REACTIONS OF HETEROCYCLIC CATIONS WITH N-CONTAINING NUCLEOPHILES.

16*. STUDY OF THE INTERACTION OF 2,6-DIPHENYLPYRYLIUM PERCHLORATE WITH DIAZOLES

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The direct interaction of 2,6-diphenylpyrylium perchlorate with pyrazoles and pyrazolones led to the synthesis of 4-azolylpyrylium salts, which readily cleave a molecule of perchloric acid in the case of the N-unsubstituted pyrazolones, being converted to pyranylidene derivatives.

It is known that the reactions of anilines, N-substituted pyrroles, indoles, and tetrahydroquinolines with 2,6-diphenylpyrylium perchlorate (I) in boiling DMF lead to the hetarylation of the electrophilic carbon atom in the pyrylium ring [2-4]. A direct method for the introduction of diazole substituents into the pyrylium ring was not developed. Moreover, it was established that the presence of the "pyridine" nitrogen atom in the nucleophiles often changes the course of the reactions of the pyrylium salts with them. Thus, in the reaction of 2,4,6-trimethylpyrylium perchlorate with some aminodiazoles and aminoazines, polymers of methylenepyrans are formed instead of the expected N-hetarylpyridinium salts [5]. In the reaction of 2,4,6-triphenylpyrylium perchlorate with 2-aminobenzimidazoles, the "pyridine" nitrogen atom of the latter participates in the recyclization; this leads to the synthesis of pyrimido-[1,2-a]benzimidazolium salts [6]. It is also known that the hydrolysis of the perchlorate (I) to 1,5,2',6'-tetraphenylpyranylidenepenten-1,5-dione (II) occurs in the presence of pyridine [7].

The present investigation was undertaken in order to determine which of the two possible mechanisms – the hetarylation of the salt (I) or its hydrolysis with the action of the "pyridine" nitrogen atom of the diazole ring – will be realized in the interaction of the perchlorate (I) with diazoles.

We found that the boiling of the salt (I) with imidazole, pyrazole, and 3,5-diphenylpyrazole in freshly distilled DMF leads to the complete hydrolysis of the salt with the formation of the 1,5-diketone (III) and the pyranylidenepentendione (II). However, the methylpyrazoles, containing a carbon atom with significant local π-excess in the ring, behave as nucleophiles and hetarylate the salt (I) resulting in the formation of 4-pyrazolyl-2,6-diphenylpyrylium perchlorates (IV). The salt (IVa) is formed in 37% yield from 3-methylpyrazole. When two and three electron-donor methyl groups are present in the pyrazole ring, the competing reaction of the hetarylation of the pyrylium salt becomes predominant, and the yields of the 4-pyrazolylpyrylium salts (IVb, c) comprise 64 and 82% respectively. Therefore, the difference in the nucleophilicity of the $C_{(4)}$ atoms of pyrazole and 3(5)-methylpyrazole, which is unimportant for the usual electrophilic substitution, becomes an important factor in the pyrylation reaction of these heterocycles.

In these reactions, as well as in those previously studied [2-4], which proceed in the absence of alkali, the reaction does not stop at the stage of the formation of the 4H-pyrans (V); these last react with the initial salt (I), formally giving its hydride ion, and form the pyrylium salts (IV). We assumed that the perchloric acid isolated at the first stage will react with the initial diazoles and convert them to the corresponding perchlorates (VI), part of which we obtained. However, dimethylamine perchlorate (VId) was isolated from the

*For Communication 15, see [1].

