AZAINDOLE DERIVATIVES

XLIX.* STUDY OF THE MECHANISM OF THE POLAROGRAPHIC OXIDATION OF AZAINDOLINES

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A mechanism for the polarographic oxidation of azaindolines that includes electrochemical and chemical steps is proposed. The preparative electrolysis of 1-phenyl-4-methyl-6-morpholino-7-azaindoline, which gives the corresponding 7-azaindole and (7-aza-5-indolinyl)-7-azaindoline, was accomplished.

In our preceding communications of this series [2, 3] we described the polarographic oxidation of 5-aza, 7-aza-, and 5,7-diazaindolines. The subsequent and more profound investigation of the principles involved in these processes necessitated a study of the mechanism of the indicated reactions.

An important characteristic necessary for this sort of study is the determination of the character of the limiting current arising during the electrochemical oxidation of azaindoline compounds. In this connection, we studied the effect of a number of factors on the magnitude of the limiting current of the indicated process. It was established that a linear dependence of the current strength (i) on the square root of the angular velocity (ω) is observed over the investigated range of rates of rotation of the electrode (800-4000 rpm). In addition, it was experimentally determined that a slight increase in the limiting current is characteristic for azaindoline compounds as the temperature rises, and this is evidently explained by the temperature changes in the magnitude of the diffusion coefficient; the temperature coefficient ranges from 1.5 to 2.3% per degree centigrade. All of these data showed that the magnitude of the current strength is determined by the rate of diffusion of the depolarizer to the electrode. This conclusion enabled us to quantitatively describe the electrode process by a convective diffusion equation [4]:

$$i=0{,}62nFD^{2/3}\nu^{-1/6}\omega^{1/2}Sc,$$

where n is the number of electrons participating in the electrode reaction, D is the diffusion coefficient, ν is the kinematic viscosity, and S is the area of the electrode surface.

It was established by cyclic volt amperometry from a comparison of the half-wave potentials and the currents of the anode and cathode branches that the electrochemical reactions have irreversible character.

On the basis of the convective diffusion equation presented above, we determined the number of electrons participating in the electrooxidation of one azaindoline molecule. In this case, the diffusion coefficients, as is examined in greater detail in the experimental section, were found by two independent methods – from the Stokes – Einstein equation [5] and on the basis of a determination of the changes in the current strengths on a stationary hemispherical microanode after switching it into the electrical circuit [6].

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*See [1] for communication XLVIII.

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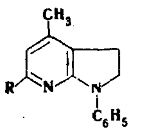
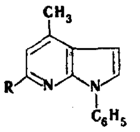
TABLE 1. Half-Wave Potentials ($E_{1/2}$), Limiting Currents (i), Diffusion Coefficients (D), and Number of Electrons (n) for 6-Amino-7-azaindolines and 6-Amino-7-Azaindoles



A



B

R	A				B
	$E_{1/2}$, V	i, μA	$D \cdot 10^6$ cm²/sec	n	$E_{1/2}$, V
NH_2	0,40	10,0	5,4	2,2—2,0	—
NHC_4H_9	0,29	7,2	6,0	1,6—2,0	—
$N(C_4H_9)_2$	0,32	6,1	4,9	1,8—2,0	0.53
NHC_6H_5	0,43	6,2	5,2	1,8—2,0	0,66
$N(C_2H_5)C_6H_5$	0,41	7,2	4,9	1,7—2,0	0,64
Morpholino	0,40	6,1	5,3	1,8—2,0	0,63
Pyrrolidino	0,42	8,4	5,4	2,0	0,72
4-Methylpiperazino	0,32	6,4	5,2	1,6—2,0	—
$N(CH_3)_2$	0,32	7,0	5,6	1,6—2,0	—

The two methods gave D values that coincide. The n values found from the equation were two. The limiting currents, diffusion coefficients, and numbers of electrons involved in the oxidation of some 7-azaindoline derivatives are presented in Table 1 as examples. It proved to be impossible to determine the n values by a microcoulometric method in these cases, inasmuch as prolonged electrolysis is accompanied by the formation of poorly conductive films on the surface of the platinum anode even at low concentrations of the compounds ($5 \cdot 10^{-4}$ M).

