AZAINDOLE DERIVATIVES

XLII.* POLAROGRAPHIC OXIDATION AND DEHYDROGENATION OF 5-AZAINDOLES AND 5,7-DIAZAINDOLINES

I. N. Palant, Yu. I. Vainshtein,
D. M. Krasnokut-skaya, and L. N. Yakhontov

UDC 547.754:04:541:138:
2.547.759.3:543.253

The polarographic oxidation of a series of 5-azaindoline, 7-azaindoline, and 5,7-diazaindoline derivatives (22 compounds) was studied, and the results are compared with the ease of dehydrogenation of these substances under the influence of quinones. It is shown that $E_{1/2}$ increases on passing from 7-azaindolines to 5-azaindolines and then to 5,7-diazaindolines. The effect of substituents is satisfactorily described by cross-correlation equations, while the deviations from the correlation are associated with the peculiarities of the lactam–lactim tautomeric equilibrium in a number of 6-hydroxy-5- and 7-azaindolines.

In connection with the increase in the resistance to oxidation on passing from 7-azaindolines to the corresponding 5-azaindolines and 5,7-diazaindolines, which is also well known from chemical experiments, for their polarographic study we used a 0.5 M solution of silver perchlorate in anhydrous acetonitrile (which has a decomposition potential of 2.2 V) as the inert electrolyte; this made it possible to study the electrochemical processes over a wider range.

Most of the investigated compounds have rather high $E_{1/2}$ values. On passing from 7-azaindolines to the analogous 5-azaindolines and then to 5,7-diazaindolines, the oxidation potential increases (compare, for example, XII, II, and XXI), but $E_{1/2}$ increases (up to 1.49 V) particularly sharply in the case of a strong electron-acceptor acyl substituent in the 1 position. (XVIII). The introduction of chlorine atoms into the 4 and 6 positions of various azaindoline molecules leads to an increase in $E_{1/2}$ (for example, I, III, and VI or II and IV). A phenyl ring attached to the pyrroline nitrogen has a similar but weaker effect. The effect is intensified (I and II, III and IV, XII, XVI, and XVII) when electron-acceptor substituents (nitro or cyano groups) are introduced into the para position of the phenyl ring. The increase in the oxidation potentials of compounds that contain an aza function in the 5 position is apparently associated with the large contribution and the high stability of the mesomeric p-quinoid structure as compared with the mesomeric o-quinoid structure for the 7-aza-substituted compounds. The greater contribution of the p-quinoid structure in the case of 5- and 6-azaindoles as compared with the o-quinoid mesomeric form in 4- and 7-azaindoles was previously also used by Adler and Albert in explaining the differences in the peculiarities of 5- and 6-azaindoles as compared with 4- and 7-azaindoles [2]. Distinct S-shaped volt-ampere curves are characteristic for all of the 7-azaindole derivatives, while the polarograms of the 5-azaindoles are misrepresented by the maxima. This phenomenon is apparently due to retardation of the electrode process by the electrooxidation products on the electrode surface. The products of electrooxidation of 7-azaindolines adsorbed on the anode do not have this sort of effect.

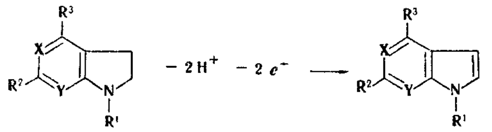
The $E_{1/2}$ values determined from the method set forth above in the present paper (in acetonitrile) and from the method presented in a previous paper [3] with the Britton–Robinson buffer are in good agreement. Thus, for example, for 1-phenyl-4-methyl-7-azaindoline (XII) these values are 0.87 and 0.88 V, respectively,

---

* See [1] for communication XLI.

All-Union Scientific-Research Institute of Chemical Reagents and Ultrapure Compounds, Moscow. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 773-776, June, 1973. Original article submitted June 20, 1972.

