SYNTHESIS AND INVESTIGATION OF PHENAZINE DERIVATIVES

XVII.* SYNTHESIS AND PROPERTIES OF SOME PHENAZINE DERIVATIVES AND THEIR N-OXIDES AND N,N'-DIOXIDES

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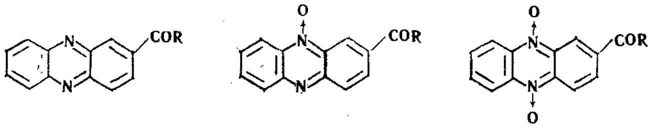
UDC 547.64.07

Several amides of phenazine-2-carboxylic acid and their N-oxides and N,N'-dioxides were synthesized. The compounds were reduced polarographically.

Many phenazine derivatives and their N-oxides are of interest as physiologically active substances [2-4]. For this reason, we synthesized the ethyl ester and several amides of phenazine-2-carboxylic acid and their N-oxides and N,N'-dioxides:



$R = OC_2H_5$; NR'_2

The ethyl ester of phenazine-2-carboxylic acid and its 10-N-oxide were obtained by the method described for the methyl ester of this acid [5]. The synthesis of the amides of phenazine-2-carboxylic acid and their 10-N-oxides was accomplished by reaction of the acid chloride or the 10-N-oxide with the corresponding amine in dry chloroform in the presence of triethylamine or a second equivalent of the reacting amine via a method analogous to that for the preparation of amides of phenazine-1-carboxylic acid [6]. The N,N'-dioxides of all of the synthesized phenazine-2-carboxylic acid derivatives were obtained by oxidation of the starting base with 30% H_2O_2 in glacial acetic acid.

One of the reasons for the biological activity of phenazine derivatives is the presence of a labile redox system in the phenazine molecule [2,7-9]. A study of the redox properties, particularly by means of the polarographic method, therefore seemed of interest.

A number of studies have been devoted to the polarographic reduction of phenazine and its derivatives. 5,10-Dihydrophenazines are formed in the cathode reduction of phenazine and its derivatives [10, 11]. The reduction of the N-oxides and N,N'-dioxides proceeds in two steps, the first of which corresponds to two- or four-electron deoxidation, while the second corresponds to two-electron reduction of the phenazine system to the dihydro base [10-14].

We carried out the polarographic reduction of the previously synthesized N-(1-phenazinylcarbonyl)- and N-(2-phenazinylcarbonyl)glycine, -valine, -proline, and their monoxides and N,N'-dioxides [1], of substances synthesized in this study, and of known phenazine derivatives (as model compounds) in order to study the effect of substituents on the reductive capacity of both the heterocyclic system and the N → O bond.

The polarographic potentials and limiting diffusion currents are presented in Table 1.

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*See [1] for communication XVI.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 563-567, April, 1972. Original article submitted May 6, 1971.

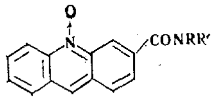
TABLE 1. Results of Polarographic Measurements

Substance	Half-wave potentials, V		Limiting diffusion current, mA	
	1st wave	2nd wave	1st wave	2nd wave
Phenazine	−0,430		0,850	
Phenazine N-oxide	−0,302	−0,453	0,600	0,600
Phenazine N,N′-dioxide	−0,301	−0,450	0,800	0,350
Phenazine-2-carboxylic acid	−0,396		0,675	
Phenazine-2-carboxylic acid 10-N-oxide	−0,242	−0,414	0,400	0,400
Phenazine-2-carboxylic acid N,N′-dioxide	−0,276	−0,426	1,975	0,900
Ethyl phenazine-2-carboxylate	−0,360		1,050	
Ethyl phenazine-2-carboxylate 10-N-oxide	−0,244	−0,378	0,975	0,975
Ethyl phenazine-2-carboxylate N,N′-dioxide	−0,275	−0,432	3,360	1,600
Phenazine-2-carboxamide	−0,385		1,425	
Phenazine-2-carboxamide 10-N-oxide	−0,235	−0,379	0,800	1,000
Phenazine-2-carboxylic acid diethylamide	−0,393		1,550	
Phenazine-2-carboxylic acid diethylamide 10-N-oxide	−0,275	−0,432	1,360	1,360
Phenazine-2-carboxylic acid diethylamide N,N′-dioxide	−0,320	−0,474	3,120	1,520
Phenazine-2-carboxylic acid anilide	−0,364		1,425	
Phenazine-2-carboxylic acid anilide 10-N-oxide	−0,218	−0,360	0,975	1,200
Phenazine-2-carboxylic acid anilide N,N′-dioxide	−0,278	−0,438	3,180	1,560
Phenazine-2-carboxylic acid anisidide	−0,360		1,250	
Phenazine-2-carboxylic acid anisidide 10-N-oxide	−0,246	−0,386	1,050	1,050
Phenazine-2-carboxylic acid anisidide N,N′-dioxide	−0,266	−0,408	1,960	0,804
N-(2-Phenazinylcarbonyl)morpholine	−0,380		1,400	
N-(2-Phenazinylcarbonyl)morpholine 10-N-oxide	−0,256	−0,407	1,350	1,500
N-(2-Phenazinylcarbonyl)morpholine N,N′-dioxide	−0,273	−0,444	3,200	1,600
N-(2-Phenazinylcarbonyl)glycine ethyl ester	−0,349		0,675	
N-(2-Phenazinylcarbonyl)glycine ethyl ester N,N′-dioxide	−0,256	−0,398	1,650	0,675
N-(2-Phenazinylcarbonyl)glycine N,N′-dioxide	−0,232	−0,380	0,855	0,550
N-(2-Phenazinylcarbonyl)valine ethyl ester	−0,372		1,250	0,600
N-(2-Phenazinylcarbonyl)valine ethyl ester N,N′-dioxide	−0,250	−0,394	1,475	0,625
N-(2-Phenazinylcarbonyl)valine N,N′-dioxide	−0,240	−0,387	1,400	
N-(2-Phenazinylcarbonyl)proline ethyl ester	−0,389		1,425	
N-(2-Phenazinylcarbonyl)proline ethyl ester N,N′-dioxide	−0,247	−0,388	0,725	0,275
N-(2-Phenazinylcarbonyl)proline N,N′-dioxide	−0,243	−0,385	0,550	0,275
Phenazine-1-carboxylic acid	−0,315		0,650	
Phenazine-1-carboxylic acid 5-N-oxide	−0,130	−0,340	0,750	0,650
N-(1-Phenazinylcarbonyl)proline ethyl ester	−0,405		1,350	
N-(1-Phenazinylcarbonyl)proline 5-N-oxide	−0,224	−0,406	0,650	0,650

