REACTIONS OF HETEROCYCLIC CATIONS WITH N-CONTAINING NUCLEOPHILES.

15.* REACTION OF 2,6-DIPHENYLPYRYLIUM PERCHLORATE WITH SEMI- AND THIOSEMICARBAZIDES

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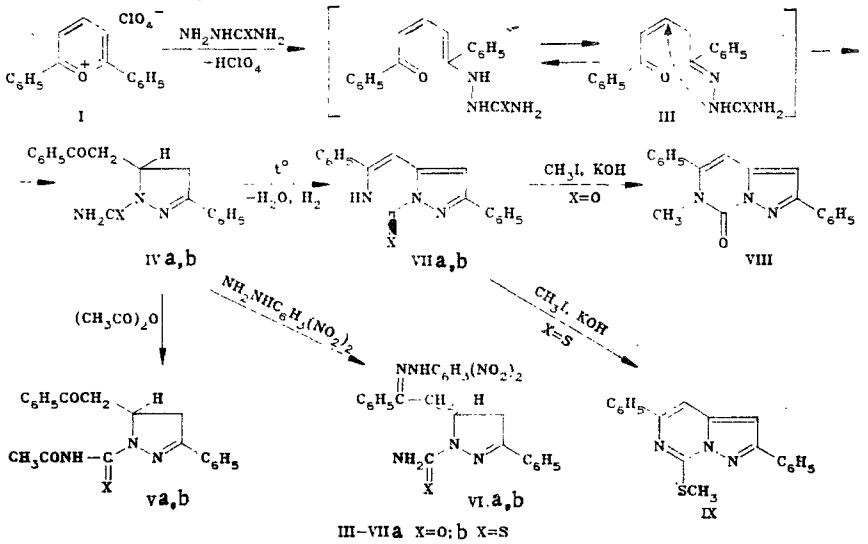
The reaction of 2,6-diphenylpyrylium perchlorate with semi- and thiosemicarbazides in ethanol leads to 1-carbamoyl- and 1-thiocarbamoyl-3-phenyl-5-phenacyl-4,5-dihydropyrazoles, the cyclization of which yields 2,5-diphenyl-7-oxo(thio)-pyrazolo[1,5-c]pyrimidines. The tautomeric form of the latter is established by comparing their electronic absorption spectra with the spectra of the methyl derivatives.

We previously studied the reaction of 2,6-diphenylpyrylium perchlordate (I) with a series of N-containing nucleophiles and found that the reactions with aniline, guanidine, 2-aminopyridine, and 2-aminobenzothiazole proceed differently in comparison with the conversion of 2,4,6-triphenylpyrylium perchlorate (II) with the same reagents [1, 2]. In the given work, the reaction of the salt (I) with semicarbazide and its sulfur analog was studied this also proceeds unusually. Thus, on heating the salt (I) with semi- or thiosemicarbazide in ethanol, the colorless substances not containing the perchlorate anion, and corresponding in composition to the compounds (III) and (IV), were isolated insteady of the expected N-ureido- or N-thioureido-substituted pyridinium salts which are formed in the reaction of the salt (II) with the same nucleophiles in alcohol [3].



The formation of the compounds (III) and (IV) can be assumed on the basis of the known mechanism of the recyclization of pyrylium salts under the action of N-containing nucleophiles [4].

The four absorption bands of the primary amino group in the region of 3055-3460 cm^{-1}, the carbonyl group at 1670 cm^{-1}, and the C=C and C=N bonds at 1585 and 1590 cm^{-1} are present in the IR spectra of the compound obtained (Table 1). The sulfur-containing compound has

*For Communication 14, see [1].

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TABLE 1. Mass Spectra of the Compounds (IV) and (VII)-(IX)

