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NITROAZINES.

4.* POLAROGRAPHIC BEHAVIOR OF 5-NITROPYRAZOLO[3,4-b]PYRIDINES AND THE ESR SPECTRA OF THEIR ELECTROCHEMICALLY GENERATED FREE RADICALS

L. Kh. Baumane, R. A. Gavar,
Ya. P. Stradyn', O. N. Chupakhin,
V. L. Rusinov, and A. Yu. Petrov

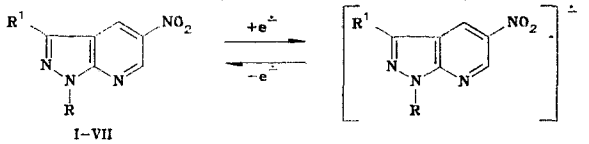
UDC 543.253:547.775'778.3'822.7

1-Methyl- and 1-phenyl-substituted derivatives of 5-nitropyrazolo[3,4-b]pyridines are reduced at a dropping mercury electrode in a single one-electron wave with the formation of radical anions in interval of potentials from −0.94 to −1.06 V. Compounds unsubstituted at the $N(_1)$ nitrogen atom give an additional polarographic wave at $E_1/_2$ = −1.4 V due to the reduction of the deprotonated form (anion). The potentials and HFS constants of the ESR spectra of the corresponding electrochemically generated free radicals are given.

Among derivatives of pyrazolo[3,4-b]pyridine are found substances which are capable of inhibiting cAMP [2, 3] and which also exhibit bactericidal, analgesic, and antiinflammatory activities [4, 5]. The biological activity of many classes of compounds is said to be connected with their capacity for forming donor–acceptor complexes with biological substrates and of interfering in redox processes of metabolism [6]. It is therefore a matter of interest to study the behavior of compounds of this type under redox conditions, and also the structures of their free radicals.

With the aim of studying the redox characteristics of the 5-nitropyrazolo[3,4-b]pyridines, in the present work we have performed the polarographic reduction of compounds (I-VII), which have been studied previously [7]. The presence of a polynitrogen heterocyclic residue in the pyrazolone[3,4-b]pyridine molecules suggested the possibility of the formation of stable radicals on their reduction.

In the polarographic reduction of the 5-nitropyrazolo[3,4-b]pyridines, the one-electron wave of the primary process — the formation of radical anions — was clearly distinguishable:



I-VII

I, III R=H; II, IV R=CH_3, V—VII R=C_6H_5; I, II, V R^1=H; III, IV, VII R^1=CH_3; VI R^1=C_6H_5

*For Communication 3, see [1].

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 689-693, May, 1985. Original article submitted March 23, 1984.

 0009-3122/85/2105-0582$09.50 © 1985 Plenum Publishing Corporation

TABLE 1. Half-Wave Potentials ($E_1/_2$) and Limiting Currents (I_{lim}) of the Electrochemical Reduction of the 5-Nitropyrazolo-[3,4-b]pyridines (I-VII)

Compound	$-E'_{1/2}$, V	I'_{lim}, μA	$-E''_{1/2}$, V	I''_{lim}, μA
I	1,04	0,70	1,40	0,48
II	1,04	1,25	—	—
III	1,06	0,45	1,44	0,52
IV	1,04	1,10	—	—
V	0,95	0,95	—	—
VI	0,94	1,10	—	—
VII	1,02	1,00	—	—

The polarographic half-wave potentials of the electroreduction process $E'_1/_2$ (Table 1) were in the range from −0.94 to −1.06 V relative to the saturated calomel electrode and depended both on the nature and on the position of the substituents.

The partial reversibility of this primary process was established by the method of cyclic voltammetry, which indicated sufficient stability of the particles formed for investigation by the ESR method (Fig. 1).

For 5-nitropyrazolo[3,4-b]pyridine (I) and 3-methyl-5-nitropyrazolo[3,4-b]pyridine (III), which have no substituents at the nitrogen atom, a second polarographic wave was observed at potentials of $E''_1/_2 \approx -1.4$ V. It may be assumed that in this case the first two waves corresponded to the one-electron reduction of two different forms of these compounds participating in a protolytic equilibrium (deprotonation at the $N(_1)$ atom). This was shown by the fact that the values of the limiting currents of the first two waves for compounds (I) and (III) were approximately equal in magnitude to the limiting current of the first wave of the N-substituted compounds (II, IV-VII) (Table 1). Cyclic voltammetry showed that the processes involved in the reduction of compounds (I) and (III) in both the first and the second waves were partially reversible (Fig. 1).

