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Note

Electrochemical Reduction of Intermediates in the Vitamin B₆ Production. II. Reduction of 2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine

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2-Methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine (I) was reduced on a mercury-pool in an electrolytic cell with a diaphragm. A mixture of acetic and hydrochloric acid was used as catholyte and diluted hydrochloric acid as anolyte. Compound I was reduced at -0.5 V to 2-methoxymethyl-3-amino-4-methyl-5-cyano-6-chloropyridine (II) (yield 67–82%). Compound II was reduced at -0.9 V to 2-methoxymethyl-3-amino-4-methyl-5-cyanopyridine (III) (yield 54–83%). Compound III was reduced at -1.1 V to 2,4-dimethyl-3-amino-5-cyanopyridine (IV) (yield 48–66%). Compound IV was reduced at constant current density to 2,4-dimethyl-3-amino-5-aminomethylpyridine (V) (yield 82,4%). Polarographic waves of I, II, and III are defined and character of limiting currents was determined according to the usual criteria.

In a former work of ours¹ the selective reduction of the 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine was studied. Four functional groups, *i. e.* $-\text{NO}_2$, $-\text{CH}_2\text{OCH}_3$, $-\text{Cl}$, and $-\text{CN}$ were reduced in three stages. In the present work the reduction of the isomeric polyfunctional molecule of 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine(I) was investigated.

EXPERIMENTAL

All cathodic potentials were measured *vs.* S.C.E. All m.p. are uncorrected. Apparatus and procedure were described in our former work¹. Electrolyses were performed in a cell with diaphragm, mercury cathode, reference electrode and platinum-wire anode, the same as in the previous investigations. The same catholyte was used, *i. e.* a mixture of acetic and hydrochloric acid.

The conditions for electrolysis at controlled potential were chosen from data shown by the curve in Fig. 1. This curve was obtained by the electrolysis on mercury-pool of the compound I at the current density calculated to M. J. Allen².

Reduction I \rightarrow II was performed by electrolysis at the controlled potential of -0.5 ± 0.02 V. After the electrolysis the content of the cathodic compartment was reduced to the volume of about 20 ml. by distillation under reduced pressure, then neutralized with an aqueous solution of NaOH (50%). After an hour's resting the formed precipitate of the raw product (II) filtered, dried for 24 hours over CaCl_2 and weighed. Light yellow crystals with m.p. 138–139°C (lit. m.p. 138–139°C)³ were obtained by recrystallization of the raw product II from the 25% aqueous ethanol (calcd.: C 51.07; H 4.76; N 19.85%; found: C 50.96; H 4.48; N 19.60%). NMR spectrum: CDCl_3 $\delta = 2.35$ singlet (4- CH_3); 3.40 singlet ($\text{CH}_3\text{O}-$); 4.65 singlet ($-\text{CH}_2-$ and $-\text{NH}_2$).

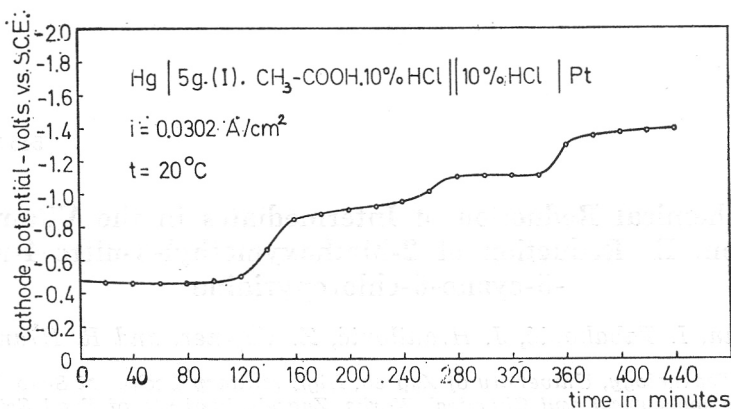


Fig. 1. Cathode potential vs. time curve for reduction of 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine(I) at constant current density.