Compound	Values of m/z (intensity, %)*
IVa	307 (1), 264 (3), 263 (2), 245 (2), 244 (2), 189 (7), 188 (51), 145 (100), 144 (49), 120 (2), 118 (1), 105 (41), 77 (49)
IVb	323 (12), 305 (1), 290 (3), 271 (3), 233 (4), 218 (15), 204 (77), 178 (7) 159 (10), 145 (94), 144 (39), 115 (100), 105 (68), 91 (18), 77 (71), 51 (6)
VIIa	287 (100), 286 (89), 259 (7), 258 (7), 230 (2), 217 (4), 215 (3), 213 (3), 183 (11), 156 (7), 129 (3), 128 (4), 116 (3), 104 (9), 77 (11)
VIIb	303 (100), 302 (91), 287 (6), 275 (6), 271 (5), 244 (5), 217 (7), 215 (5), 213 (4), 199 (11), 145 (24), 115 (13), 104 (24), 77 (15)
VIII	301 (100), 300 (61), 272 (3), 257 (3), 245 (3), 244 (3), 215 (15), 213 (8), 189 (3), 169 (8), 118 (31), 77 (54), 51 (8)
IX	317 (100), 316 (21), 284 (8), 170 (29), 257 (2), 246 (5), 244 (5), 241 (5), 215 (17), 214 (46), 213 (17), 169 (8), 168 (17), 140 (8), 77 (8), 51 (4)

*The peaks of the ions with the relative intensity ≥1% are presented.

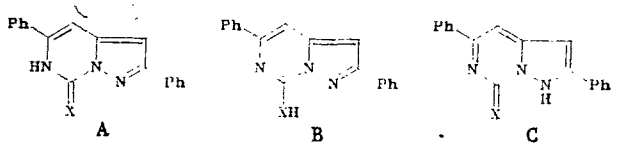
the band of the C=S bond at 1215 cm^{-1}. The presence of the amino group is also confirmed by the isolation of the acyl derivatives (V); the presence of the carbonyl group is confirmed by the isolation of the 2,4-dinitrophenylhydrazones (VI).

The PMR spectrum of the compound with X = O contains a multiplet of 10 aromatic protons at 7.1-7.8 ppm and a singlet of the two protons of the amino group at 5.6 ppm, disappearing on deuteration. The protons of the CH and CH_2 groups appear in the form of multiplets at 2.7-4.2 ppm ($2CH_2$) and 4.6-5.1 ppm (CH) with the 4:1 ratio of the integral intensities. The PMR spectrum of the compound with X = S is analogous. The data of these spectra indicate that the pyrazolines (IV), containing two CH_2 groups and one group each of CH and NH_2, are formed in the reaction. It is known that the magnetic nonequivalence of the protons of the same CH_2 groups occurs in the PMR spectra of structurally similar pyrazolines [4, 5]. Moreover, the presence of the fragment ions $[M - PhCOCH_2]^+$ with the mass numbers of 188 and 204 in the mass spectra of the compounds (Table 1) confirms the presence of the phenacyl substituent in the compounds (IV). Therefore, the pyrazolines (IV) are formed by the reaction of the salt (I) with semi- and thiosemicarbazides in alcohol.

On heating the compounds (IV) above their melting temperatures, intramolecular condensation with dehydrogenation and the formation of the pyrazolo[1,5-c]pyrimidines (VII) takes place.

Compound (VIIa) is also formed on heating the pyrazoline (IVa) in acetic acid in the presence of perchloric acid, or by the reaction of the salt (I) with semicarbazide in boiling DMF. However, it is formed in a low yield in the latter case.

The IR spectra of the compounds (VII), taken in mineral oil and in chloroform, show the absence of the absorption bands of the primary amino groups; the absorption of the carbonyl group is absent from the spectrum of compound (VIIb). The mass spectra of the compounds (VII) are characterized by the maximal intensity of the peaks of the molecular ions 287 (X = O) and 303 (X = S); this indicates the high degree of conjugation of the systems formed in (VII). In the PMR spectra of the compounds obtained, the multiplet of the aromatic protons is present, and the signals of the CH_2 group are absent; this also confirms the formation of heteroaromatic dehydro derivatives.



On the basis of the PMR spectral data, the three tautomeric forms A, B, and C can be proposed for the compounds (VII).

However, the presence of the absorption bands of the C=O and C=S groups in the IR spectra permits the exclusion of the structure B for them. The decision as to whether the compounds (VII) occur in the tautomeric form A or C was arrived at by the comparison of their UV spectra with the spectra of the products of the methylation of (VIII) and (IX) (Fig. 1).

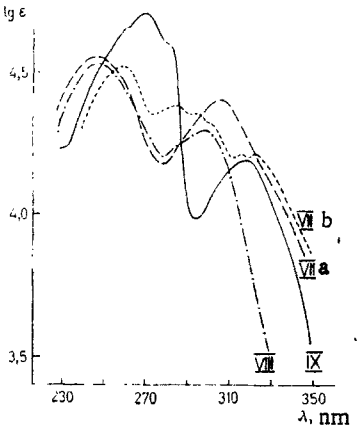


Fig. 1. UV spectra of the compounds (VII)-(IX).