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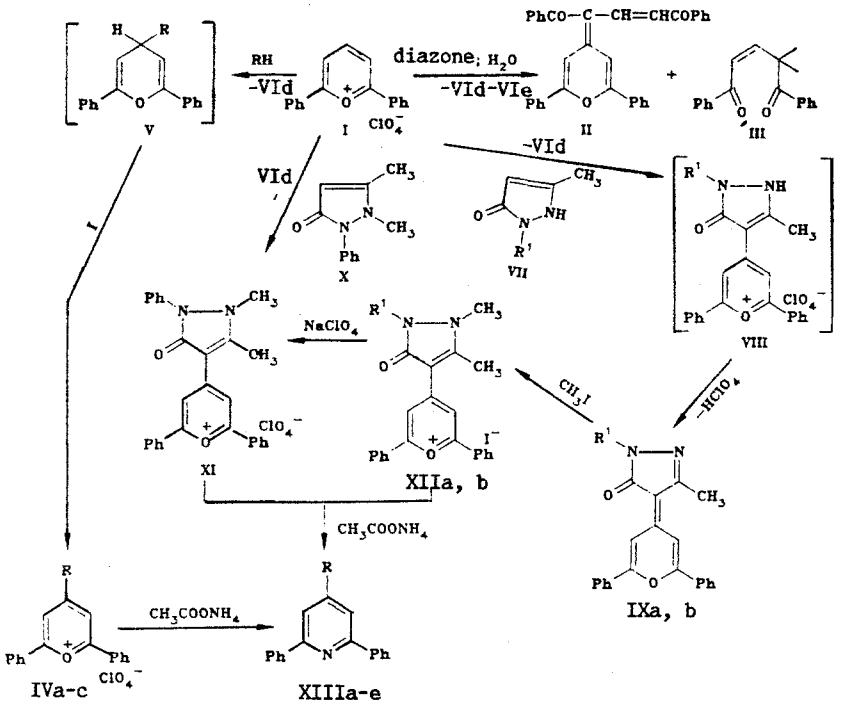
products of the reaction of the methylpyrazoles with the salt (I). The perchloric acid which is formed does not react with the pyrazoles, the basicity of which is low (the pK_α of 3,5-dimethylpyrazole is 4.38 units [8]), but with the solvent DMF, catalyzing its hydrolysis and further combining with the resulting dimethylamine. Therefore, in spite of the presence of the "pyridine" nitrogen atom in the methylpyrazones, it does not participate in the reaction; the ratio of the salt (I) to the diazole which is necessary for its completion remains at the same value of 2:1 as in the reactions with pyrrole and indole. The partial hydrolysis of the salt (I) proceeds in parallel with the formation of the compounds (II) and (III).



Diazole = pyrazole, 3,5-diphenylpyrazole, imidazole; (IV). (V) a, R = 3(5)-methyl-4-pyrazolyl, b, R = 3,5-dimethyl-4-pyrazolyl, c, R = 1,3,5-trimethyl-4-pyrazolyl; (VI) a, 3,5-dimethylpyrazole perchlorate, b, 1, 3,5-trimethylpyrazole perchlorate, c, antipyrine perchlorate, d, dimethylamine perchlorate, e, imidazole perchlorate; (VII), (IX), (XII), a, $R^1 = C_6H_5$, b, $R^1 = p\text{-}CH_3C_6H_4$; (XIII), a, R = 3(5)-methyl-4-pyrazolyl, b, R = 3,5-dimethyl-4-pyrazolyl, c, R = 1,3,5-trimethyl-4-pyrazolyl, d, R = 1-phenyl-2,3-dimethylpyrazol-5--on-4-yl, e, R = 1-p-tolyl-2,3-dimethylpyrazol-5-on-4-yl.

It is interesting to note that the perchlorate (VId) was also isolated in experiments with pyrazole and 3,5-diphenylpyrazole. In fact, the hydrolysis of the salt (I) proceeds under these conditions in the presence of DMF. However, if 17% of the compound (II) is isolated together with the diketone (III) from the reaction with 3,5-diphenylpyrazole, then virtually only the diketone (III) is formed by boiling the salt (I) in DMF. Evidently, the 3,5-diphenylpyrazole fulfills the role of the base, in the resence of which the Michael reaction, partially takes place. Imidazole (pK_α 6.95 [8]) itself reacts with perchloric acid, being converted to the perchlorate (VIe).

