

AZAINDOLE DERIVATIVES

XXVIII. The Dehydrogenation of Substituted 7-Azaindoles*

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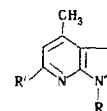
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A comparative study of the dehydrogenation of azaindoles by chemical (under the action of quinones) and electrochemical (anode polarography at a rotating platinum disc electrode) methods has been made. The influence of substituents in positions 1 and 6 of the azaindole molecule on the ease of oxidation of the compounds has been investigated. The results are discussed using the method of correlation equations.

The dehydration of indolines and azaindoles is of fundamental importance for the synthesis of indole and azaindole derivatives. The general method that we have developed for the preparation of various 7-azaindoles from 2-chloro-3-(β -chloroethyl)pyridines [1, 2] has permitted the synthesis of these compounds in high yields and the study of methods for their dehydrogenation. The systematization and generalization of the experimental material described in part in preceding communications of this series [3-6] permitted certain conclusions to be drawn concerning the influence of substituents in the azaindole molecule on the ease of dehydrogenation. Thus, in a number of cases it was found that the introduction of halogen atoms into the 1 and 6 positions of the 7-azaindoles hinders the dehydrogenation process. In the case of 1-aryl-6-chloro-7-azaindoles [3] and 4, 6-dichloro-7-azaindoles [4], the oxidation potential of chloranil proves insufficient, and to convert these compounds into 7-azaindole derivatives a stronger oxidizing agent, 2, 3-dichloro-5, 6-dicyanobenzoquinone, is required. Conversely, the introduction of a methoxy group into position 6 of the 7-azaindoles [5] facilitates dehydrogenation. While, for example, 4-methyl-1-phenyl-7-azaindoline is oxidized by chloranil only in boiling xylene, 6-methoxy-4-methyl-1-phenyl-7-azaindoline readily undergoes dehydrogenation even at the boiling point of benzene. The nature of the substituent on the pyrroline nitrogen atom has a similar influence on the dehydrogenation process. We showed this for the case of 4-methyl-1-phenyl-7-azaindoline (75% dehydrogenation takes place when the substance is boiled with chloranil in xylene for 1.5 hr), 1-(*p*-methoxyphenyl)-4-methyl-7-azaindoline (88% dehydrogenation under the same conditions), and 4-methyl-1-(*p*-nitrophenyl)-7-azaindoline (the substance remains unchanged on being boiled with chloranil in xylene; even under the action of 2, 3-dichloro-5, 6-dicyano-benzoquinone the corresponding 7-azaindole derivative is formed with a yield of only 20%) [6].

The introduction into position 1 of the azaindoline molecule of still stronger electron-accepting residues than *p*-nitrophenyl, acyl groups, causes a further increase in the stability of these compounds to the action of oxidizing agents. The dehydrogenation of 1-acetyl- and 1-cinnamoyl-4-methyl-7-azaindoles, for example, does not take place either when the substances are boiled with chloranil in xylene or when they are heated for 4 hr with sulfur to 240° C or with selenium to 300° C [7]. In all cases, the initial compounds are recovered. Conversely, on passing from 7-azaindoles (just as from the 5-azaindoles and the indolines) to their *N*-sodium derivatives (more accurately, anions), because of the marked increase in the electron density on the nitrogen of the pyrroline ring, the reduction potentials of the compounds increase sharply and even a mild oxidizing agent, such as atmospheric oxygen, proves to be sufficient to convert these substances into 7-azaindoles (or 5-azaindoles or indoles, as the case may be) [8, 9].



In order to give quantitative characteristics of the influence of substituents in the azaindoline molecule on the ease of their dehydrogenation and to elucidate the mechanism of this influence, we have carried out the polarographic oxidation of 7-azaindoles of the general formula given above and have used correlation equations to consider the half-wave potentials $E_{1/2}$ obtained. Before our own papers, there was no information in the literature concerning an electrochemical study of azaindoline and azaindole systems.

The polarographic oxidation of the 7-azaindoles was carried out at a rotating platinum disc electrode ($D = 2$ mm, rate of rotation 700 rpm), which permitted the anode processes to be carried out in the range of potentials excluded when a dropping mercury electrode is used because of the solubility of the mercury. Of various methods for regenerating the surface of the solid electrodes, the best results were given by the mechanical cleansing of the anode with fine abrasive paper followed by washing with distilled water. The reproducibility with respect to the limiting current was $\pm 10\%$ rel. and with respect to the half-wave potential ± 10 mV. The comparison electrode was a saturated calomel electrode. The determinations were carried out in a thermostated cell at $25.0 \pm 0.1^\circ$ C on

*For part XXVII, see [16].

