SYNTHESIS AND STUDY OF HETEROCYCLIC DERIVATIVES WITH BIOLOGICAL ACTIVITY

X. Study of the Formation of Semiquinones in the Phenazine Series in Dependence on the Nature of the Substituents*

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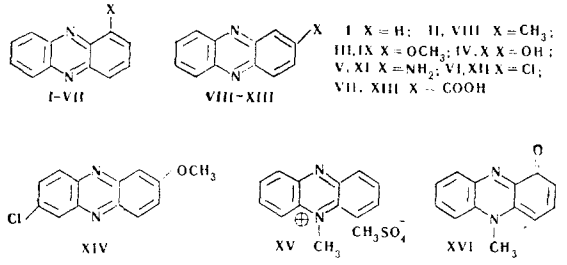
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 5, pp. 909–911, 1968

UDC 547.864.2.4.6.07:541.127'69

The kinetics of the formation of semiquinones has been studied for substituted phenazine derivatives, some of which are biologically active compounds. The influence of the substituents on the rate of reduction was investigated. Attempts have been made to correlate the rate constants with the σ-constants of the substituents by means of Hammett's equation.

In continuation of the study begun on the one-electron process of reduction with the formation of semiquinones in the phenazine series [1], we undertook a study of the kinetics of this process for several 1- and 2-substituted phenazines (I–XIII) in order to obtain information on the influence of electron-donating and electron-accepting groups, on the one hand, and the position of entry of the substituent, on the other hand:



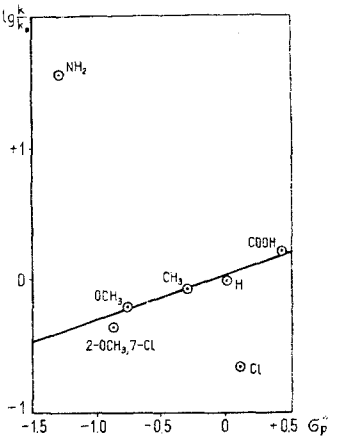
In addition, among the compounds investigated were included XIV, with two substituents in different rings, and two representatives of the phenazine series possessing biological activity (the quaternary salt, N-methylphenazine methosulfate XV and pyocyanin XVI).

The reduction kinetics were studied spectrophotometrically under conditions that we have described previously for compounds I, IV, V, XI, and XIII [1].

The absorption spectra of the semiquinones in the visible region have a shape convenient for the spectrophotometric recording of the kinetic parameters of the reduction process.** The strongest absorption band is in the 428–494 nm region.

Identification of the formation of semiquinones was carried out by the EPR method. Under experimental conditions, the semiquinones of all the above-mentioned substances gave a HFS of seven components.

The kinetic curves obtained are described by a first-order equation. The rate constants of the process, calculated from these curves, are given in the table.



Rate constant of the reduction of phenazine derivatives in an acid medium as a function of the σ_p^+-constants of the substituents.

In order to follow the interrelationship between the properties of the substituents and the changes in the free energy of activation of the reduction process on passing from one phenazine derivative to another, we used Hammett's equation in the form $\log (k/k_0) = \rho\sigma + a$, where k_0 is the rate constant for the reduction of unsubstituted phenazine and k is the rate constant for its derivative.

For correlation with the values of the potentials of the polarographic reduction of phenazine derivatives in an aprotic solvent, Gordienko [2] used the σ-constants taking into account only the inductive effect of the substituent.

In the case of the 2-substituted phenazines, we found the best correlation when we used the σ_p^+-constant, taking into account the polar conjugation of a substituent in the para position with the reaction center [3]. The numerical value of ρ was 0.330 (see figure).

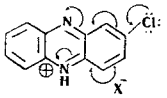
It must be mentioned that for 2-chlorophenazine (XII) no correlation was observed. Apparently, the chlorine atom participates in this process as an electron-donating substituent hindering reduction. This behavior from the chlorine atom can be explained by the fact that the p-electrons of its unshared pair are strongly displaced in the direction of the central heterocycle, which has a deficient electron density in quaternary phenazine salts.

*For part IX, see [1].

**An exception is the semiquinone of 2-hydroxphenazine (X), the absorption curve of which masks the curve of the initial quaternary salt; consequently only qualitative observations of its formation were made.

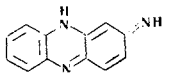
Values of the Rate Constants for the Production of a Number of Phenazine Derivatives

No.	Compound	$k \times 10^{-3}$, sec^{-1}	No.	Compound	$k \times 10^{-3}$, sec^{-1}
II	1-Methylphenazine	0.253	VIII	2-Methylphenazine	0.562
III	1-Methoxyphenazine	0.449	IX	2-Methoxyphenazine	0.408
IV	1-Hydroxyphenazine	2.846	X	2-Hydroxyphenazine	—
V	1-Aminophenazine	34.350	XI	2-Aminophenazine	23.780
VI	1-Chlorophenazine	0.458	XII	2-Chlorophenazine	0.141
VII	Phenazine-1-carboxylic acid	4.394	XIII	Phenazine-2-carboxylic acid	1.085
XV	N-Methylphenazine methosulfate	13.200	XVI	Pyocyanin	83.100
			XIV	7-Chloro-2-methoxyphenazine	0.290
I	Phenazine	0.650			



Because of the influence of the chlorine atom, relation is disturbed also for 7-chloro-2-methoxyphenazine (XIV).

An amino group in position 2 gives a very marked deviation, but this can be explained by the fact that, by participating in the formation of a readily-reduced quinoid structure, the amino group, partially becomes a reaction center of the molecule.



For the 1-substituted phenazines, this correlation is followed less strictly. The deviations observed for 1-amino- (V), 1-hydroxy- (IV), and 1-chlorophenazines (VI) are explained by the factors mentioned above.

Attention is also drawn to the fact that N-methylphenazine methosulfate (XV) and pyocyanin (XVI) possess high reduction rate constants. In the first case this is explained by the considerable noncompensated positive charge in the phenazine system due to the formation of the quaternary salt, and for pyocyanin by a disturbance of the stable aromatic system and the formation of a labile o-quinoid structure.

This capacity of N-methylphenazine methosulfate for readily undergoing conversion into a semiquinoid form agrees well with its antihypoxic property [4, 5] and that of pyocyanin with its antibacterial activity.

In summary it can be said that with an increase in the reduction rate constant one may expect an increase in biological activity of the phenazine derivatives acting as electron-transfer agents.

We express our gratitude to Yu. S. Rozum for kindly making some samples of compounds available to us.

REFERENCES

1. Z. V. Pushkareva and V. F. Gryazev, KhGS [Chemistry of Heterocyclic Compounds], 1, p. 425, 1967.

2. L. L. Gordienko, Elektrokhimiya, 1, 1497, 1965.

3. V. A. Pal'm, Usp. khim., 30, 1069, 1961.

4. M. J. Hardonk, C. A., 63, 2054b, 1965.

5. V. M. Vinogradov, F. M. Rachinskii, L. V. Pastushenkov, and I. M. Markelov, Subjects of Papers at the All-Union Conference on "Connection between the Pharmacological Activity of Medicinal Substances and Their Physicochemical Properties" [in Russian], Leningrad, p. 23, 1966.

6. P. Desaive and J. Garson, Compt. rend. soc. biol., 150, 803, 1965.

27 September 1966

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