In addition, all the compounds studied were characterized by further irreversible electrochemical reduction at higher potentials (from −1.74 to −2.00 V) which was not studied in detail in the investigation. The one-electron nature of the reduction processes at the potentials of the first and second waves, $E'_1/_2$ and $E''_1/_2$, and also the partial reversibility of these processes indicated the possible formation of radicals the lifetimes of which had

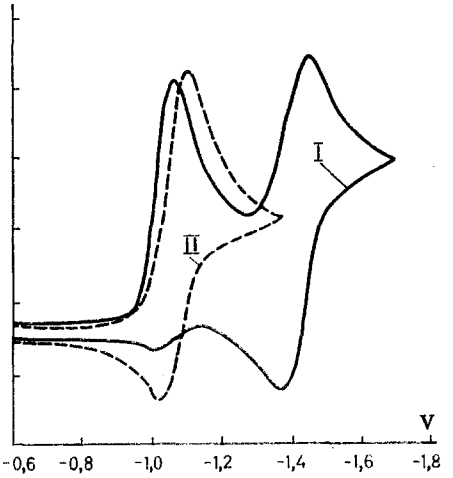


Fig. 1. Cyclic voltammetric curves for compounds (I) and (II). Scan rate 0.1 V/sec.

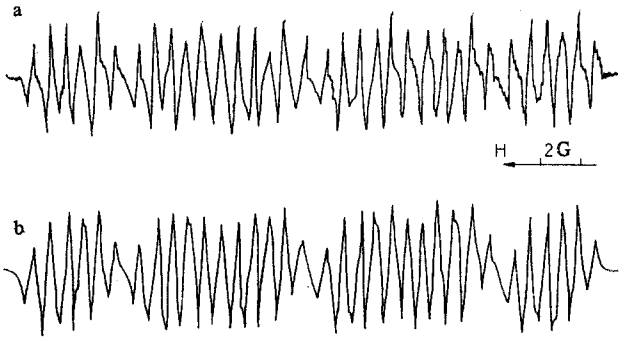


Fig. 2. ESR spectrum of the radical anion of 5-nitropyrazolo[3,4-b]pyridine (I); a) experimental spectrum; b) simulated spectrum (the nature of the spectrum and the values of the constants are given in Table 2, the shape of the lines being Lorenzian and their width being 0.2 G).

magnitudes of the same order as the time for scanning the potentials of the voltammetric cycle. In actual fact, these radicals were obtained by electrochemical generation and their ESR spectra were recorded. As was to be expected from the structures of the compounds under investigation, the ESR spectra of the π-type radicals obtained had a complex hyperfine structure (HFS) which was difficult to interpret (Figs. 2 and 3).

For compounds (I) and (III), unsubstituted at the $N_{(1)}$ atom, it was possible to obtain two varieties of free-radical particles, depending on the generation potential — radical anions and radical dianions, formed, respectively, on the electrochemical reduction of the undissociated molecules and of the deprotonated particle. A similar effect of deprotonation has been observed in the electrochemical generation of free-radical particles in the case of nitro derivatives of pyrazole, of imidazole, and of 1,2,4-triazole, but the radical anion proved to be too unstable for recording under the experimental conditions selected by the authors and the ESR spectra of only the radical dianions were obtained [8].