Results of the Polarographic Oxidation of 7-Azaindoles

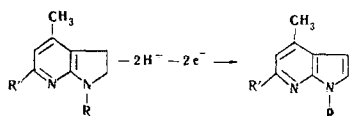
Compound	Name and reference for the method of preparation	R	R'	σ^+ for R	σ^+ for R'	E 1/2 V	
						found	calculated
I	4-Methyl-7-azaindoline [7]	H	H	0.49	0.00	0.84	0.87
II	1,4-Dimethyl-7-azaindoline [15]	CH ₃	H	0.00	0.00	0.80	0.80
III	1-Butyl-4-methyl-7-azaindoline [2]	C ₄ H ₉	H	-0.13	0.00	0.73	0.78
IV	1-Benzyl-4-methyl-7-azaindoline [15]	C ₆ H ₅ CH ₂	H	0.215	0.00	0.82	0.83
V	4-Methyl-1-phenyl-7-azaindoline [2]	C ₆ H ₅	H	0.60	0.00	0.88	0.88
VI	1-(p-Methoxyphenyl)-4-methyl-7-azaindoline [6]	<i>n</i> -C ₆ H ₄ OCH ₃	H	0.28 ^a	0.00	0.67	0.84
VII	1-(p-Dimethylaminophenyl)-4-methyl-7-azaindoline [6]	<i>n</i> -C ₆ H ₄ N(CH ₃) ₂	H	-0.28 ^a	0.00	0.73	0.76
VIII	6-Chloro-4-methyl-7-azaindoline [7]	H	Cl	0.49	0.114	0.78	0.91
IX	6-Chloro-1,4-dimethyl-7-azaindoline [1]	CH ₃	Cl	0.00	0.114	0.84	0.84
X	1-Butyl-6-chloro-4-methyl-7-azaindoline [1]	C ₄ H ₉	Cl	-0.13	0.114	0.81	0.82
XI	1-Benzyl-6-chloro-4-methyl-7-azaindoline [15]	C ₆ H ₅ CH ₂	Cl	0.215	0.114	0.90	0.87
XII	6-Chloro-4-methyl-1-phenyl-7-azaindoline [1]	C ₆ H ₅	Cl	0.60	0.114	0.91	0.92
XIII	6-Chloro-1-(p-methoxyphenyl)-4-methyl-7-azaindoline [6]	<i>n</i> -C ₆ H ₄ OCH ₃	Cl	0.28 ^a	0.114	0.78	0.88
XIV	6-Chloro-1-(p-dimethylaminophenyl)-4-methyl-7-azaindoline [6]	<i>n</i> -C ₆ H ₄ N(CH ₃) ₂	Cl	-0.28 ^a	0.114	0.78	0.80
XV	6-Amino-4-methyl-1-phenyl-7-azaindoline [14]	C ₆ H ₅	NH ₂	0.60	-0.66	0.36	0.64
XVI	6-Acetylamino-4-methyl-1-phenyl-7-azaindoline [14]	C ₆ H ₅	NHCOCH ₃	0.60	-0.60	0.75	0.66
XVII	1-Butyl-6-hydroxy-4-methyl-7-azaindoline [14]	C ₄ H ₉	OH	-0.13	-0.92	0.32	0.44
XVIII	6-Hydroxy-4-methyl-1-phenyl-7-azaindoline [14]	C ₆ H ₅	OH	0.60	-0.92	0.36	0.54
XIX	6-Methoxy-4-methyl-7-azaindoline [7]	H	OCH ₃	0.49	-0.764	0.58	0.59
XX	1-Butyl-6-methoxy-4-methyl-7-azaindoline [14]	C ₄ H ₉	OCH ₃	-0.13	-0.764	0.48	0.50
XXI	6-Methoxy-4-methyl-1-phenyl-7-azaindoline [14]	C ₆ H ₅	OCH ₃	0.60	-0.764	0.61	0.60

^aThe values of σ^+ for compounds VI, VII, VIII, and XIV include σ^0 of the para substituents: -0.16 for OCH₃ and -0.44 for the N(CH₃)₂ group.

a polarograph of type RA-102 (Yanahimoto, Japan). A weighed sample of the substance (5×10^{-4} mole/l) was dissolved in dimethylformamide and a Britton-Robinson buffer was added to an amount of 50% of the total volume of the working solution, which enabled the investigations to be carried out over a wide pH range (pH 2–12). The inertness of the electrolytes was confirmed by the fact that various 7-azaindoline derivatives had the same values of $E_{1/2}$ at the same pH for the Britton-Robinson buffer and, respectively, hydrogen phthalate, phosphate-citrate, and ammonia buffers [11]. In the selection of the optimum conditions for the polarographic determinations it was found that a change in the ionic strength of the solution (created by the addition of the calculated amount of KCl) had no influence on the value of $E_{1/2}$, but changed the shape of the wave. The steepest wave was found when $\mu = 1$, and the main determinations were carried out under these conditions.

