THE CYANOETHYLATION REACTION AND ELECTRONIC STRUCTURE OF N-PHENYLATED THIOAMIDES OF THE 1,2,4-TRIAZOLE AND TETRAZOLE SERIES

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The cyanoethylation reactions of 1-phenyl-1,2,4-triazoline-3-thione (I) and of 1-phenyl-1,2,4,-triazoline-5-thione (II) have been studied. The cyanoethylation of I forms only S-cyanoethyl derivates,and the cyanoethylation of II only N-cyanoethyl derivatives. The structures of the reaction products were confirmed by UV spectroscopy and by independent synthesis. On the basis of a quantum-mechanical analysis of the compounds, their tautomeric forms, and the assumed primary reaction products, it has been concluded that the mechanism of the cyanoethylation and transcyanoethylation reactions of these heterocyclic thioamides is a common one.

In a study of the connection between the structure and properties of heterocyclic thioamides it was found [1,2] that the replacement of one nitrogen atom in the tetrazole ring by a CH group with a passage to the 1,2,4-triazole series leads to considerable qualitative changes in the properties of the corresponding thioamides. Thus, the cyanoethylation of 1-phenyltetrazoline-5-thione (XIII) leads initially to the formation of the isolatable S-cyanoethyl derivative, which is converted into the N isomer under the reaction conditions. In the cyanoethylation of 4-phenyl-1,2,4-triazoline-3-thione (XIV), however, only the N-cyanoethyl derivative is obtained.

Continuing our comparative study of the properties of thioamides of the 1,2,4-triazole series and of the influence of the position of an N-phenyl substituent on the thione-thiol tautomerism in the triazolinethiones, we have investigated the cyanoethylation of two isomers not previously studied: 1-phenyl-1,2,4-triazoline-3-thione (I) and 1-phenyl-1,2,4-triazoline-5-thione (II). It was found that the cyanoethylation of I gives only the S-cyanoethyl derivative (III), and the cyanoethylation of II only the N-cyanoethyl derivative (VIII). It is an interesting fact that the reaction of I with acrylonitrile takes place readily not only in an alkaline but also in an acid (acetic or formic acid) medium, and even simply in solution in acrylonitrile. Compound II reacts with acrylonitrile only in the presence of an alkaline catalyst (triethylamine). Compounds I and II also react with β-chloropropionitrile (I in an alkaline medium or in a neutral high-boiling solvent, II in an alkaline medium) with the formation of compounds identical with those obtained by the reactions of I and II with acrylonitrile. The structures of the cyanoethylation products were shown by their chemical reactions (scheme) and were confirmed by UV spectroscopy.

On being oxidized with potassium permanganate in acetic acid, compound III formed the sulfone IV. The hydrolysis of III with hydrochloric acid leads to the formation of the acid V, identical with the S-acid obtained by the alkylation of I with β-chloropropionic acid and having a known structure, since this alkylation reaction is of the S_N2 type [3,4]. Finally, the hydrolysis of IV and the oxidation of V gave one and the same acid VI. The UV spectrum of III differs considerably in the shape of the curve and the positions of the absorption maxima from the UV spectrum of I and is similar to that of the S-acid V obtained by

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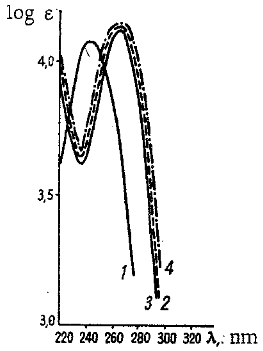


Fig. 1

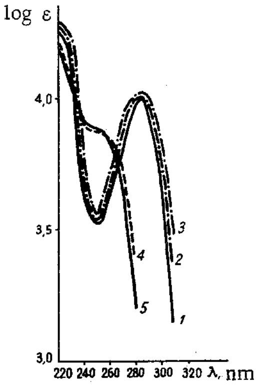
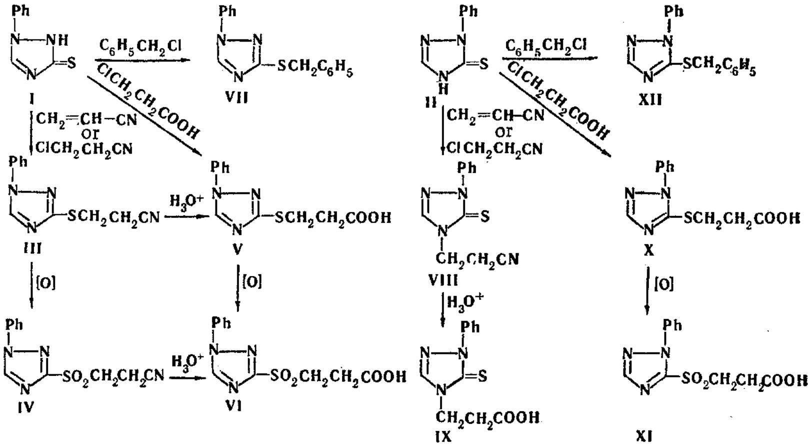