In the IR spectra of compound (VIII), taken in mineral oil and deuterochloroform, the band of the carbonyl absorption (1708 and 1700 cm^{-1}) is retained. In its PMR spectrum, there is the single (3H) with the chemical shift characteristic of the N-methyl group (3.3 ppm). Consequently, compound (VIII) can have one of the tautomeric forms A or C. The intense peak of the $Ph-C\equiv\overset{+}{N}-CH_3$ ion (m/z 118) is observed in the mass spectrum of compound (VIII); this also confirms the presence of the N-methyl group. The presence of the $[M - NCH_3CO]^+$ (m/z 244) and $[M - CH_2NCO]^+$ (m/z 245) peaks in the spectrum permits the proposal that the methyl group is connected to the nitrogen atom of the pyrimidine ring. The signal of the protons of the methyl group lies at higher field (2.6 ppm) in the PMR spectrum of the compound (IX); it follows from this that the methylation went through at the thio group. This is confirmed by the presence, in the mass spectrum of compound (IX), of an intense peak with the mass number 270 which corresponds with the elimination of the SCH_3 group from the molecular ion. The absorption band of the C=S group is absent from the IR spectra of the compound (IX) taken in mineral oil and chloroform.

The comparison of the UV spectra of the compounds (VIIa) and (VIII) (Fig. 1) permits the conclusion that the indicated structures pertain to the same chromophoric systems and that, consequently, compound (VIIa) occurs in the form A. The difference in the position of the absorption maxima in the UV spectra of the compounds (VIIb) and (IX) confirms the data of the IR spectroscopy on the fact that the hydrogen atom in the compound (VIIb) is not linked to the sulfur atom, but to the nitrogen atom of the pyrimidine, since the UV spectra of the compounds (VIIb) and (VIII) are analogous. Therefore, the pyrazolo[1,5-c]-pyrimidines (VII) occur in the form A in the crystalline state and in solution.

The pyrazolo[1,5-c]pyrimidines with methyl substituents at the $C_{(2)}$ and $C_{(5)}$ atoms, which were obtained from dehydracetic acid and semi- and thiosemicarbazides as well as aminoguanidine, were first described in 1972 [6]. They were later also obtained from 2,6-dimethyl-γ-pyrone [7]. After this, pyrazolo[1,5-c]pyrimidines with alkoxycarbonyl substituents were described; they were obtained by the condensation of N-aminopyrimidinium salts with acetic anhydride [8], and by the reaction of diazopyrrolinones with esters of acetylenedicarboxylic acid [9, 10]. We synthesized 7-oxo(thio)-2,3a,5-triaryl-3H-pyrazolo[1,5-c]-pyrimidines from 2,4,6-triarylpyrylium perchlorates and semi(thiosemi)carbazides [11]. One of these compounds was later described by other authors [12]. Analogous compounds, but not containing functional groups, were obtained from 2,4,6-triphenylpyrylium tetrafluoroborate and amidrazones [13]. The pyrazolo[1,5-c]pyrimidines with two phenyl substituents, which were synthesized by our method, were not described.