The 5-hydroxypyrazoles (VII), which exist in the oxo form, hetarylate the perchlorate (I) by the same mechanism. However, the resulting pyrylium salts (VIII) cleave a molecule of perchloric acid, and the deeply colored pseudobases (IX) as well as the perchlorate (VId) are isolated from the reaction medium in the amount corresponding to all of the separated acid. This fact can be explained by the tendency of the salt (VIII) to form the energetically more favorable compound (IX) with the significant conjugation of the double bonds. The analogous conversion was observed in the interaction of the salt (I) with thiazolidones [9]. At the same time, antipyrine (X), which contains a methyl substituent at the nitrogen atom in

TABLE 1. Characteristics of the Compounds Synthesized

Compound	mp*, deg C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Found, %				Empirical formulas	Calculated, %				Yield, %
				C	H	Hal	N		C	H	Hal	N	
IVa	271	1100, 1500, 1530, 1575, 1595, 1630, 3200	—	60,8	4,4	8,9	6,6	$C_{21}H_{17}ClN_2O_5$	61,1	4,1	8,6	6,8	37
IVb	292—293	1100, 1500, 1520, 1560, 1600, 1640, 3250	—	61,9	4,3	8,6	6,4	$C_{22}H_{19}ClN_2O_5$	61,9	4,5	8,4	6,6	64
IVc	278—279	1100, 1500, 1525, 1570, 1600, 1640	—	62,4	4,9	8,2	6,1	$C_{23}H_{21}ClN_2O_5$	62,7	4,8	8,1	6,4	82
VIa	46—47	1100, 1420, 1545, 1610, 1640, 3250, 3400	—	30,8	4,5	17,8	13,9	$C_5H_9ClN_2O_4$	30,5	4,6	18,1	14,2	100
VIb	102—103	1120, 1425, 1515, 1600, 3150	—	34,1	5,2	16,6	13,3	$C_6H_{11}ClN_2O_4$	34,2	5,2	16,9	13,3	100
VIc	141—142	1100, 1415, 1500, 1550, 1575, 3160	—	45,4	4,3	12,1	9,7	$C_{11}H_{13}ClN_2O_5$	45,7	4,5	12,3	9,7	100
VId	177	1100, 1410, 1510, 1600, 1640, 3220	2,90 (s, 6H, 2-CH_3); 7,20 (s, 2H, NH_2)	16,4	5,6	24,7	9,5	$C_2H_8ClNO_4$	16,5	5,5	24,4	9,6	100
VIe	262—263	1100, 1530, 1590, 1650, 3170, 3260	—	21,3	2,7	21,2	16,3	$C_3H_5ClN_2O_4$	21,4	3,0	21,1	16,6	100
IXa	251	1500, 1530, 1545, 1580, 1600, 1630, 1670	2,45 (s, 3H, CH_3); 7,30—8,00 (m, 17H, arom.)	79,9	4,9	—	6,7	$C_{27}H_{20}N_2O_2$	80,2	5,0	—	6,9	100
IXb	287	1510, 1545, 1580, 1600, 1630, 1665	—	80,1	5,3	—	6,4	$C_{28}H_{22}N_2O_2$	80,4	5,3	—	6,7	100
XI	243—244	1100, 1520, 1555, 1590, 1625, 1670	2,63 (s, 3H, CH_3); 3,35 (s, 3H, NCH_3); 7,33—8,35 (m, 17H, arom.)	65,1	4,2	7,2	5,1	$C_{28}H_{23}ClN_2O_6$	64,8	4,4	6,9	5,4	100
XIIa	236—237	1510, 1580, 1620, 1670	—	61,2	4,1	23,6	5,0	$C_{28}H_{23}IN_2O_2$	61,5	4,2	23,3	5,1	100
XIIb	268—269	1500, 1520, 1575, 1635, 1680	—	61,8	4,3	23,0	4,9	$C_{29}H_{25}IN_2O_2$	62,1	4,5	22,7	5,0	100
XIIIa	177	1530, 1560, 1600, 3200	2,60 (s, 3H, CH_3); 7,45—8,63 (m, 13H, arom.)	80,2	5,5	—	13,3	$C_{21}H_{17}N_3$	80,0	5,5	—	13,5	100
XIIIb	226—227	1500, 1540, 1580, 1610, 3250	2,38 (s, 6H, 2-CH_3); 7,40—7,80 (m, 12H, arom.)	81,0	6,0	—	12,7	$C_{22}H_{19}N_3$	81,2	5,9	—	12,9	100
XIIIc	145	1500, 1535, 1570, 1600	2,30 (s, 6H, 2-CH_3); 3,80 (s, 3H, NCH_3); 7,43—8,03 (m, 12H, arom.)	81,3	6,2	—	12,3	$C_{23}H_{21}N_3$	81,4	6,2	—	12,4	100
XIIId	178—179	1540, 1580, 1600, 1670	2,45 (s, 3H, CH_3); 3,35 (s, 3H, NCH_3); 7,38—7,89 (m, 17H, arom.)	80,6	5,7	—	9,8	$C_{28}H_{23}N_3O$	80,6	5,5	—	10,0	100
XIIIe	225—226	1500, 1540, 1605, 1675	—	80,7	5,8	—	9,8	$C_{29}H_{25}N_3O$	80,7	5,8	—	9,7	80