Fig. 2

Fig. 1. UV spectra (in ethanol) at a concentration of 10^{-3} M. SF-4 instrument: 1) 1-phenyl-1,2,4-triazoline-3-thione (I); 2) 3-β-cyanoethylthio-1-phenyl-1,2,4-triazole (III); 3) 3-β-ethoxycarbonylthio-1-phenyl-1,2,4-triazole (V); 4) 3-benzylthio-1-phenyl-1,2,4-triazole (VII).

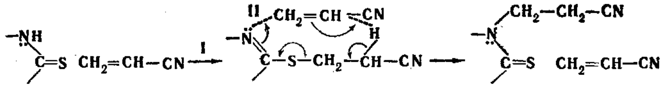
Fig. 2. UV spectra (in ethanol) at a concentration 10^{-3} M. SF-4 instrument: 1) 1-phenyl-1,2,4-triazoline-5-thione (II); 2) 4-β-cyanoethyl-1-phenyl-1,2,4-triazoline-5-thione (VIII); 3) 4-β-carboxyethyl-1-phenyl-1,2,4-triazoline-5-thione (IX); 4) 5-β-carboxyethylthio-1-phenyl-1,2,4-triazole (X); 5) 5-benzylthio-1-phenyl-1,2,4-triazole (XII).

the alkylation of I with β-chloropropionic acid. The UV spectrum of the S-acid V, in its turn, is fairly similar to the UV spectrum of the S-benzyl derivative VII (Fig. 1).



On hydrolysis, compound VIII gave the N-acid IX, the melting point and UV spectrum of which differed from those of the acid X obtained by the alkylation of II with β-chloropropionic acid. In contrast to the N-acid IX, the S-acid X gave the sulfonyl acid XI on oxidation. The UV spectra of compounds II, VIII, and IX are of the same type and differ substantially from the UV spectrum of the S-acid X, which resembles the spectrum of the S-benzyl compound XII (Fig. 2).

In order to explain the cyanoethylation of 1-phenyltetrazoline-5-thione (XIII), the S-cyanoethyl derivatives of which rearrange into the N isomer comparatively slowly during the reaction, a reaction mechanism was previously [5] proposed which included in a second stage the attack by a second molecule of acrylonitrile on a nitrogen atom of the tetrazole ring of the S-cyanoethyl compound, since this atom bears an unshared pair of electrons which does not participate in conjugation with the π electrons of the ring:



Taking this reaction mechanism as a basis, it is not difficult to explain the cyanoethylation of 4-phenyl-1,2,4-triazoline-3-thione (XIV) and of 1-phenyl-1,2,4-triazoline-5-thione (II), in which, thanks to the lower electronegativity of the triazole ring as compared with the tetrazole ring, the negative charge on the the atom of nitrogen attacked is greater in absolute magnitude than in the tetrazoles. Consequently, their transcyanoethylation with the formation of the N isomer takes place very rapidly. However, it is difficult to give satisfactory interpretation on the basis of the mechanism proposed above of the formation of only the S-cyanoethyl derivative, which has no tendency to transcyanoethylation, in the case of 1-phenyl-1,2,4-triazoline-3-thione (I).

