SYNTHESIS AND PROPERTIES OF N-HETARYLPYRIDINIUM SALTS

É. A. Zvezdina, M. P. Zhdanova,
V. A. Bren', and G. N. Dorofeenko

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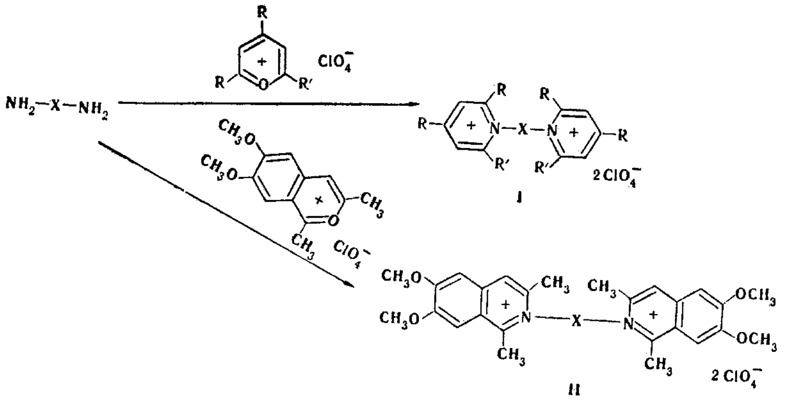
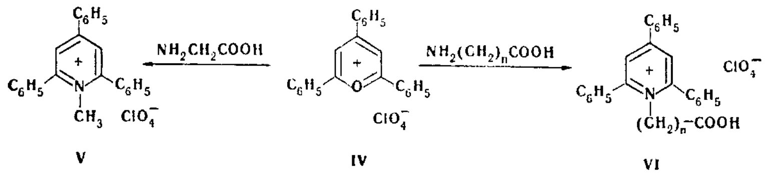
Methods for the synthesis of N-hetarylpyridinium perchlorates are examined. The basicity constants of a number of the indicated compounds were measured. It is shown that 2,4,6-trimethyl- and 2,4,6-triphenylpyridinium cations lower the electron density in N-hetarylpyridinium salts. N-Acyl derivatives of 1-(2-benzimidazolylalkyl)-2,4,6-triphenylpyridinium perchlorates were obtained. The corresponding ylids were obtained from 1-(5-tetrazolyl)- and 1-(2-benzimidazolyl)-2,4,6-triphenylpyridinium perchlorates.

We recently described the syntheses of N-hetarylpyridinium perchlorates by reactions of pyrylium salts with heterocyclic amines [1-3] and their azomethines [4]. In addition to them, a number of the indicated salts were obtained by reaction of pyrylium perchlorates with aliphatic and aromatic diamines:



I a R=R'=C_6H_5, X=$(CH_2)_6$; b R=CH_3, R'=C_6H_5, X=$(CH_2)_6$; c R=R'=C_6H_5, X=p-phenyl.; II X=$(CH_2)_6$

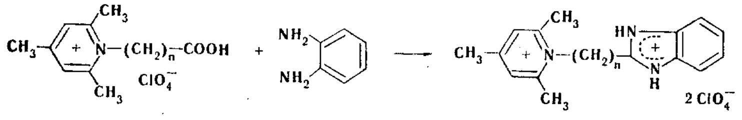
N-(2-Benzimidazolylalkyl)pyridinium perchlorates are also obtained from 2-aminoalkylbenzimidazoles [2]. The synthesis of the latter is difficult, since the cyclization of o-phenylenediamine with amino acids, in which the acidities are reduced significantly under the influence of the amino group, does not proceed completely and requires a long time (30-100 h) [5]. It might have been expected that blocking of the amino groups in the amino acids with pyrylium salts would eliminate this difficulty. The reaction of 2,4,6-trimethylpyrylium perchlorate (III) with amino acids has been described [6, 7]. We have shown that, in contrast to perchlorate III, 2,4,6-triphenylpyrylium perchlorate (IV), does not react with α-amino acids. Perchlorate V is formed quantitatively only in the case of refluxing with a fourfold excess of glycine, probably as a result of decarboxylation of the glycine and reaction of salt IV with the liberated methylamine:



a n=2; b n=3

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 334006. Scientific-Research Institute of Biology, Rostov-on-Don 334091. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 944-949, July, 1978. Original article submitted July 4, 1977.