*The compounds (IVa-c) and (XIIb) were purified by recrystallization from the ethanol-acetonitrile mixture. The compounds (VIa-e) were recrystallized from the chloroform–acetic acid mixture. The compounds (XIIIa-e) were recrystallized from ethanol. The compounds (IXa) and (IXb) were recrystallized from DMF. The compounds (XI) and (XIIa) were recrystallized from acetic acid.

the 2 position, forms the stable pyrylium salt (XI). Compound (IX) reacts with difficulty with methyl iodide thereby forming the pyrylium iodides (XII). The pyrylium salt (XI) is obtained by the reaction of the iodide (XIIa) with sodium perchlorate; this confirms the structure of the compounds (IX). When they are subjected to the action of 70% $HClO_4$, yellow colored salts, which are converted to the initial compounds in the attempt to recrystallize them, are formed. The IR spectra of the compounds (IXa) and (IXb) contain the absorption bands of the C=C, C=N (1500, 1540, 1580, 1600, and 1630 cm^{-1}), and C=O (1665 and 1670 cm^{-1}) groups. The PMR spectrum of the compound (IXa) contains a singlet of the methyl protons of the pyrazolone ring at 2.45 ppm and the multiplet of the aromatic and methine protons at 7.30-8.00 ppm. The ratio of the integral intensities is 3:17. The data of the mass spectrometry confirm the proposed structure of the substance (IXb) as well as its high stability – the peak of the molecular ion has 100% intensity.

The structure of the salts (IV), (XI), and (XII) was confirmed by the presence of absorption bands characteristic of the heteroaromatic cation (1560, 1600, and 1620 cm^{-1}) in their IR spectra; the IR spectra of the salts (IV) and (XI) showed the presence of the perchlorate ion at 1100 cm^{-1}. The IR spectra of the salts (IVa) and (IVb) have the characteristic broad absorption band of the NH group at 3200-3250 cm^{-1}; the salts (XI) and (XIIa, b) have the absorption band of the CO groups at 1670 and 1680 cm^{-1}. The PMR spectrum of the salt (XI) contains two singlets of the methyl groups at 2.63 and 3.35 ppm as well as the multiplet at 7.33-8.35 ppm corresponding to the protons of the C_6H_5 and CH groups. The ratio of the integral intensities is 3:3:17.

The structure of the salts obtained (IV), (XI), and (XII) was confirmed, in addition, by their conversion to the pyridines (XIIIa-e) by the reaction with ammonium acetate. The composition of the pyridines (XIIIa-e) was confirmed by the data of the elemental analysis; their structure was confirmed by the IR and PMR spectra (Table 1).

Therefore, we found that the complete hydrolysis of the salt (I) proceeds in the presence of imidazole and DMF. However, when a carbon atom with a raised local π-excess is present in the molecules of the diazoles, it can hetarylate the perchlorate (I). As a result, a method for the direct introduction of the pyrazole and pyrazolone substituents into the pyrylium cation was developed.

EXPERIMENTAL

The IR spectra were taken on a Specord 71-IR spectrometer in mineral oil. The PMR spectra were taken on a Tesla BS-767C instrument (60 MHz); the solvents were acetone-D_6, $CDCl_3$, C_6D_6, and CF_3COOH. The internal standard was HMDS. The mass spectra were recorded on a Varian MAT-112 spectrometer with 70 eV as the energy of the ionizing electrons, 180°C as the temperature of the ionization chamber, and the direct input of the sample into the ion source. The purity of the compounds obtained was monitored using TLC on plates with silicic acid or alumina; the detection of the substances was carried out in a chamber with iodine vapor. We obtained 1,3,5-trimethylpyrazole by the methylation of 3,5-dimethylpyrazole with methyl iodide in DMSO with NaOH by analogy with the method of [10]; the yield was 47%.