TABLE 2. Diffusion Coefficients of a Number of Bases of Phenazine Derivatives

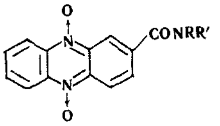
Compound	Diffusion coef., $D \cdot 10^{-6}$, cm^2/sec	$D \cdot 10^{-3}$
Phenazine-1-carboxylic acid	2,520	1,585
Phenazine-2-carboxylic acid	2,735	1,650
Ethyl phenazine-2-carboxylate	1,664	1,280
Phenazine-2-carboxamide	3,020	1,738
Phenazine-2-carboxylic acid diethylamide	3,570	1,890
N-(2-Phenazinylcarbonyl)morpholine	2,955	1,720
Phenazine-2-carboxylic acid anilide	3,040	1,740
Phenazine-2-carboxylic acid anisidide	2,330	1,525
N-(2-Phenazinylcarbonyl)glycine ethyl ester	2,710	1,645
N-(2-Phenazinylcarbonyl)valine ethyl ester	2,970	1,724
N-(2-Phenazinylcarbonyl)proline ethyl ester	3,020	1,738
N-(1-Phenazinylcarbonyl)proline ethyl ester	2,710	1,645

TABLE 3



R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
H										
C_2H_5	H	280	$C_{13}H_9N_3O_2$	64,6	3,5	17,3	65,3	3,8	17,6	84
H	C_2H_5	131	$C_{17}H_{17}N_3O_2$	68,9	5,9	14,3	69,1	5,8	14,2	50
H	C_6H_5	236	$C_{19}H_{13}N_3O_2$	72,8	4,5	13,5	72,4	4,1	13,3	86
	$C_6H_4OCH_3$-*p*	231	$C_{20}H_{15}N_3O_3$	69,9	4,5	12,4	69,6	4,3	12,2	78
$(CH_2CH_2)O$		204	$C_{17}H_{15}N_3O_3$	69,6	5,3	14,2	69,5	5,1	14,3	46

TABLE 4



R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
C_2H_5	C_2H_5	139	$C_{17}H_{17}N_3O_3$	65,7	5,6	13,5	65,6	5,5	13,5	59
H	C_6H_5	218	$C_{19}H_{13}N_3O_3$	68,6	4,1	12,8	68,9	3,9	12,7	66
H	$C_6H_4OCH_3$-*p*	202	$C_{20}H_{15}N_3O_4$	66,5	4,1	11,7	66,5	4,9	11,6	50
$(CH_2CH_2)O$		185	$C_{17}H_{15}N_3O_4$	62,5	4,7	12,9	62,8	4,6	12,9	60

A study of the dependence of the magnitude of the limiting current on the depolarizer concentration and the height of the mercury column made it possible to establish that, within the limits of the selected concentrations, the polarographic waves for these compounds have diffusion character.

As should have been expected, a shift in the reduction half-wave potentials to positive values under the influence of a carboxyl group occurs on comparison of the reduction potentials of the compounds obtained and the reduction potentials of phenazine and its monoxide and N,N'-dioxide. A carbethoxy group intensifies this effect (Table 1).