In order to explain the different directions of the cyanoethylation of compounds I, II, XIII, and XIV, we have performed a quantum-mechanical calculation by the MO LCAO method in Hückel's approximation of the π-electronic charges on the atoms of these compounds (Fig. 3). The calculations were performed with Pullman's parameters [6,7]. In agreement with Mulliken's formula [8], the η parameter was taken as 1.1 for the $=\dot{N}-\dot{N}=$ bond, 1.2 for the $-\underset{|}{\ddot{N}}-\dot{N}=$ bond, and 1.3 for the $-\underset{|}{\ddot{N}}-\underset{|}{\ddot{N}}-$ bond. In the case of compounds II and XIII, the total π-electronic energies for the two possible thioamide structures IIa,b and XIIIa,b were also calculated. The values of these energies show that the classical structures IIa and XIIIa have the greatest stability, and we discuss this subsequently in an interpretation of the results obtained.

As can be seen from the molecular diagrams of compounds I, IIa, XIIIa, and XIV, in all compounds apart from I the maximum negative charge is concentrated on the sulfur atom. In view of the fact that, because of its ready polarizability, the sulfur atom possesses greater nucleophlicity than a nitrogen atom, the general conclusion can be drawn that the primary step of the reaction includes an attack by the positive β-terminal carbon atom of the acrylonitrile on the sulfur atom of the thioamide group of the heterocycle. The existence of the greatest negative charge on the sulfur atom of compound I explains the fact noted above that this compound undergoes cyanoethylation in the absence of an alkaline catalyst. The other compounds, II, XIII, and XIV, require an alkaline catalyst, apparently in order to split off a proton from the thioamide group and, because of this, to increase the negative charge on the sulfur atom, Thus, for all the thioamides the formation of S-cyanoethyl derivatives is the most probable direction of the first stage of the reaction.

To explain the behavior of these S-cyanoethyl compounds, we calculated the π-electronic charges of the imidothiol forms of the initial compounds as model structures of the S-cyanoethyl derivatives formed (Fig. 4). This approximation of the calculation is sufficiently justified by the fact that the perturbation exerted by the cyano group through the dimethylene bridge on the π system can be regarded as negligibly small. As can be seen from the molecular diagrams of compounds Ia, IIc, XIIIc, and XIVa (Fig. 4), in compounds IIc, XIIIc, and XIVa the second molecule of acrylonitrile attacks precisely that hydrogen atom which is capable of participating in the rearrangement with the formation of N-cyanoethyl compound. In addition to this, the values of the charges on these atoms show the greater possibility of the attack by acrylonitrile on the nitrogen atoms in the triazole compounds IIc and XIVa (Fig. 4) than in the tetrazole compound (XIIIc). This corresponds to experiment: in the cyanoethylation of compounds II and XIV the rate of transcyanoethylation is so high that it is impossible to isolate the S isomers, while when XIII is cyanoethylated for a short time it is possible to isolate this isomer [2]. Compound I, which forms only the S isomer and does not undergo transcyanoethylation, in spite of ideas on the comparative electronegativity of the triazole and tetrazole rings, has the lowest negative charge on the nitrogen atom capable of participating in rearrangement: consequently, the transcyanoethylation of this compound must take place at a still lower rate. Moreover, a considerably greater charge is concentrated on the other "pyridine" nitrogen atom of this compound, but this nitrogen atom cannot participate in the rearrangement reaction. The low negative charge on the nitrogen atom capable of participating in the rearrangement and the competition arising from the second nitrogen atom for the addition of a molecule of acrylonitrile permit the conclusion that the transcyanoethylation of the S-cyanoethyl isomer Ia is unlikely. Furthermore, since transcyanoethylation is connected with the splitting out of the acrylonitrile molecule added originally, such splitting out is more likely for com-