The data on the compounds obtained are presented in the Table 1.

Reaction of the Perchlorate (I) with DMF. The solution of 1 g (3 mmole) of the salt (I) in 15 ml of DMF is boiled for 1.5 h prior to cooling, the addition of 50 ml of ether, stirring and the decanting of the solution. The isolated oily product is crystallized by trituration with 10 ml of water. The residue (0.1 g) is a mixture which is separated with difficulty. The aqueous solution is evaporated; the perchlorate (VI) (mp 177°C; according to the data of [11], the mp is 177-179°C) is obtained in a yield of 0.32 g (73%). The solvent of the decanted solution is evaporated; the residue is dissolved in 5 ml of benzene and applied to a column with alumina (the height of the layer is 40 cm; the diameter is 3 cm). By eluting with the 3:1 mixture of benzene and chloroform, 0.24 g (32%) of the diketone (III) [1] (R_f 0.9) and 0.02 g (3%) of the compound (II) (R_f 0.7) are obtained sequentially.

The reaction of the salt (I) with 3,5-diphenylpyrazole proceeds analogously. However, the yields of the compound (II) and compound (III) are 17 and 40% respectively.

Reaction of the Perchlorate (I) with Imidazole. The mixture of 1 g (3 mmole) of the salt (I) and 0.25 g (3.6 mmole) of imidazole in 10 ml of freshly distilled DMF is boiled for 1 h. After cooling, 50 ml of water are added, and the brown oily residue is filtered off. The

filtrate is concentrated, and 0.58 g (100%) of imidazole perchlorate (VIe) is obtained. The residue isolated with water is dissolved in 5 ml of benzene and separated on a column with alumina (the height of the layer is 40 cm; the diameter is 3 cm). By the sequential elution with hexane and the 4:1 mixture of benzene and chloroform, 0.26 g (35%) of the diketone (III) is obtained. The column of the support which is colored red is cut out; it is treated with acetone. The solution is concentrated; 0.28 g (39%) of the compound (II) is obtained.

4-[3(5)-Methylpyrazol-4-yl]-2,6-diphenylpyrylium Perchlorate (IVa). To 1 g (3 mmole) of the salt (I) is added the solution of 0.15 ml (0.15 g, 1.8 mmole) of 3(5)-methylpyrazole in 10 ml of freshly distilled DMF; the mixture is boiled for 1 h. After cooling, 70 ml of ether are added; the mixture is stirred, and the solution is decanted. The isolated residue is treated with 20 ml of water, and 0.23 g of the pyrylium perchlorate (IVa) is filtered off. The aqueous solution is concentrated, and 0.21 g (95% of the theoretically possible amount) of the perchlorate (VId) is obtained. The decantation solution is concentrated; the residue is dissolved in 5 ml of benzene and applied to a column with alumina (the height of the layer is 30 cm; the diameter is 3 cm). After the elution with hexane, 0.07 g (9%) of the compound (III) is obtained. The column of the support which is colored red is cut out; it is treated with acetone prior to the concentration of the solution and the isolation of 0.34 g (48%) of the compound (II).

The 4-(3,5-dimethylpyrazol-4-yl)-, 4-(1,3,5-trimethylpyrazol-4-yl)-, and 4-(1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)-2,6-diphenylpyrylium perchlorates (IVb), (IVc), and (XI) are obtained by the analogous method from the salt (I) and 3,5-dimethylpyrazole, 1,3,5-trimethylpyrazole, and 1-phenyl-2,3-dimethyl-5-pyrazolone correspondingly.

2,6-Diphenyl-4-(1-phenyl-3-methyl-5-pyrazolon-4-ylidene)-pyranylidene (IXa). The mixture of 0.66 g (2 mmole) of the salt (I) and 0.21 g (1.2 mmole) of 1-phenyl-3-methyl-5-pyrazolone (VIIa) in 5 ml of freshly distilled DMF is boiled for 1 h. After cooling, 0.41 g of the compound (IXa) is filtered off. The filtrate is diluted with 40 ml of ether; the separated oil is triturated with 20 ml of water. The filtered aqueous solution is concentrated prior to the isolation of 0.30 g (100%) of the perchlorate (VId).