Therefore, the perchlorate (I) is converted to pyrazolines in contrast to the salt (II) which forms pyridinium salts with semi- and thiosemicarbazides in alcohol. This means that the attack of the $C_{(4)}$ atom is preferable to the attack of the $C_{(6)}$ atom in the iminoketone (III), i.e., the absence of the phenyl substituent at $C_{(4)}$ puts an end to the steric hindrance to the course of this reaction. Moreover, the absence of the phenyl substituent at $C_{(3)}$ in the pyrazoline (IV) assists the steric separation of the phenacyl and amide (or thioamide) groups; this significantly hinders the reaction of intramolecular condensation with the formation of pyrazolo[1,5-c]pyrimidines. The absence of the phenyl substituent opens up the possibility of the dehydrogenation and aromatization of the molecule of the condensed heterocycle. For this case, 2,6-diphenylpyrylium perchlorate (I) and its derived pyrazolines (IV) appear to be characteristic.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	mp, °C*	IR spectrum (in mineral oil), cm^{-1}†	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
IVa	182—183	3460, 3320, 3250, 3140, 1670, 1590, 1500, 1440, 1355	70,0	5,8	13,7	—	$C_{18}H_{17}N_3O_2$	70,3	5,6	13,7	—	85
IVb	163	3350, 3270, 3160, 3055, 1670, 1585, 1500, 1440, 1350, 1215	66,6	5,3	12,8	9,6	$C_{18}H_{17}N_3OS$	66,9	5,3	13,0	9,9	73
Va	164	3260, 1700, 1520, 1490, 1470, 1300	68,5	5,8	12,3	—	$C_{20}H_{19}N_3O_3$	68,8	5,5	12,0	—	99
Vb	161,5—162	3260, 1690, 1675, 1600, 1490, 1405, 1330, 1285, 1265, 1245, 1215	65,9	5,0	11,3	8,5	$C_{20}H_{19}N_3O_2S$	65,7	5,2	11,5	8,8	86
VIa	225	3465, 3285, 1675, 1620, 1585, 1510, 1335, 1310	59,2	4,1	20,1	—	$C_{24}H_{21}N_7O_5$	59,1	4,3	20,1	—	33
VIb	230	3415, 3290, 1615, 1580, 1520, 1425, 1335, 1315	57,4	4,1	19,2	6,1	$C_{24}H_{21}N_7O_4S$	57,2	4,2	19,5	6,4	67
VIIa	271—272	3200, 3100, 1690, 1630, 1550, 1500, 1340	75,1	4,9	14,3	—	$C_{18}H_{13}N_3O$	75,3	4,6	14,6	—	64
VIIb	215	3170, 3120, 1630, 1515, 1435, 1330, 1260	71,0	4,6	13,6	10,3	$C_{18}H_{13}N_3S$	71,3	4,3	13,9	10,6	58
VIII	189	1708, 1640, 1600, 1550, 1420, 1365	75,8	5,1	13,6	—	$C_{19}H_{15}N_3O$	75,7	5,0	13,9	—	80
IX	126—126,5	1600, 1580, 1535, 1515, 1402	71,7	4,6	12,9	9,8	$C_{19}H_{15}N_3S$	71,9	4,8	13,2	10,1	82

*Compounds (IVb) and (VIII) were recrystallized from benzene. Other compounds were recrystallized as follows: (IVa) from 80% aqueous ethanol, (Va) from butanol, (Vb) and (IX) from ethanol, (VIIa) from DMF, and (VIIb) from the 3:5 mixture of ethanol and chloroform.
†In chloroform: 3425, 1720, 1637 cm^{-1} (VIIa); 3400, 1635, 1260 cm^{-1} (VIIb); 1605, 1585 cm^{-1} (IX). In deuterochloroform: 1700, 1640 cm^{-1} (VIII).

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-71 instrument in mineral oil, $CDCl_3$, and chloroform. The UV spectra were taken on a Specord M-40 spectrometer in propan-2-ol. The PMR spectra were taken on a Tesla BS-467c instrument with the internal standard of HMDS. The mass spectra were obtained on a Varian MAT-112 instrument with the direct introduction of the sample into the ion source, 70 eV energy of the ionizing electrons, and 180°C as the temperature of the ionization chamber. The purity of the compounds obtained was monitored by the method of TLC on alumina, with chloroform as the eluent. The characteristics of the synthesized compounds are presented in Table 2.

Reaction of 2,6-Diphenylpyrylium Perchlorate (I) with Semicarbazide. To the suspension of 7.0 g (6.0 mmole) of semicarbazide hydrochloride in 12.5 ml of ethanol are added 2.5 ml of an aqueous solution of 0.24 g (6.0 mmole) of sodium hydroxide followed, after 10 min, by 1.66 g (5.0 mmole) of the perchlorate (I). The reaction mixture is boiled for 1 h 20 min. After cooling the mixture, 1-carbamoyl-3-phenyl-5-phenacyl-4,5-dihydropyrazole (IVa) (1.30 g) is filtered off. The PMR spectrum in $CDCl_3$ is as follows: 2.75-3.75 (multiplet, 3H), 4.1 (quartet, 1H), 4.6-5.0 (multiplet, 2H), and 7.1-8.0 ppm (multiplet, 10H aromatic).