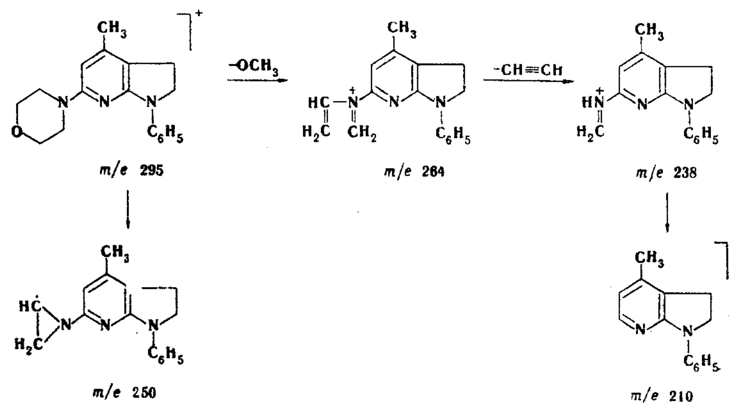
The determination of the n values and the analogy with the results of chemical oxidation of azaindoline compounds [2] enabled us to assume that the final products of the electrochemical reactions are the corresponding 7-azaindoles. To confirm this assumption, we carried out the preparative electrolysis of azaindoline compounds at a controllable potential under conditions close to those of the polarographic measurements with isolation and identification of the final electrolysis products. The process was studied in greatest detail in the case of 1-phenyl-4-methyl-6-morpholino-7-azaindoline (I), for which the isolation and identification of the electrochemical oxidation products was proved to be easiest in a preparative respect [7]. The electrolysis was carried out at a potential corresponding to the start of the limiting current plateau. Individual samples of the reaction mixture selected during the electrolysis were analyzed polarographically, and 1-phenyl-4-methyl-6-morpholino-7-azaindole (II), the concentration of which increased during the electrolysis, was detected in the electrooxidation products; the concentration of starting azaindoline I decreased simultaneously (Fig. 1).

Gas-liquid chromatography (GLC) was additionally used for the identification of I and II and also for the determination of the ratio of these products during electrolysis. After the preparative electrolysis, azaindole II, identical to a genuine sample, was isolated from the electrochemical oxidation products by column chromatography with aluminum oxide.

Deactivation of the platinum anode due to deposition of a light-yellow substance on its surface was observed during the experiments involving the preparative electrochemical oxidation of azaindoline I, and this led to a decrease in the current and necessitated periodic purification of the platinum surface. In addition, the formation of a precipitate from the working solution with properties similar to those of the substances deposited on the anode was observed during the electrooxidation, and the pH of the solution decreased from 3.6 to 1.8.

Alkalization of the solid obtained by filtration of the electrolysis solution gave 1-phenyl-4-methyl-5-(1-phenyl-4-methyl-6-morpholino-7-azaindolin-5-yl)-6-morpholino-7-azaindoline (III), the structure of which was confirmed by data from the mass and PMR spectra.

The mass spectrum of I has a molecular ion peak with m/e 295, and the subsequent fragmentation of the ion is realized primarily through cleavage of the morpholine ring to give ions with m/e 264, 250, 238, 210, and others:



A molecular ion peak with m/e 588 is observed in the mass spectrum of III, and the most intense fragment ion has m/e 294 and is evidently associated with disintegration of the "dimeric" structure III into "monomeric" radicals. The subsequent fragmentation of the fragment with m/e 294 is similar to the above-presented fragmentation of the molecular ion of I (peaks with m/e 263, 249, 237, 209, etc.). Ions with m/e 557, 543, 531, and 503, which are also due to disintegration of the morpholine ring similar to that in "monomeric" product I, are observed in the high-molecular-weight portion of the spectrum of III. The PMR spectra of I and III are presented in the experimental section.

The material balance of the potentiostatic electrolysis process, which was determined from the results of polarographic analysis with allowance for the amount of electricity consumed (463 C), enabled us to calculate the yield of II with respect to the current (84%) and with respect to the compound (40%); the yield of the "dimeric" product III was 15% with respect to the compound.