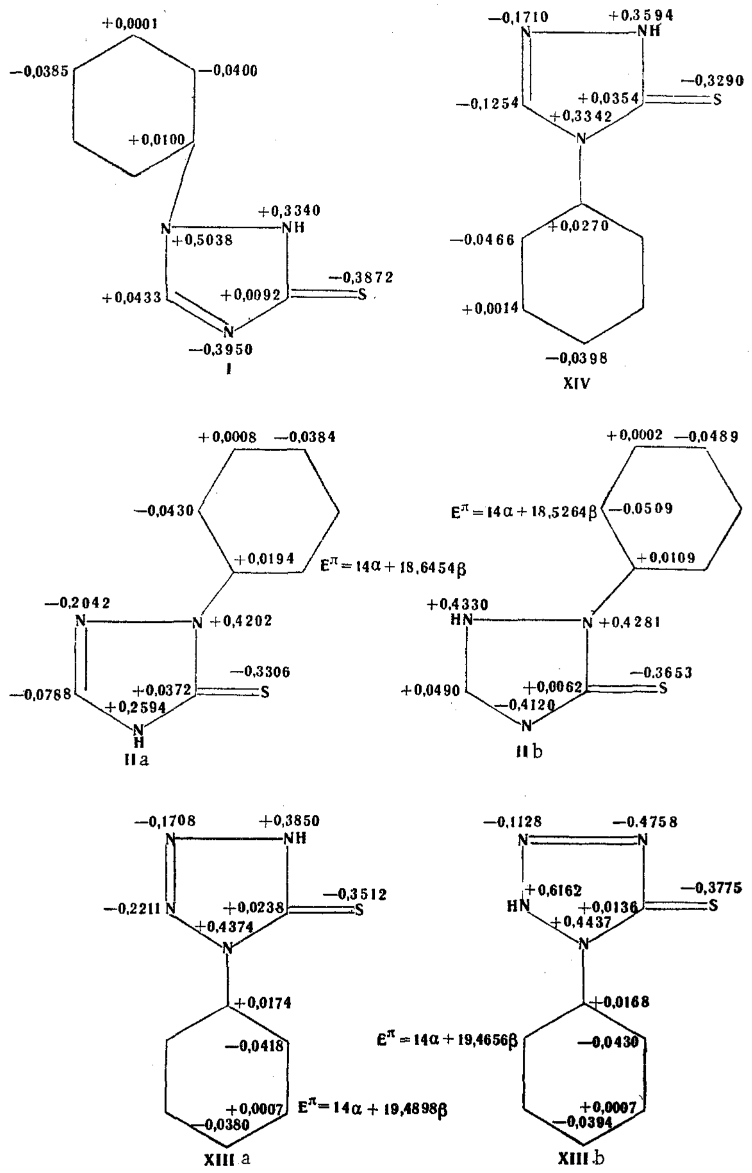


Fig. 3. π-Electronic charges of the N-phenylated thioamides of the 1,2,4-triazole and tetrazole series.

pounds IIc and XIVa (Fig. 4) since they have positive charges on the sulfur atom and the adjacent carbon of the heterocycle which, thanks to their electron-accepting action, destabilize the cyanoethyl grouping, increasing the mobility of the hydrogen attached to the α-carbon atom of this group. Compound XIIIc (Fig. 4), which is less capable of transcyanoethylation, has a lower positive charge on the sulfur atom, and the carbon atom adjacent to the sulfur atom contains an even smaller excess of electrons. And, finally, compound Ia has on the sulfur atom the positive charge that is lowest in absolute value and on the carbon atom of the heterocycle adjacent to the sulfur the highest negative charge, and it is therefore incapable of transcyanoethylation.

Thus, the quantum-mechanical analysis performed completely confirms the cyclic mechanism of the transcyanoethylation process with the synchronous transfer of electrons proposed previously and permits the conclusion that this mechanism is a general one for the whole series of heterocyclic thioamides studied.