TABLE 1. Results of the Polarographic Oxidation of Aza- and Diazaindolines



Compound	Name and reference to the synthetic method used	X	Y	R^1	R^2	R^3	$+E_{1/2}$, V
I	5-Azaindoline [6]	N	CH	H	H	H	0,95
II	1-Phenyl-5-azaindoline [6]	N	CH	C_6H_5	H	H	0,97
III	6-Chloro-5-azaindoline [7]	N	CH	H	Cl	H	1,07
IV	1-Phenyl-6-chloro-5-azaindoline [6]	N	CH	C_6H_5	Cl	H	1,12
V	1-Benzyl-6-chloro-5-azaindoline [6]	N	CH	$CH_2C_6H_5$	Cl	H	1,09
VI	4,6-Dichloro-5-azaindoline [8]	N	CH	H	Cl	Cl	1,21
VII	1-Phenyl-6-hydroxy-5-azaindoline [6]	N	CH	C_6H_5	HO	H	1,45
VIII	1-Benzyl-6-hydroxy-5-azaindoline [6]	N	CH	$CH_2C_6H_5$	HO	H	1,21
IX	5-Methyl-6-oxo-5-azaindoline [9]	N—CH_3	CH	H	O	H	1,24
X	6-Isopropxy-5-azaindoline [9]	N	CH	H	$OCH(CH_3)_2$	H	0,98
XI	1-Benzyl-6-isopropoxy-5-azaindoline [9]	N	CH	$CH_2C_6H_5$	$OCH(CH_3)_2$	H	0,96
XII	1-Phenyl-4-methyl-7-azaindoline [10]	CH	N	C_6H_5	H	CH_3	0,87
XIII	4-Methyl-6-chloro-7-azaindoline [11]	CH	N	H	Cl	CH_3	0,95
XIV	4-Methyl-7-azaindoline [11]	CH	N	H	H	CH_3	0,82
XV	4-Methyl-6-methoxy-7-azaindoline [11]	CH	N	H	OCH_3	CH_3	0,61
XVI	1-(p-Cyanophenyl)-4-methyl-7-azaindoline [12]	CH	N	p-C_6H_4CN	H	CH_3	1,07
XVII	1-(p-Nitrophenyl)-4-methyl-7-azaindoline [12]	CH	N	p-$C_6H_4NO_2$	H	CH_3	1,12
XVIII	1-Acetyl-4-methyl-7-azaindoline [11]	CH	N	$COCH_3$	H	CH_3	1,49
XIX	1-Phenyl-4-methyl-6-hydroxy-7-azaindoline [13]	CH	N	C_6H_5	HO	CH_3	0,90
XX	1-Butyl-4-methyl-6-hydroxy-7-azaindoline [13]	CH	N	C_4H_9	HO	CH_3	0,79
XXI	1-Phenyl-5,7-diazaindoline [14]	N	N	C_6H_5	H	H	1,12
XXII	1-Benzyl-5,7-diazaindoline [15]	N	N	$CH_2C_6H_5$	H	H	1,28

while the values obtained for 4-methyl-7-azaindoline (XIV) and 4-methyl-6-methoxy-7-azaindoline (XV) are, respectively, 0.82 and 0.84 V and 0.61 and 0.58 V. The $E_{1/2}$ values determined in acetonitrile for XVI and XVII, which have electron-acceptor substituents in the para position of the phenyl ring, are in good agreement with the theoretical values calculated for these substances from the cross-correlation equation [3] derived on the basis of a polarographic analysis of substituted 7-azaindolines in Britton–Robinson buffer solutions (for XVI, calculated 0.98, found 1.07; for XVII, calculated 1.00, found 1.12). For 4-methyl-6-chloro-7-azaindoline (XIII), the $E_{1/2}$ value found in acetonitrile (0.95) is in much better agreement with the value calculated from the correlation equation (0.91) than that determined previously in [3], in which the measured potential values are close to the decomposition potential of the electrolyte used. For 6-hydroxy-7-azaindoline derivatives (XIX and XX), which are characterized by lactam–lactim tautomerism [13], the equilibrium state of which is determined by the polarity of the solvent, extremely different $E_{1/2}$ values are observed, depending on the medium in which they are determined. Thus, for example, XIX in acetonitrile has $E_{1/2}$ 0.90 V as compared with 0.36 V in dimethylformamide–aqueous Britton–Robinson buffer, and the corresponding values for XX are 0.79 V and 0.32 V. Such a sharp decrease in the oxidation potential is apparently associated with the state of the tautomeric equilibrium in the indicated media. For 6-hydroxy-5-azaindolines (VII and VIII), in which, as is well known, the tautomeric equilibrium is practically completely shifted to the oxo form, regardless of the polarity of the solvent [4], $E_{1/2}$ is found to be quite high (1.21–1.45 V), and no sharp decrease in it is observed on passing to the Britton–Robinson buffer (The $E_{1/2}$ values of the substance lie beyond the limits of the oxidation potential of the electrolyte).