The interpretation of the ESR spectra and the determination of the values of the HFS constants were carried out with the aid of a calculation of the spectra by the simulation method. It was found, for example, that the HFS of the ESR spectrum of the anion radical of compound (I) was due to the interaction of the unshared electron with the nuclei of six nonequivalent atoms of the molecules and had the splitting characteristic $3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 3_N \cdot 2_H$, with values of the constants 10.10, 5.78, 1.62, 0.94, 0.94, and $\leqslant 0.18$ G, respectively. It can be seen from the nature of the HFS that the ESR spectrum of the anion radical of this compound shows an interaction of the unpaired electron with all the hydrogen nuclei, but of the four nitrogen atoms only two appear. The largest constant, a_N = 10.10 G, may, as is usual for radical anions of heteroaromatic mononitro compounds, be assigned to an interaction with the nucleus of the nitrogen atom of the nitro group. It was impossible to determine the nature of the other constants directly from the ESR spectrum, but by comparing the HFS constants found for the ESR spectra of the radical anions of all the compounds under consideration (Table 2) it was possible to assign the remaining HFS constants with greater or smaller confidence. Thus, the second constant, because of the 3_N nature of the splitting, must be assigned to the interaction of the unpaired electron with the nitrogen atom in position 1. This conclusion was confirmed by the ESR spectra of the radical anions of compounds (II) and (IV), for which a characteristic 4_H interaction of the unpaired electron and the CH_3 group and the nitrogen atom in position 1 appeared.

For all the radicals studied, the two largest HFS constants, having splitting of the 2_H type, could be assigned to an interaction with the protons in positions 4 and 6 of the 5-nitropyrazolo[3,4-b]pyridines. The validity of this conclusion was shown by the fact that HFS constants of the same magnitude and nature were observed for all the radicals of the compounds that we studied, regardless of the nature of the substituents R and R'. It was impossible to assign these constants more precisely on the basis of the available information, but, as for the radical anions of 3-nitropyridine [9], the a_H constant with the largest value can be assigned to the hydrogen atom in position 6 and the a_H constant next in magnitude to the

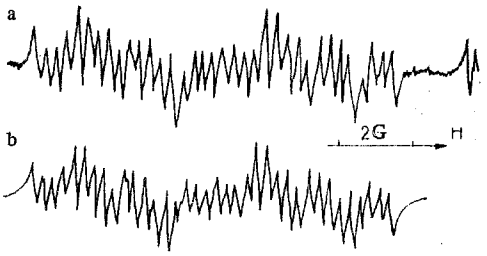


Fig. 3. Low-field (1/3) part of the ESR spectrum of the radical dianion of 5-nitropyrazolo[3,4-b]pyridine (I): a) experimental spectrum; b) simulated spectrum (the nature of the spectrum and the values of the constants are given in Table 2, the shapes of the lines being Lorenzian and their width 0.1 G).

TABLE 2. Nature of the HFS of the ESR Spectra and Values of the HFS Constants (a, G) of the Free Radicals of the 5-Nitropyrazolo[3,4-b]pyridines (I-VII) Generated Electrochemically in DMFA

Compound	Nature of the HFS	$a_{N(NO_2)}$	$a_{6\text{-H}}$	$a_{4\text{-H}}$	$a_{3\text{-H}}$	$a_{1\text{-H}}$	$a_{N(7)}$	$a_{N(1)}$
I	$3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 2_H \cdot 3_N$	10,10	5,78	1,62	0,94	$\leqslant$0,18	—	0,94
I*	$3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 3_N \cdot 3_N$	11,34	4,30	1,25	0,95	—	0,22	0,69
II	$3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 4_H \cdot 3_N$	10,10	5,95	1,54	1,14	0,26	—	0,91
III	$3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 3_N$	10,65	5,70	1,65	—	0,82	—	0,95
III*	$3_N \cdot 2_H \cdot 2_H \cdot 4_H \cdot 3_N \cdot 3_N$	11,50	4,70	1,45	0,89	—	0,18	0,77
IV	$3_N \cdot 2_H \cdot 2_H \cdot 4_H \cdot 4_H \cdot 3_N$	9,52	5,50	1,55	0,71	0,39	—	0,65
V	$3_N \cdot 2_H \cdot 2_H \cdot 2_H \cdot 3_N$	9,55	5,79	1,70	0,92	—	—	0,92
VI	$3_N \cdot 2_H \cdot 2_H \cdot 3_N$	8,87	5,85	1,43	—	—	—	0,85
VII	$3_N \cdot 2_H \cdot 2_H \cdot 4_H \cdot 3_N$	9,80	5,60	1,80	0,68	—	—	0,97

*No substituent R.

hydrogen atom in position 4. The remaining two hyperfine coupling constants with protons in the anion radical of compound (I) (a_H = 0.94 and $a_H \leqslant 0.18$ G) must therefore be assigned to the 1-H and 3-H protons, and from a comparison of the constants of the radical anions (II), (V), and (VII) it follows that a_H = 0.94 G relates to the proton in position 3 of radical (I), although for the radical anion (III) an interaction with the 1-H atom and not with the protons of the methyl group in position 3 is observed. The HFS constants of the radical anion of compounds (II-VII), given in Table 2, were identified in the same way.