The relatively low yield of II with respect to the compound and the formation of "dimeric" product III (the amount of which increases if the electrolysis process is interrupted, during which the amount of starting azaindoline I simultaneously continues to decrease, whereas the concentration of azaindole II remains constant) as a result of anode oxidation constitutes evidence for the complex character of the transformations under investigation. The electrode oxidation of the azaindoline compounds apparently includes two types of reactions – electrochemical and purely chemical. Some of the peculiarities of the polarography of the azaindoline compounds also attest to this. Thus, for example, when the $E_{1/2}$ values of 6-amino-7-azaindoline and 6-amino-7-azaindole derivatives are compared (Table 1), it is seen that the latter are oxidized at more positive potentials ($\Delta E_{1/2} \approx 0.2$ V). Two oxidation waves with $\Delta E_{1/2} \approx 0.2$ V are observed on the polarograms of mixtures of substituted 6-amino-7-azaindolines and the corresponding azaindoles. In addition, only one wave appears on the polarogram of the oxidation of substituted 6-amino-7-azaindolines, and waves of oxidation of the products of the electrode reaction are absent. This phenomenon is not associated with reaction of the products of electrochemical oxidation of azaindoles with solution components or the electrode material. The overall form of the volt–ampere curves does not change when various base electrolytes – 0.1 M solution of lithium chloride in ethanol, a 0.1 M solution of hydrochloric acid, and a 0.1 M solution of tetrabutylammonium hydroxide in ethanol – are used, whereas the $E_{1/2}$ values vary with their usual dependence on the pH values of the working solutions. Comparative polarographic investigations with rotating disk electrodes prepared from platinum and SU-2500 carbon glass show that $E_{1/2}$ and the overall form of the polarization curves are practically independent of the anode material.

It was established on the basis of polarographic analysis by the method of "latent" limiting currents [8] that the azaindoles formed in the electrolysis do not react with the starting azaindolines (Fig. 2).

In addition, a second wave characteristic for oxidation of the corresponding azaindoles arises in addition to the wave of the azaindoline compound during an oscillographic investigation of azaindoline compounds with multiplex imposition of fast polarization pulses (0.125-4.0 V/sec) on a stationary platinum electrode. The height of the first wave in the successive volt–ampere curves remains constant, while the height of the second wave increases. This phenomenon also may be associated with the complex character of the electrochemical oxidation of azaindoline compounds. It is possible that the rate of the final chemical step in the process is lower than that of electrochemical oxidation and that the intermediates have time to diffuse into the solution.

When multiplex current pulses are used, the electrode surface changes qualitatively with respect to the type of anode–cathode activation, and this facilitates the reproducibility of the limiting current of the

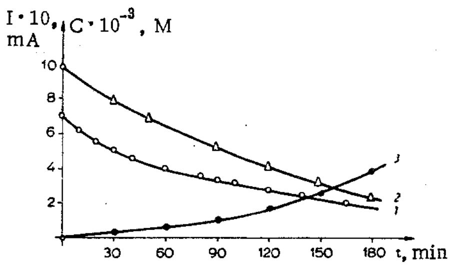


Fig. 1

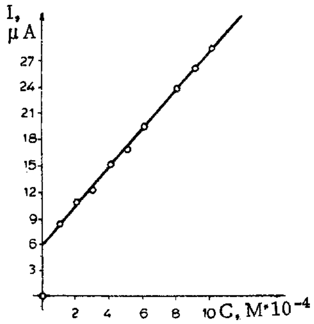


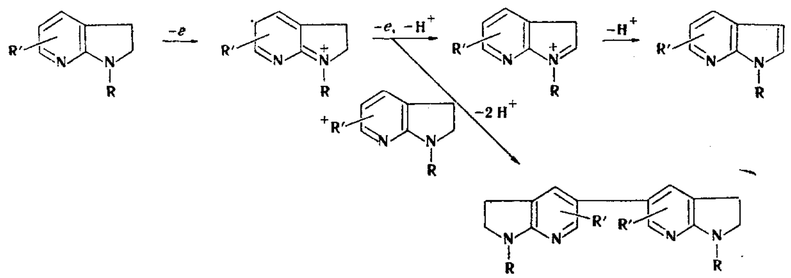
Fig. 2

Fig. 1. Dependence of the current strength (1), 1-phenyl-4-methyl-6-morpholino-7-azaindoline concentration (2), and 1-phenyl-4-methyl-6-morpholino-7-azaindole concentration (3) on the time (t) during the electrolysis.

Fig. 2. Dependence of the overall limiting current (I) on the concentration of azaindole II at a constant azaindoline I concentration ($5 \cdot 10^{-4}$ M).

azaindoline compound. The changes in the electrode surface probably catalyze the oxidation process in the rate-determining step, and there is sufficient time for recording of the formation of azaindole derivatives on the electrode surface; this is determined from the appearance of a second wave.

