOH + 45 ml 10% HCl)

head of mercury ($h^{1/2}$) support the assumption that these limiting currents are diffusion-controlled.

Compound II exhibits only two polarographic waves with $E_{1/2}$ -values equal to those of the second and third waves, respectively, of compound I. Compound III has a polarogram that does not differ from the polarogram of the supporting electrolyte.

These results indicate that the first polarographic wave on the polarogram of compound I corresponds to a six-electron reduction converting the nitro group into an amino group; the second and third waves represent two-electron reductions involving the methoxymethyl group in position 4, and the C—Cl bond in position 6.

Reduction of the cyano group proceeds at a potential more negative than the proton-reduction potential, hence reaction $\text{III} \rightarrow \text{IV}$ probably was effected by nascent hydrogen. This might account for the fact that the yield of IV is large (82.4% of the theoretical amount) despite of a very low current yield (4.95%).

A comparison of the potential-time curve in Fig. 1 with the polarogram of compound I in Fig. 4 reveals that a working electrode potential of -0.5 V in the electrolysis cell is correlated to the diffusion current plateau of the first polarographic wave, while the cathode potential of -1.1 V corresponds to the diffusion current plateau of the third polarographic wave. The separation of half-wave potentials of the second and the third wave ($\Delta E = 0.1$ V), as seen on the polarograms is too small to permit a separation of the corresponding two-electron processes in an electrolytic cell with the large mercury cathode. It could not be possible, therefore, to separate the reductions of the

C—O and C—Cl bonds under the experimental conditions described in this paper.

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IZVOD

Elektrokemijska redukcija 2-metil-3-nitro-4-metoksimetil-5-cijano-6-kloropiridina

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2-Metil-3-nitro-4-metoksimetil-5-cijano-6-kloropiridin (I) reduciran je na živinoj katodi u elektrolitskoj ćeliji s dijafragmom. Katolit je bio smjesa octene i solne kiseline, a razrijeđena solna kiselina upotrebljena je kao anolit.

Spoj I reduciran je kod potencijala od $-0,5$ prema Z. K. E. u 2-metil-3-amino-4-metoksimetil-5-cijano-6-kloropiridin (II). Spoj II reduciran je kod potencijala od $-1,1$ V prema Z. K. E. u 2,4-dimetil-3-amino-5-cijanopiridin (III). Spoj III reduciran je pri konstantnoj gustoći struje u 2,4-dimetil-3-amino-5-aminometilpiridin (IV).

Izučavan je utjecaj različitih faktora (koncentracija depolarizatora, koncentracija elektrolita i temperatura) na iskorištenje produkata svakog stupnja reakcije. Snimljeni su polarogrami spojeva I, II i III i određen je karakter graničnih struja prema uobičajenim kriterijima.

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