Reduction II → III was performed by electrolysis at the controlled potential of -0.9 ± 0.02 V. The isolation of product III after electrolysis was performed in the same way as the isolation of product II of reduction I → II. The formed raw product III was recrystallised from water. Needlelike white crystals m.p. 100–102°C (calcd.: C 61.34; H 5.72; N 23.85%; found: C 61.41; H 5.72; N 23.96%) were obtained. The IR spectrum shows absorption at 3500 (m) cm^{-1} ($-\text{NH}_2$ double band); at 2240 (m) cm^{-1} ($-\text{CN}$ band); and at 1070 (s) cm^{-1} ($\text{C}-\text{O}$ band), NMR spectrum: CDCl_3 : $\delta = 2.35$ singlet (4- CH_3); 3.40 singlet ($\text{CH}_3\text{O}-$); broad signal centred at 4.68 ($-\text{NH}_2$); 4.72 singlet ($-\text{CH}_2-$) 8.2 singlet (6-H).

Reduction III → IV was performed by electrolysis at the controlled potential of -1.1 ± 0.02 V. The isolation of product IV was performed according to the above described procedure in reduction I → II. Colourless needlelike crystals m.p. 164–166°C, were obtained by recrystallisation from 80% aqueous ethanol. This substance (IV) gave identical IR and NMR spectra as 2,4-dimethyl-3-amino-5-cyanopyridine¹.

Reduction IV → V was performed at constant current density and described in the former work¹.

RESULTS AND DISCUSSION

On the basis of the isolation and identification of the product of reduction I → II as well as coulometrically determined number of electrons ($n = 5.5$) it can be concluded that the first process (Fig. 1), corresponds to the six-electron reduction of the nitro group to the amino group. In the reduction II → III breaking of $\text{C}-\text{Cl}$ bond occurs in position 6. The coulometrically determined number of electrons ($n = 1.8$) indicated a two-electron process. In the reduction III → IV breaking of $\text{C}-\text{O}$ bond of methoxymethyl group occurs in position 2.

Polarography. — Polarograms of 5×10^{-4} M solutions of the compounds I, II, III, and IV in a mixture of glacial acetic acid and 10% hydrochloric acid (volume ratio 105 : 45) at 25°C are presented in Fig. 2.

Compound I shows three polarographic waves with half-wave potential values of: -0.198 , -0.850 , and -1.0 V. The number of electrons calculated from Ilkovič's equation is $n = 5.38$ for the first wave and $n = 1.94$ for the second wave, under the assumption that the diffusion coefficient of compound I was approximately equal to the diffusion coefficient of the benzoate ion (8.28×10^{-6} cm^2/sec). Compound II shows two polarographic waves whose

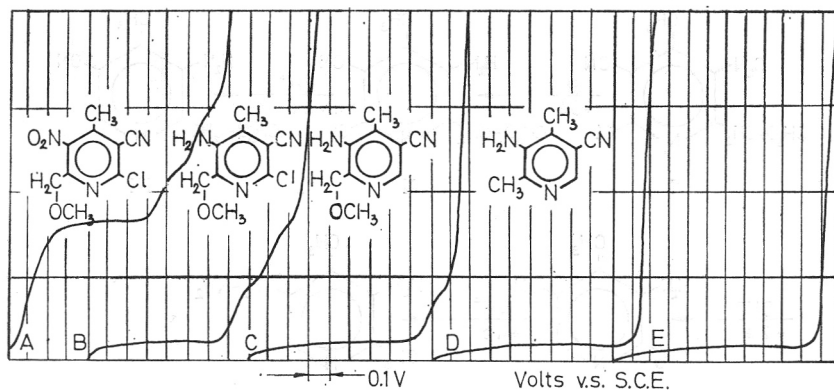


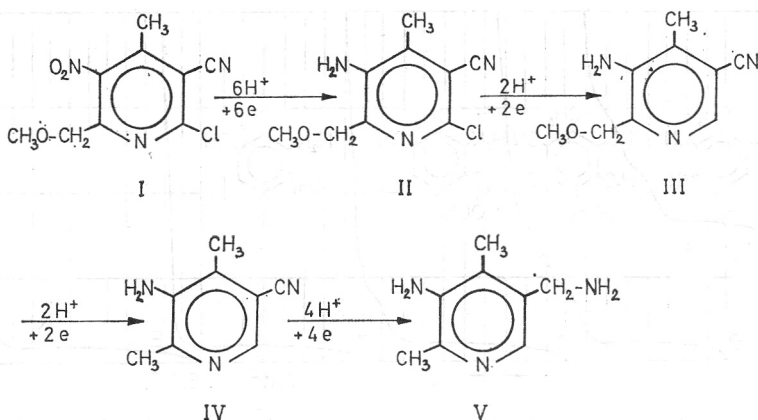
Fig. 2. Polarographic curves of 5×10^{-4} M solutions (starting with -0.1 V vs. S. C. E.). A. 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine. B. 2-methoxymethyl-3-amino-4-methyl-5-cyano-6-chloropyridine. C. 2-methoxymethyl-3-amino-4-methyl-5-cyanopyridine. D. 2,4-dimethyl-3-amino-5-cyanopyridine. E. Supporting electrolyte (105 ml. CH_3COOH + 45 ml. 10% HCl).