For the radicals obtained on the reduction of compounds (I) and (III) in the second polarographic wave, therewas no HFS constant due to the proton in position 1, which shows the formation of these radicals by the one-electron reduction of the deprotonated form of compounds (I) and (III). As compared with the anion radicals, in the dianion radicals the unpaired electron interacted with two nitrogen atoms, apparently those present in positions 1 and 7.

The results of Table 2 show that the unpaired electron in each of the anion radicals of compounds (I-VII) and their deprotonated forms is delocalized both on the nitro group and on the heterocycles, but its presence on the $N(_2)$ atom was not detected although for the radical anions and radical dianions of the nitropyrazoles the unpaired electrons are observed on all the atoms of the pyrazole ring [10].

By comparing the values of the HFS constants for the anion radical of 3-nitropyridine, $a_{N(NO_2)}$ = 8.93, $a_{H(2)}$ = 3.18, $a_{H(6)}$ = 4.58, $a_{H(5)}$ = 1.09, $a_{H(4)}$ = 3.72 and $a_{N(1)}$ = 1.32 G [8] with the corresponding values given in Table 2 it is possible to judge the changes in the relative electrophilicities in the frontal vacant orbitals of the various positions of the pyridine ring on passing from 3-nitropyridine to 5-nitropyrazolo[3,4-b]pyridine. In the case of 3-nitropyridine,

the electrophilicities of the positions adjacent to the nitro group are almost the same [9]. In the 5-nitropyrazol[3,4-b]pyridine derivatives that we have studied, however, the electrophilicity of position 6 was more than three times higher than that of position 4, although the total electrophilicity of those two positions differed insigificantly from that for 3-nitropyridine. Changes also took place on the pyridine nitrogen atoms. While in 3-nitropyridine this atom exhibits considerable electrophilicity ($a_{N(1)}$ = 1.32 G), in the anion radicals of compound (I-VII) no interaction of the unpaired electron with the corresponding nitrogen atom was detected.

The deprotonation of the pyrazole ring in compounds (I) and (III) at the $N(_1)$ atoms increases the relative electrophilicity of the nitrogen atom of the pyridine ring, and in the ESR spectra of the radical dianions constants appear which are due to the interaction of the unshared electron with this atom ($a_{N(7)} \sim 0.2$ G), but the electrophilicities of the positions adjacent to the carbon bearing the nitro group decrease, whereupon their relative electrophilicities also fall slightly. Such a splitting out of the proton also causes a change in the relative electrophilicities of the nitrogen atoms of the pyrazole fragment and of the nitro group; the values of the corresponding constant $a_{N(1)}$ decreases and $a_{N(NO_2)}$ increases.

EXPERIMENTAL

The investigation were performed in DMFA and 0.1 N tetrabutylammonium hexafluorophosphate (supporting electrolyte) for the polarographic investigations. The concentration of the compounds in the solutions was $5 \cdot 10^{-4}$ M, except for the electrochemical generation of the free radicals when it was 10^{-3} M. The solutions were deoxygenated by the passage of argon through them. The DMFA was purified by a published method [11]. Classical polarograms were recorded on a PAR-170 polarograph (USA) using a three-electrode cell. The cathode was a dropping mercury electrode with forced detachment of the drops. The reversibility of the reduction mechanisms of the compounds was evaluated from the cyclic volt-ampere curves, which were also obtained with the aid of the PAR-170 polarograph, using a stationary electrode (of the PAR-9329 type). The scan rate the potential was 0.1 V/sec. The comparison electrode was a saturated aqueous calomel electrode fitted with a bridge for the connection to DMFA, and the anode was a platinum wire. The possible error in the determination of $E_{1/2}$ amounted to 1.10 V.

The 5-nitropyrazolo[3,4-b]pyridines were obtained as described previously [1].