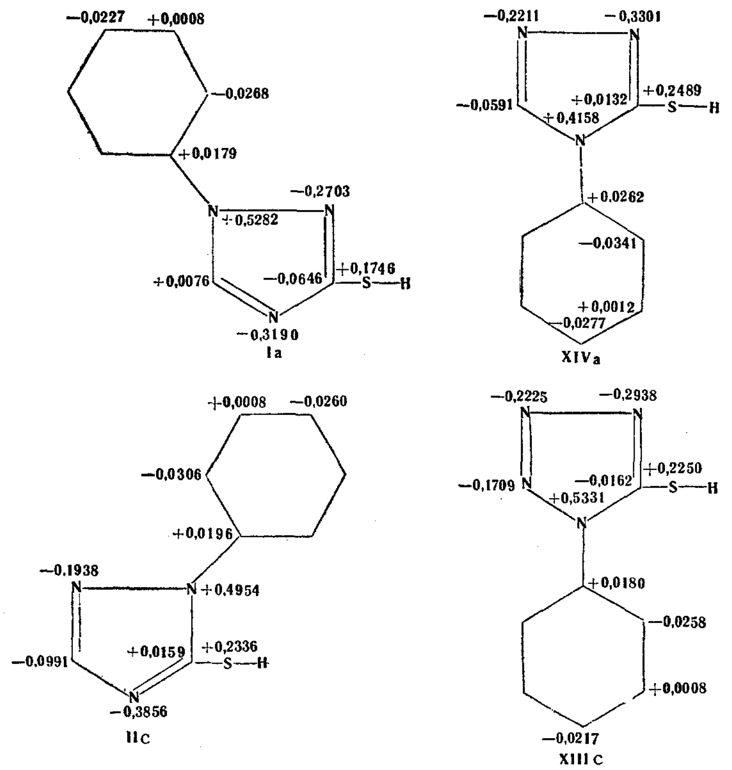


Fig. 4. π-Electronic charges of the imidothiol isomers of N-phenyl-1,2,4-triazole and of N-phenyltetrazole.

EXPERIMENTAL

1-Phenyl-1,2,4-triazoline-3-thione (I) and 1-phenyl-1,2,4-triazoline-5-thione (II) were obtained by methods which we have described previously [9].

3-β-Cyanoethyl-1-phenyl-1,2,4-triazole (III). a. With stirring, 2 ml of triethylamine was added to a suspension of 8.9 g (0.05 mole) of I in 30 ml of ethanol and 5.3 g (0.1 mole) of acrylonitrile. The temperature of the mixture rose and it became homogeneous. After 20-30 min, the solvent was distilled off and the residue was poured into 50-70 g of crushed ice. The precipitate that deposited was filtered off and crystallized from a mixture of ethanol and water. Yield 11.1 g (96%). Elongated needles: mp 46°C. Found, %: N 24.16. Calculated for $C_{11}H_{10}N_4S$, %: N 24.33.

b. A mixture of 8.9 g (0.05 mole) of I and 4.5 g (0.05 mole) of β-chloropropionitrile in 50 ml of m-xylene was boiled until the evolution of hydrogen chloride ceased. After the bulk of the solvent had been distilled off under vacuum, on cooling the reaction mass was solidified. Crystallization gave 10.8 g (94%) of product with mp 45-46°C. A mixture with a sample obtained by method (a) gave no depression of the melting point.

3-β-Cyanoethylsulfonyl-1-phenyl-1,2,4-triazole (IV). A concentrated aqueous solution of potassium permanganate was added to a solution of 0.23 g (0.001 mole) of III in 3 ml of glacial acetic acid with stirring until a sample showed a permanent pink spot on filter paper. After cooling, a small amount of concentrated sodium bisulfate solution was added to the reaction mixture to decolorize it, and the precipitate that had deposited was filtered off and crystallized from water. Yield 0.23 g (88%). Elongated needles: mp 105-106°C. Found, %: C 50.08; H 4.03; S 12.09. Calculated for $C_{11}H_{10}N_4SO_2$, %: C 50.37; H 3.84; S 12.22.

3-β-Carboxyethylthio-1-phenyl-1,2,4-triazole (V). a. A mixture of 0.69 g (0.003 mole) of III and 10 ml of concentrated hydrochloric acid was boiled. After cooling, 0.85 g (quantitative) of the hydrochloride of V precipitated with mp 170-171°C; on crystallization from water it lost hydrogen chloride and gave V with mp 116-117°C. Found, %: C 53.52; H 4.47; N 17.20; S 13.20. Calculated for $C_{11}H_{11}N_3SO_2$, %: C 53.00; H 4.45; N 16.86; S 12.86.

b. A mixture of 1.77 g (0.01 mole) of I, 1.08 g (0.01 mole) of β-chloropropionitrile, and 5 ml of 30% caustic soda in 25 ml of water was boiled for 15 min. After cooling and acidification with dilute hydrochloric acid, the reaction mixture deposited a precipitate, which was crystallized from water. Yield quantitative, mp 116-117°C. It gave no depression of the melting point with a sample obtained by method (a).

3-β-Carboxyethylsulfonyl-1-phenyl-1,2,4-triazole (VI). a. A mixture of 2.5 g (0.01 mole) of V, 10 ml of perhydrol, and 20 ml of glacial acetic acid was boiled for 30 min. The reaction mixture was evaporated to dryness on the water bath, and the residue was crystallized from water. Yield 2.7 g (96%): mp 154-155°C. Found, %: N 14.93; S 11.49. Calculated for $C_{11}H_{11}N_3SO_4$, %: N 14.94; S 11.40.

b. A mixture of 2.62 g (0.01 mole) of IV and 1 ml of concentrated hydrochloric acid was boiled, and the precipitate that deposited on cooling was crystallized from water. Yield quantitative; mp 154-155°C. The substance gave no depression of the melting point in admixture with a sample obtained by method (a).