Summarizing the results of our investigation, the overall mechanism of the electrochemical oxidation of 7-azaindolines can be represented by the following probable scheme:



This scheme makes it possible to explain the formation, as a result of the electrolysis of azaindoline compounds, of two types of products – azaindole derivatives and dimeric compounds – and also the changes in the ratios of the amounts of these products in those cases in which electrolysis is interrupted, to understand the reasons for the irreversability of the electrochemical oxidation of azaindoline compounds, etc. Nevertheless, this scheme does not pretend to give a complete description of the mechanism of electro-oxidation of azaindoles and is only a first working hypothesis that opens up the possibility of further research in this direction.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The mass spectra were recorded with an LKB-9000 spectrometer at an ionizing-electron energy of 70 eV. Gas–liquid chromatographic analysis was carried out with a Pye-Unicam 104 chromatograph with a flame-ionization detector and a 1.5 m by 4 mm glass column; the stationary phase was FS-1 silicone elastomer (3%) applied on silanized Celite (80-100 mesh), the column temperature was 235°, and the nitrogen flow-rate was 30 ml/min.

The volt–ampere curves were recorded with a PA-101 polarograph (Yanagimoto, Japan). In all cases except for those specially stipulated in the text, the $E_{1/2}$ values were determined by polarographic oxidation on a rotating (1880 rpm) platinum disk electrode ($S = 0.031\ cm^2$) in an inert electrolyte – 0.5 M $NaClO_4$ in ethanol – at 25.0 ± 0.1°; the comparison electrode was a saturated calomel half-cell, and the accuracy in the measurements was ± 0.01 V. The cyclic volt–amperograms were recorded under the same conditions with a stationary platinum electrode (5 mm by 0.5 mm wire) at various rates of measurement of the potential (from 2 to 1000 mV/sec). Artificially prepared mixtures with a constant concentration ($5 \cdot 10^{-4}$ M) of I and a variable concentration (10^{-4}-10^{-3} M) of II and, vice versa, with a constant concentration of II and a variable concentration of I were used in the polarographic analysis by the method of "latent" limiting currents.

The apparatus for preparative electrolysis at a controllable potential consisted of an electrolyzer (cell) and an ASA-100-1C potentiostat (Tacussel, France). The anode was platinum gauze (60 by 65 mm), and the cathode was prepared from tin ($S = 80\ cm^2$). To avoid reduction of the starting compounds and the electrolysis products the experiments were carried out in an electrolyzer with a ceramic diaphragm, which was a cylindrical beaker terminating in a conical part (for seating in the electrolyzer): the height of the beaker was 100 mm, and the height of the cone was 50 mm. To improve the electrical conductivity, the diaphragm was treated with electrolyte prior to placement in the vessel, from which the air was evacuated, after which the electrolyte was drawn in from another vessel. This operation was repeated two to three times, after which the diaphragm was retained in the vessel with the electrolyte. Stirring during the electrolysis was accomplished with a magnetic stirrer; the inert electrolyte was an 1 M solution of $LiClO_4$ in ethanol, and the comparison electrode was a saturated calomel half-cell. To eliminate deactivation of the platinum anode by the film deposited on the surface, it was treated periodically with hot 50% sulfuric acid and washed with distilled water.

Preparative Electrolysis of 1-Phenyl-4-methyl-6-morpholino-7-azaindoline (I). A solution of 2.08 g of azaindoline I in 700 ml of ethanol containing 74 g of $LiClO_4$ was electrolyzed at 0.5 V for 20 h, after which the resulting precipitate (0.73 g) was removed by filtration. The alcohol solution, which, according to the results of polarographic determination, contained 0.25 g of starting azaindoline I and 0.51 g of II, was vacuum evaporated to dryness. Water (200 ml) and 5 ml of a 50% potassium carbonate solution were added to the residue, and the mixture was extracted with benzene. The benzene extract was dried with potassium carbonate and evaporated to give 0.96 g of residue, which was applied to a chromatographic column (24.5 by 3.5 cm) filled with Al_2O_3; the reaction products were eluted with ether–hexane (7 : 3) with monitoring of the separation from the luminescence of the substances in UV light. The contents of the column were then separated mechanically into six fractions, which were eluted separately with chloroform. The purity of the eluted products was monitored by thin-layer chromatography (TLC) on plates with Al_2O_3 in ether–hexane (7 : 3) and detection by UV irradiation. In connection with the fact that the eluates of the first three fractions contained impurities, they were not subjected to further workup. The eluates of the next three fractions (0.43 g of material), according to TLC data, contained only 1-phenyl-4-methyl-6-morpholino-7-azaindole (II) containing a small amount (5%) of azaindoline I. Recrystallization from acetone gave 0.2 g of pure azaindole II with mp 147-148°. No melting-point depression was observed for a mixture of this product with an authentic sample of II [7]. The two samples had identical UV and IR spectra.