The reaction of the perchlorate (I) with thiosemicarbazide is performed by boiling the indicated substances in the 1:1.2 ratio in ethanol for 1 h 30 min, whereby the pyrylium salt is added in portions to the heated mixture of the remaining components. After the slow cooling of the reaction mixture, 1-thiocarbamoyl-3-phenyl-5-phenacyl-4,5-dihydropyrazoline (IVb) is filtered off. The PMR spectrum in $CDCl_3$ is as follows: 2.9-3.75 (multiplet, 3H), 4.45 (quartet, 1H), 5.15-5.5 (multiplet, 1H), 6.5 (singlet, 2H), and 7.25-7.95 ppm (multiplet, 10H aromatic).

Acetylation of the Pyrazolines (IV). The solution of 1.2 mmole of the pyrazoline (IV) in 2 ml of acetic anhydride is warmed up in the course of 5 min; the mixture is left to cool for 30 min. Compound (V) is isolated with ether. The PMR spectrum of the pyrazoline (Vb) in $CDCl_3$ is as follows: 2.6 (singlet, 3H), 3.0-3.7 (multiplet, 4H, 2CH2), 4.3-4.6 (multiplet, 1H), 7.1-8.0 (multiplet, 10H aromatic), and 9.7 ppm (singlet, 1H, NH).

1-Carbamoyl-3-phenyl-5-phenacyl-4,5-dihydropyrazole 2,4-Dinitrophenylhydrazone (VIa). Equimolar amounts of the pyrazoline (IVa) and 2,4-dinitrophenylhydrazine are boiled for 4 h in acetic acid. The residue which separated out after cooling is filtered off and washed with hot chloroform. The 2,4-dinitrophenylhydrazone (VIb) is obtained analogously, but with the boiling for 6 h.

2,5-Diphenyl-7-oxopyrazolo[1,5-c]pyrimidine (VIIa). A. The pyrazoline (IVa) (1.5 g) is maintained at 210-225°C in the course of 1 h 20 min; the melt is cooled and treated with 5 ml of acetone. Compound (VIIa) (0.9 g) is filtered off. The PMR spectrum in DMSO-D_6 is as follows: 7.1 (doublet, 2H, heteroaromatic), 7.5-8.25 (multiplet, 12H aromatic and heteroaromatic), and 11.75 ppm (singlet, NH).

B. The pyrazoline (IVa) is boiled for 1 h in acetic acid in the presence of the equimolar amount of 70% $HClO_4$. The residue of compound (VIIa), which forms after cooling, is filtered off. The yield is 50%.

C. The perchlorate (I) and semicarbazide in the ratio of 1:1.2 are boiled in DMF for 40 min; the mixture is cooled and diluted with ether. The ether layer is decanted. The caramel-forming residue is triturated with water and then with acetone. Compound (VIIa) is filtered off with the yield of 21%.

2,5-Diphenyl-7-thiopyrazolo[1,5-c]pyrimidine (VIIb). This compound is obtained from the pyrazoline (IVb) by analogy to the method A for compound (VIIa); however, the duration of the reaction is 45 min. The PMR spectrum in DMSO-D_6 is as follows: 7.0-8.0 (multiplet, 12H, aromatic and heteroaromatic) and 8.3 ppm (singlet, NH).

7-Oxo-6-methyl-2,5-diphenylpyrazolo[1,5-c]pyrimidine (VIII). To the solution of 0.58 g (2.0 mmole) of compound (VIIa) in 5 ml of DMSO is added 0.08 g (2.0 mmole) of finely ground sodium hydroxide; the mixture is heated and maintained for 10 min at 70°C. After this, the mixture is cooled to 50°C. Methyl iodide (0.29 g, 2 mmole) is added dropwise; the reaction is continued for 1 h 10 min at this temperature. Then, the reaction mixture is filtered and cooled; the residue of 0.14 g of compound (VIII) is filtered off. An additional 0.47 g of the same substance is precipitated from the filtrate with water. The PMR spectrum in $CDCl_3$ is as follows: 3.3 (singlet, 3H, CH_3), 6.3 (singlet, 1H), 6.6 (singlet, 1H), 7.4 (singlet, 8H, aromatic), and 7.8-8.1 ppm (multiplet, 2H, aromatic).

7-Methylthio-2,5-diphenylpyrazolo[1,5-c]pyrimidine (IX). This compound is obtained analogously by methylating compound (VIIb). The PMR spectrum in CCl_4 is as follows: 2.6 (singlet, 3H, CH_3), 6.4 (singlet, 1H, 3-H), and 7.05-7.85 ppm (multiplet, 11H, aromatic and heteroaromatic).

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