3-Benzylthio-1-phenyl-1,2,4-triazole (VII). A solution of 1.27 g (0.01 mole) of benzyl chloride in 4 ml of ethanol was added to a solution of 1.77 g (0.01 mole) of I in 25 ml of water containing 0.56 g of caustic potash and the mixture was boiled for 20 min. Then the bulk of the solvent was distilled off. On cooling a precipitate deposited which was filtered off and crystallized from a mixture of ethanol and water. Yield 2.67 g (quantitative). mp 76-77°C. Found, %: N 16.05; S 11.95, Calculated for $C_{15}H_{13}N_3S$, %: N 15.72; S 11.99.

4-β-Cyanoethyl-1-phenyl-1,2,4-triazoline-5-thione (VIII). A mixture of 0.25 g (0.0014 mole) of II, 0.8 g of acrylonitrile, and 0.5 g of triethylamine in 5 ml of ethanol was boiled for 20 min. Then the reaction mixture was poured onto 10 g of ice and triturated. Fine crystals deposited, which were recrystallized from a mixture of ethanol and water. Yield 0.26 g (80%), mp 76°C. Found, %: N 24.68; S 13.67. Calculated for $C_{11}H_{10}N_4S$, %: N 24.33; S 13.92.

4-β-Carboxyethyl-1-phenyl-1,2,4-triazoline-5-thione (IX). A mixture of 0.15 g (0.65 mmole) of VIII and 5 ml of concentrated hydrochloric acid was boiled for 30 min. The crystals that deposited on cooling were filtered off and recrystallized from water. Yield 0.13 g (80%), mp 113°C. Found, %: N 17.02; S 12.96. Calculated for $C_{11}H_{11}N_3SO_2$, %: N 16.86; S 12.86.

5-β-Carboxyethylthio-1-phenyl-1,2,4-triazole (X). A mixture of 0.35 g (0.002 mole) of II, 0.21 g of β-chloropropionic acid, and 0.6 g of caustic potash in a mixture of 3 ml of methanol and 5 ml of water was boiled for 5 hr. The methanol was distilled off and the solution was acidified with hydrochloric acid. The precipitate that deposited was crystallized from water. Yield 0.43 g (86%). mp 139-140°C. Found, %: N 16.54; S 12.61. Calculated for $C_{11}H_{11}N_3SO_2$, %: N 16.86; S 12.86.

5-β-Carboxyethylsulfonyl-1-phenyl-1,2,4-triazole (XI). 0.25 g (0.001 mole) of X was oxidized with potassium permanganate in a similar manner to compound III. Yield 0.22 g (74%). mp 102-103°C. It crystallized with 1 molecule of water. Found, %: N 14.53; S 10.66. Calculated for $C_{11}H_{11}N_3SO_4 \cdot H_2O$, %: N 14.14; S 10.79.

5-Benzylthio-1-phenyl-1,2,4-triazole (XII) was obtained as described by Fromm and Baumhauer [10]. mp 63-64°C (according to the literature mp 64°C).

LITERATURE CITED

1. I. L. Shegal and I. Ya. Postovskii, KhGS [Chemistry of Heterocyclic Compounds], 1, 443 (1965).
2. V. L. Nirenburg and I. Ya. Postovskii, ZhOKh, 34, 3200 (1964).
3. N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, J. Am. Chem. Soc., 77, 6269 (1955).
4. B. Stanovnik and M. Tišler, Croat. Chem. Acta. 36, 81 (1964).
5. V. L. Nirenburg, Candidate's Dissertation [in Russian], Urals Polytechnic Institute, Sverdlovsk (1966).
6. B. Pullman and A. Pullman, Quantum Biochemistry [Russian translation], IL, Moscow (1965) p. 92.
7. B. Pullman, Rev. Mod. Phys., 32, 428 (1960).
8. R. S. Mulliken, J. Phys. Chem., 56, 295 (1952).
9. E. G. Kovalev and I. Ya. Postovskii, KhGS [Chemistry of Heterocyclic Compounds], 4, 740 (1968).
10. E. Fromm and H. Baumhauer, Ann., 361, 345 (1908).