A shift in the potentials to favor positive values relative to the reduction potentials of the compound with a free carboxyl group is observed during the polarographic reduction of amides of phenazine-2-carboxylic acid. The introduction of electron-acceptor substituents into the amide group leads to the same result.

The reduction of the N → O bond in the monoxide and N,N'-dioxides of phenazine derivatives occurs at more positive potentials, which is in agreement with the literature data [10, 11].

The number of electrons going into the reduction in stages was calculated for the bases of the phenazine derivatives by means of coulometric measurements. The measurements indicated that the polarographic waves of these compounds correspond to two-electron transitions. Proceeding from the results of coulometric measurements, we used the Il'kovich equation [15] to calculate the diffusion coefficient for a number of unoxidized bases (Table 2). The average value of the diffusion coefficient for the phenazine derivative bases (2.730 cm^2/sec) was used to calculate the number of electrons participating in the polarographic reduction of the N-oxides and N,N'-dioxides of the synthesized compounds as substances of similar structure. It was found that the reduction of N-oxides of phenazine derivatives proceeds in two two-electron steps, while the first polarographic wave for the synthesized N,N'-dioxides corresponds to four-electron reduction, which is in agreement with the literature data.

The $\varepsilon_{1/2}$ values for the newly synthesized compounds are of interest for a discussion of a possible correlation with the results of biological tests.

EXPERIMENTAL

Ethyl Phenazine-2-carboxylate 10-N-Oxide. A mixture of 4.5 g (16 mmole) of phenazinecarboxylic acid 10-N-oxide, 45 ml of anhydrous ethanol, and 2.25 ml of concentrated H_2SO_4 was refluxed for 3 h. The alcohol was evaporated, the residue was treated with 5% Na_2CO_3 solution, and the precipitate was removed by filtration, dried, and crystallized from ethanol to give 2.5 g (55%) of yellow crystals with mp 170°. Found: C 67.7; H 4.7; N 10.4%. $C_{15}H_{12}N_2O_3$. Calculated: C 67.2; H 4.5; N 10.4%.

Phenazine-2-carboxylic Acid Anilide. A 0.8-ml (8 mmole) sample of aniline and 0.83 g (8 mmole) of triethylamine were added to a solution of 2 g (8 mmole) of phenazine-2-carboxylic acid chloride in 100 ml of dry chloroform, and the solution was stirred at room temperature for 3 h. The chloroform was evaporated, and the solid material was removed by filtration, dried, and crystallized from glacial acetic acid to give 1.7 g (85%) of yellow crystals with mp 223°. Found: C 76.2; H 4.1; N 13.8%. $C_{19}H_{13}N_3O$. Calculated: C 76.2; H 4.3; N 14.0%.

Phenazine-2-carboxylic Acid Anisidide. A 1.08-g (8 mmole) sample of p-anisidine and 0.83-g (8 mmole) of triethylamine were added to a solution of 2 g (8 mmole) of phenazine-2-carboxylic acid chloride in 100 ml of dry chloroform, and the solution was stirred at room temperature for 3 h. The chloroform was evaporated, and the residue was treated with water. The resulting precipitate was removed by filtration, dried, and crystallized from ethanol to give 1.2 g (70%) of yellow crystals with mp 231°. Found: C 73.0; H 4.7; N 12.6%. $C_{20}H_{15}N_3O_3$. Calculated: C 72.9; H 4.5; N 12.8%.

N-(2-Phenazinylcarbonyl)morpholine was similarly obtained in 65% yield as yellow crystals with mp 176° (from acetone). Found: C 69.6; H 5.3; N 14.2%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.5; H 5.1; N 14.3%. This method was also used to prepare amides of phenazine-2-carboxylic acid 10-N-oxide (Table 3).

Ethyl Phenazine-2-carboxylate 5,10-Dioxide. A total of 10 ml of 30% H_2O_2 was added to a solution of 1.5 g (5.3 mmole) of ethyl phenazine-2-carboxylate in 20 ml of glacial acetic acid, and the mixture was heated at 50° for 20 h. The solution was then poured into cold water, and the resulting precipitate was removed by filtration, dried, and crystallized from ethanol to give 0.9 g (60%) of red crystals with mp 153°. Found: C 63.4; H 4.6; N 10.1%. $C_{15}H_{12}N_2O_4$. Calculated: C 63.4; H 4.3; N 9.8%.

The remaining 5,10-dioxides of the phenazine derivatives were similarly obtained (Table 4).

The reduction potentials were measured with LP-60 and ON-102 polarographs relative to a saturated calomel electrode. The polarographic reduction was performed in an alcohol–acetate buffer at pH 6.1 with a depolarizer concentration of $4 \cdot 10^{-4}$ or $2 \cdot 10^{-4}$ M.

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