The solid material (0.73 g) that was removed by filtration from the alcohol solution after electrolysis (mp 258-260°) was, according to the results of elementary analysis, a perchlorate salt. It was treated with 4 ml of 10% aqueous sodium hydroxide solution, and the resulting base was extracted with benzene. The benzene solution was dried with potassium carbonate and evaporated to give 0.64 g (15%) of base III with mp 307-308° (from ethyl acetate). Found: C 73.2; H 6.9; N 14.2%. $C_{36}H_{40}N_6O_2$. Calculated: C 73.4; H 6.9; N 14.3%. PMR spectrum: δ 1.99 (s, CH_3), 4.05 (t, CH_2 in the α positions relative to the pyrroline nitrogen atom), 3.53 (t, CH_2O), 305 (m, CH_2 in the β positions of the pyrroline rings and the α positions relative to the nitrogen atoms of the morpholine rings), 6.92 (t), 7.34 (t), and 7.75 (d) ppm – signals of the protons of the phenyl ring in, respectively, the para, meta, and ortho positions relative to the pyrroline nitrogen atoms. The absence of the signal of the 5-H proton of the azaindoline rings constitutes evidence for joining of the azaindoline systems in the 5 and 5' positions.

PMR spectrum of azaindoline I: δ 2.09 (s, CH_3), 3.94 (t, CH_2 in the α positions relative to the pyrroline nitrogen atom), 2.89 (t, CH_2 in the β position), 3.04 (m, CH_2 in the α positions relative to the nitrogen atom of the morpholine ring), 3.75 (m, CH_2O to the oxygen atom), and 5.76 (s, 5-H), 6.89 (t), 7.28 (t), and 7.75 (d) ppm – signals of the protons of the phenyl ring in, respectively, the para, meta, and ortho positions relative to the pyrroline nitrogen atom.

The kinematic viscosity (ν) was measured with an Ubelhode viscosimeter (VPZh-2); $\nu = 2.16 \cdot 10^{-2}$ cm^2/sec for the working 0.5 M solution of $NaClO_4$ in ethanol. The Stokes–Einstein equation was used for the determination of the diffusion coefficients.

The dynamic viscosity of the medium (η) was determined from the equation $\eta = \nu \rho$, where ν is the kinematic viscosity and ρ is the density of the solution found experimentally by means of a pycnometer. The densities (d) of the azaindoline compounds were also measured with a pycnometer with a liquid that did not dissolve the compound but ensured that it was completely moistened; the saturated (at 25°) solution of the substance to be analyzed in ethanol was filtered. The following values were found for 1-phenyl-4-methyl-6-dibutylamino-7-azaindoline at 25°: $\rho = 0.860$ g/cm^3, $d = 1.2$ g/cm^3, and $\eta = 1.86 \cdot 10^{-2}$ g/sec · cm.

The D values were determined by a second method as follows: a platinum electrode was treated thoroughly with hot 50% sulfuric acid, washed with water, and maintained at 25° for 5-10 min and 0.03 V, after which the potential corresponding to the start of the plateau of the limiting current was established and the recorder of the polarograph was simultaneously switched on. Inasmuch as the rate of movement of the paper of the recording apparatus is constant (10 cm/min), the graphical dependence of the current strengths on the time was automatically recorded. After brief electrolysis (2-18 sec), the diffusion front was propagated at a very small distance as compared with the radius of curvature of the electrode, and, in this connection, the change in the current strength in the first seconds after the surge is subject, on a spherical electrode, to the linear diffusion law [6], whereas the change in the area of the electrode situated under the current for no more than 25 sec is slight due to the liberated substances. Each new surge current was recorded with a completely depolarized electrode, the degree of depolarization of which was confirmed by return of the arrow of the recorder to the zero position. The graph of the dependence of i on $1/\sqrt{t}$, which was described by the equation $i = a + bt^{1/2}$, confirming that the linear diffusion law is in good agreement in the first second after the current surge, was constructed from the experimental data. The a and b coefficients in the equation are, respectively, $ncDFSr^{-1}$ and $ncD^{1/2}FS\pi^{-1/2}$, where, in addition to the symbols mentioned above, r, the experimentally determined electrode radius, is used. The D value found by this method for 1-phenyl-4-methyl-6-dibutylamino-7-azaindoline was $4.83 \cdot 10^{-6}$ cm^2/sec. The diffusion coefficients for the other compounds were calculated from the equation $D_1/D_2 = \sqrt{M_2}/\sqrt{M_1}$, where M_1 and M_2 are the molecular weights [9].

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