half-wave potential values correspond to the values of the second and third polarographic wave of compound I. Compound III shows only one polarographic wave with $E_{1/2} \approx -1.0$ V, this corresponds to the third polarographic wave of compound I. Compound IV is polarographically inactive in given conditions. The dependence of the limiting current on temperature, concentration of the depolarizer, and the height of the head of mercury, as revealed by measurements, point to the fact that both electrode processes, corresponding to the first and second polarographic wave, are controlled by diffusion. The logarithmic analysis of these waves indicates their irreversible character. The obtained results show that the first polarographic wave of compound I corresponds to the six-electron reduction of the nitro group to the amino group. The second polarographic wave represents a two-electron reduction of C—Cl bond in position 6, and the third polarographic wave corresponds to the two-electron reduction of C—O bond of methoxymethyl group in position 2. A comparison of cathodic potential-time curve in Fig. I. and polarogram of compound I in Fig. 2 shows that working potentials of the cathode, *i. e.* -0.5 , -0.9 , and -1.1 V, correspond to the potentials on the plateau of the diffusion current of the first, second and third wave.

On the basis of all above mentioned results we propose that the reduction of the compound I, with the methoxymethyl group in position 2, takes place in four stages according to the scheme (see page 388).

In the former work¹ the reduction of the isomeric compound with the methoxymethyl group in position 4 *i. e.* 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine was performed. The nitro group was converted into the amino group by electrolysis at controlled potential, but it was not possible to separate reductions of C—O and C—Cl bonds due to insufficient difference of half-wave potentials ($\Delta E_{1/2} = 0.1$ V) and, accordingly, it was impossible to state which of these two reductions was primary.

This problem has been solved by the present work. It is well-known that the reducibility of a substituent depends on its position on the pyridine nucleus and that it decreases in order $4 > 2 > 3$.



In the reduction of compound I, *i. e.* 2-methoxymethyl-3-nitro-4-methyl-5-cyano-6-chloropyridine, the half-wave potential for the reduction of C—O bond of methoxymethyl group in position 2 is more negative than the half-wave potential for the reduction of the isomeric compound with methoxymethyl group in position 4. The potential difference formed in this way ($\Delta E_{1/2} = 0.15$ V) has proved to be sufficient for a selective reduction of the C—Cl bond and methoxymethyl group in position 2.

REFERENCES

1. M. Lačan, I. Tabaković, J. Hranilović, N. Bujas, and Z. Stunić, *Croat. Chem. Acta* **43** (1971) 229.
2. M. J. Allen, *Can. J. Chem.* **37** (1959) 257.
3. D. Huyl, E. Luz, and S. Harris, *J. Am. Chem. Soc.* **78** (1956) 4474.

IZVOD

Četverostepena selektivna redukcija 2-metoksimetil-3-nitro-4-metil-5-cijano-6-klorpiridina

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2-Metoksimetil-3-nitro-4-metil-5-cijano-6-klorpiridin (I) reduciran je na živoj katodi u elektrolitskoj ćeliji s dijafragmom. Smjesa octene i solne kiseline upotrebljena je kao katolit, a razrijeđena solna kiselina kao anolit. Spoj I reduciran je kod potencijala od $-0,5$ V prema Z. K. E. u 2-metoksimetil-3-amino-4-metil-5-cijano-6-klorpiridin (II) (iskorištenje od 67 do 82%).

Spoj II reduciran je kod $-0,9$ V u 2-metoksimetil-3-amino-4-metil-5-cijanopiridin (III) (iskorištenje od 54 do 83%).

Spoj III reduciran je kod $-1,1$ V u 2,4-dimetil-3-amino-5-cijanopiridin (IV) (iskorištenje od 48 do 66%).

Spoj IV reduciran je pri konstantnoj gustoći struje u 2,4-dimetil-3-amino-5-aminometilpiridin (V) (iskorištenje 82,4%).

Dati su polarografski valovi spojeva I, II i III i određen je karakter polarografskih graničnih struja prema uobičajenim kriterijima.

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