It is interesting to note that the $E_{1/2}$ values for "fixed" tautometric forms of 6-hydroxy- and 6-oxo-5-azaindolines differ sharply. The $E_{1/2}$ value for the "fixed" oxo form (IX) is 1.24 V and is close in magnitude to unfixed 6-oxo-5-azaindolines (VII and VIII). The "fixed" hydroxy form (X and XI) is characterized by another order of magnitude of $E_{1/2}$ values, equal to 0.96-0.98 V.

The results of the dehydrogenation of aza- and diazaindoline derivatives to the corresponding aza- and diazaindoles under the influence of quinones and other oxidizing agents are also in good agreement with the data from polarographic analysis. Thus, all of the substances with $E_{1/2}$ values lower than 1.1 V are oxidized to azaindoles by chloroanil, while a stronger oxidizing agent – dichlorodicyanoquinone – is required for the dehydrogenation of compounds with $E_{1/2}$ values from 1.1 to 1.2 V. Substances with $E_{1/2}$ values above 1.4 V cannot be converted to the corresponding azaindoles even on heating with sulfur to 240° or with selenium to 300° or by dehydrogenation with palladium.

EXPERIMENTAL

The polarographic oxidation of the compounds was carried out on a platinum rotating disk anode (with a diameter of 2 mm and an angular rate of rotation of 1480 rpm). The methods used in the research and purification of the electrode were previously described in [2]. The comparison electrode was a saturated calomel electrode connected to the test solution by an electrolytic switch filled with an inert electrolyte. The acetonitrile was purified by the method in [5]. The depolarizer concentration was $5 \cdot 10^{-4}$ M. The volt-ampere curves were recorded with a PA-101 electronic polarograph (Yanagimoto, Japan). The results are presented in Table 1.

LITERATURE CITED

1. L. N. Yakhontov, D.M.Krasnokut-skaya, A. N. Akalaev, I. N. Palant, and Yu. I. Vainshtein, Khim. Geterotsikl. Soedin., 789 (1971).
2. T. K. Adler and A. Albert, J. Chem. Soc., 1794 (1960).
3. Yu. S. Vainshtein, I. N. Palant, L. N. Yakhontov, D. M.Krasnokut-skaya, and M. V. Rubtsov, Khim.. Geterotsikl. Soedin., 1106 (1969).
4. L. N. Yakhontov, D. M.Krasnokut-skaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Dokl. Akad. Nauk SSSR, 176, 613 (1967).
5. J. W. Loweland and G. R. Dimeler, Anal. Chem., 33, 1196 (1961).
6. L. N. Yakhontov and E. I. Lapan, Khim. Geterotsikl. Soedin., 27 (1970).
7. L. N. Yakhontov, E. I. Lapan, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., 550 (1969).
8. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubstov, Khim. Geterotsikl. Soedin., 918 (1965).
9. E. I. Lapan and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 859 (1972).
10. L. N. Yakhontov and M. V. Rubtsov, Zh. Obshch. Khim., 31, 3281 (1961).
11. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, Zh. Obshch. Khim., 34, 1449 (1964).
12. L. N. Yakhontov, D. M. Krasnokut-skaya, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., 66 (1966).
13. L. N. Yakhontov (Jakhontov), D. M. Krasnokut-skaya, E. M. Peresleni, Yu. N. Sheinker, and M. V. Rubtsov, Tetrahedron, 22, 3233 (1966).
14. L. N. Yakhontov, M. S. Sokolova, N. I. Koretskaya, K. A. Chkhikvadze, O. Yu. Magidson, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., 145 (1969).
15. K. A. Chkhikvadze, N. I. Koretskaya, N. S. Rodnyanskaya, and O. Yu. Magidson, Khim. Geterotsikl. Soedin., 138 (1969).