2,6-Diphenyl-4-(1-p-tolyl-3-methyl-5-pyrazolon-4-ylidene)-pyranylidene (IXb). This compound is isolated by an analogous method from the salt (I) and 1-p-tolyl-3-methyl-5-pyrazolone (VIIb). Found: M 418; calculated: M 418, 499. The mass spectrum (m/z, the fragment ion, the relative intensity, %*) is as follows: 418, M^+, 100; 341, $[M - Ph]^+$, 7; 313, $[M - PhCO]^+$, 9; 298, $[(M - PhCO) - CH_3]^+$, 5; 272 $[(M - PhCO) - CH_3CN]^+$, 52; 209, $[(M - PhCO) - C_2H_3Ph]^+$, 29; 139, $[C_8H_9NO]^+$, 25; 105, $PhCO^+$, 15; 91, $[C_6H_4CH_3]^+$, 9; 77, Ph^+, 17.

4-(1-p-Tolyl-2,3-dimethyl-5-pyrazolon-4-yl)-2,6-diphenylpyrylium Iodide (XIIb). Into a three-necked flask equipped with a stirrer, a dropping funnel, and an effective reflux condenser is placed 0.4 g (1 mmole) of the compound (IXb) prior to the addition of 10 ml of nitromethane. The solution of 1.4 g (0.62 ml, 10 mmole) of methyl iodide in 10 ml of nitromethane is added dropwise with stirring. The mixture is heated to boiling, and is boiled with stirring for 80 h. After cooling, 80 ml of ether are added; the separated residue is filtered off. It is suspended in 10 ml of ethanol, and a stream of sulfur dioxide is passed through the resulting suspension for 3 h. After the dilution with 50 ml of ether, 0.54 g of the salt (XIIb) is filtered off.

The iodide (XIIa) is obtained analogously from the compounds (IXa).

Reaction of the Iodide (XIIa) with Sodium Perchlorate. To the suspension of 0.14 g (0.25 mmole) of the salt (XIIa) in 10 ml of acetone is added the solution of 0.62 g (5.1 mmole) of sodium perchlorate in 10 ml of acetone; the mixture is boiled for 1 h. After cooling, 50 ml of water are added to the resulting suspension prior to the filtering of 0.13 g of the orange residue of the perchlorate (XI); this is washed on the filter twice with 10 ml of water and dried. The yield is quantitative.

4-[3(5)-Methylpyrazol-4-yl]-2,6-diphenylpyridine (XIIIa). To the suspension of 0.41 g (1 mmole) of the salt (IVa) in 5 ml of glacial acetic acid is added 0.77 g (10 mmole) of ammonium acetate; the mixture is boiled for 1 h. After cooling, 20 ml of water are added; 0.31 g of the pyridine (XIIIa) is filtered off.

*The peaks of the ions with the relative intensity $\geq$5% are presented.

The compounds 4-(3,5-dimethylpyrazol-4-yl)-, 4-(1,3,5-trimethylpyrazol-4-yl)-, 4-(1-phenyl-2,3-dimethyl-5-pyrazolon-4-yl)-, and 4-(1-p-tolyl-2,3-dimethyl-5-pyrazolon-4-yl)-2,6-diphenylpyridine (XIIIb), (XIIIc), (XIIId), and (XIIIe) are obtained analogously from the salts (IVb), (IVc), (XI), and (XIIb) correspondingly.

3,5-Dimethylpyrazole Perchlorate (VIa).. To the suspension, cooled to 5°C, of 0.92 g (10 mmole) of 3,5-dimethylpyrazole in 1 ml of ethanol is added, dropwise, 0.86 ml (1.44 g, 10 mmole) of 70% $HClO_4$. The mixture is stirred carefully prior to the dilution with 20 ml of ether and the filtering of 1.9 g (quantitative) of the perchlorate (VIa).

The perchlorates (VIb) and (VIc) are obtained analogously from 1,3,5-trimethylpyrazole and antipyrine respectively.

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