To study the influence of substituents on the ease of polarographic oxidation of 7-azaindoline derivatives it was necessary to show that all the compounds of this series are oxidized by the same mechanism. For this reason we studied the dependence of $E_{1/2}$ on the pH and found that for all the compounds investigated, with the exception of the 6-hydroxy derivatives of the 7-azaindolines, an increase in the pH from 3 to 6 was accompanied by a shift in $E_{1/2}$ in the negative direction ($\delta E_{1/2}/\Delta \text{pH} \approx 20$ mV) while in the alkaline region (pH 7–12) it remained unchanged. A logarithmic analysis of the polarographic oxidation curves of various derivatives showed that the slopes of the graphs of $\log [i/(i_\alpha - i)]$ as a function of the potential E were the same in all cases.

In a microcoulometric determination it was established that two electrons take part in the electrode process. To identify the products of the electrochemical oxidation of the azaindolines, a comparative determination of the values of $E_{1/2}$ of the reaction products and of the corresponding 7-azaindoles was carried out. For this purpose, in the electrochemical oxidation of the azaindolines the electrode was kept at the potential of the limiting current; then a second wave appeared on the chromatogram the $E_{1/2}$ value of which coincided with that of samples of the corresponding 7-azaindoles prepared synthetically. For example, in the case of 6-methoxy-1-phenyl-7-azaindoline the potential of the limiting current is $E = +0.8$ V; $E_{1/2}$ for the second wave is $+1.28$ V. From the results obtained it can be stated that the polarographic oxidation of the 7-azaindolines takes place by the following mechanism:



To determine the redox potentials in the 7-azaindoline–7-azaindole systems, we carried out the polarographic reduction of a number of 7-azaindoles [4-methyl-1-phenyl-7-azaindole, 6-methoxy-4-methyl-1-phenyl-7-azaindole, and 4-methyl-1-(p-nitrophenyl)-

7-azaindole]. The reduction was carried out with graphite and dropping mercury electrodes in Britton-Robinson buffer solutions (pH 2–12), containing 50% of dimethylformamide and also in a 0.1 N solution of tetrabutyl ammonium iodide in dimethylformamide. In the reduction of the 4-methyl-1-(p-nitrophenyl)-7-azaindole, a wave characteristic for the reduction of the nitro group ($E_{1/2} = 0.6$ V at pH 4.5) was obtained. However, the wave of the reduction of the pyrrole part of the molecule could not be found in any of the compounds investigated (or in indole, taken for comparison). The 7-azaindoline–7-azaindole system proved to be electrochemically irreversible.

In the treatment of the results of the polarographic oxidation of the 7-azaindolines by the correlation equation method, it was shown that the value of $E_{1/2}$ correlates well with Taft's induction constants for the substituents on the pyrroline nitrogen. A similar correlation has been observed previously for the influence of substituents on the pK_a values of 7-azaindoline derivatives [12]. At the same time, the different positions of the reaction centers in the two processes considered (protonation and electrochemical oxidation) led to a dissimilar nature of the transfer of the influence of substituents in position 6 of the azaindoline molecule. In contrast to the pK_a value, on polarographic oxidation this influence is not limited by the induction effect expressed by σ_I . The $E_{1/2}$ values do not correlate with σ_m and σ_p , either, but give a satisfactory correlation with the electrophilic constants σ^+ taking into account the contribution of conjugation between the substituent and the reaction center. As a result of the correlation analysis, a general equation for cross-correlation taking into account the influence of substituents both in position 1 and in position 6 on the value of $E_{1/2}$ for oxidation was found:

$$E_{1/2} = 0.8 + 0.37\sigma^+ + 0.14\sigma^6.$$

The correlation coefficient calculated by the method of mathematical statistics [13] is $r = 0.985$. Compounds XVII and XVIII, containing a hydroxy group in position 6 of the azaindoline ring do not come within the correlation. This is obviously due to the previously described [14] lactam–lactim tautomeric equilibrium of these substances. The unsatisfactory correlation of the 6-amino and the 1-(p-methoxyphenyl) derivatives of azaindolines (XV, VI and XIII) is possibly connected with the instability of these compounds, leading to a somewhat different course of the electrochemical processes.

The results obtained in the polarographic oxidation of the various 7-azaindolines and the treatment of the material by the method of correlation equations are given in the table. The half-wave potentials of the compounds were compared at pH 7.5, i. e., in that region where the $E_{1/2}$ values are practically independent of the pH.

A comparison of the results of the chemical oxidation (under the action of quinones) and of the electrochemical oxidation of various 7-azaindolines shows a parallelism of the influence of the nature of the sub-

stituents in positions 1 and 6 on the course of both processes. Both in the case of dehydrogenation with the aid of quinones and in the case of the polarographic oxidation, substituents increasing the electron density of the pyrrole nitrogen facilitate, and electron-accepting substituents hinder, the reactions. In this respect it is also interesting that on passing from the 7-azaindoles to the indolines, which have no electron-accepting aza group, the value of $E_{1/2}$ likewise shifts in the negative direction, i. e., the oxidation process is facilitated. Thus, for example, the values of $E_{1/2}$ which we measured for 4-methyl-7-azaindoline and for indoline are, respectively, 0.84 and 0.44 V.

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