The free radicals of the compounds investigated were generated under steady-state conditions at the potential of the limiting current of the polarographic waves on a platinum electrode in a ECG cell placed in the rectangular resonator (H_{102} type) of an ESR spectrometer (Carl Zeiss, Jena, GDR) [12]. ESR spectra were recorded of the magnetic field at scan rate of 0.04 G/sec with a time constant of 0.45 sec and a depth of the high-frequency (100 kHz) modulation of the magnetic field of 0.05-0.2 G. The scanning of the magnetic field was calibrated from the ESR spectrum of the radical anion of nitrobenzene [13]. The simulation of the ESR spectra was carried out by a program which we have drawn up on a HP-2116C minicomputer linked to a ER-9 spectrometer by an "on line" system [14].

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CONDENSED IMIDAZO-1,2,4-AZINES.

12.* SYNTHESIS AND STRUCTURE OF SUBSTITUTED 5-H-IMIDAZO[1,2-b]-1,2,4-TRIAZEPIN-4-ONES (-THIONES)

V. P. Kruglenko, N. S. Patalakha,
P. B. Kurapov, N. A. Klyuev, V. A. Idzikovskii,
I. I. Grandberg, and M. V. Povstyanoi

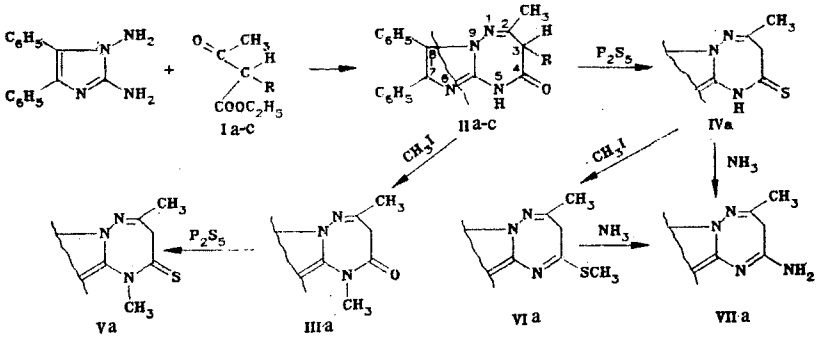
UDC 547.892'781.5.07:541.62:543.422

The synthesis has been effected of new representatives of the imidazo[1,2-b]-1,2,4-triazepin-4-ones (-thiones). It has been shown with the aid of IR and UV spectroscopic and mass spectrometric methods that the lactam (thione) form is the predominant one for the compounds synthesized.

In 1976, we performed the synthesis of the first representatives of a new heterocyclic system — 2,4-dimethyl-substituted imidazo[1,2-b]-1,2,4-triazepines[2]. Later, following the principle that we had proposed for forming an annelated triazepine ring with the use of a 1,2-diaminoimidazole, we studied the reaction of the latter with acetoacetic ester (AAE) [3], with fluorinated β-diketones [4], and with chalcones [5].

Continuing work in this direction, we have synthesized new 5H-imidazo[1,2-b]-1,2,4-triazepin-4-ones (IIa-c) and have studied their reactivities and we have also investigated the structure of the compounds obtained.

The imidazotriazepin-4-ones (IIa-c) were obtained by the method of Bruker et al. [3] by boiling 1,2-diamino-4,5-diphenylimidazole [6] with AAE or its ethyl or bromo derivative (Ia-c) in acetic acid in the presence of the sodium acetate.



I-VIIa R=H; b R = C_2H_5; c R = Br

When compound (IIa) was treated with methyliodide in methanol containing sodium methanolate, alkylation took place at the N(5) atom with the formation of the 2,5-dimethylimidazotriazepine (IIIa). This conclusion was based on the identity of the IR, UV, and mass spectra of compound (IIIa) and a sample with the authentic structure obtained by condensing 1-amino-2-methylamino-4,5-diphenylimidazole with AAE [3].

*For Communication 11, see [1].

Kherson Industrial Institute. K. A. Timiryazev Moscow Agricultural Academy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 694-699, May, 1985. Original article submitted April 24, 1984.

0009-3122/85/2105-0587$09.50 © 1985 Plenum Publishing Corporation