The reaction of perchlorate IV with β-alanine and γ-aminobutyric acid leads to the corresponding pyridiniumcarboxylic acids (VI). The reactions are carried out in alcohol, acetic acid, or dimethylformamide (DMF), but the yield in the case of DMF is lower because of simultaneous cleavage of VI to give 2,4,6-triphenylpyridine. β-(N-Collidinia)propionic and γ-(N-collidinia)butyric acid perchlorates react with o-phenylenediamine in 5.5 N HCl after 17-20 h to give VII.



VII a,b

VII a n = 2; b n = 3

The products are obtained in 43-48% yields, and, with allowance for the perchloric acid deficit, the yields are close to quantitative. However, we were unable to raise them by introduction of an additional calculated amount of perchloric acid, since its presence promoted resinification of the reaction mixture. The same reaction proceeds at 150°C in 4 h in polyphosphoric acid (PPA), and monoperchlorate salts VII are formed in ~60% yields. N-Collidiniaacetic and α-(N-collidinia)propionic acid salts do not undergo cyclization under the indicated conditions.

Acids VI do not undergo reaction with o-phenylenediamine in 5.5 N HCl; however, VIb undergoes cyclization at 150°C after 4 h in PPa, and the corresponding perchlorate VIIIf is formed in 57% yield, whereas VIa does not undergo reaction under these conditions.

The starting compounds were isolated in all cases in attempts to condense β-alanine, γ-aminobutyric acid, and β-(N-collidinia)propionic and γ-(N-collidinia)butyric acid perchlorates with 2,4,5-triamino-6-hydroxypyrimidine, 5,6-diaminouracil, o-aminophenol, and o-aminothiophenol in 5.5 N HCl and PPA. In experiments with aminophenols in PPA an increase in the temperature and the reaction time led to resinification of the reaction mixture.

Thus we were unable to substantially facilitate the cyclization of the amino acids by replacement of the amino group by a pyridinium fragment. There is evidently an optimal electron density on the carbonyl group below which the reaction proceeds sluggishly. In addition, this method also makes it possible to obtain pyrylium salts with benzimidazolyl substituents.

The basicity constants (Table 1) were measured for some of the N-hetarylpyridinium perchlorates (VIII and IX) described here and previously [2, 4].

Pyridinium groups Y and Z are powerful electron acceptors. Their effect on the electron density of the basic nitrogen atom of the pyridine or benzimidazole ring is probably realized via an inductive mechanism (see [10]). It is most apparent in VIIIg-i, in which the reaction center is separated from the substituent by two bonds ($pK_a < 5$). The basicity is increased several orders of magnitude when one or several methylene groups are introduced between the donor and acceptor portions of the molecules (VIIIc-f). However, the acceptor effect of the pyridinium ring is perceived even in VIIIf (pK_a 12.65). By way of comparison, the pK_a of benzimidazole is 13.25 [8].

The acceptor effect of a substituent on the reaction center through four bonds is greater in VIIIb than in VIIIe. This may be associated with the increased ability of the multiple bonds to transmit the inductive effect as compared with ordinary σ bonds [11].

The effect of an acceptor substituent in pyridine (the pK_a of pyridine is 12.33 [9]) is also large; it is greater in the 2 position (IXa) than in the 4 position (IXb). Replacement of the methyl substituents by phenyl substituents in the ring of pyridinium perchlorate has only a slight effect on the basicities of the compounds (for example, in the case of VIIIa, b and VIIIc, d).

The methylene group in VIIId does not undergo reaction with benzaldehyde, p-nitrosodimethylaniline, ethyl orthoformate, and diazonium salts, evidently because of steric hindrance. Acylation of the NH group of the benzimidazole ring is observed when these reactions are carried out in acetic anhydride. The C–N bond attached to the quaternary nitrogen atom is cleaved in the acylation of VIIIe, and this leads to the formation of 1-acetyl-2-vinylbenzimidazolium perchlorate and 2,4,6-triphenylpyridine:*

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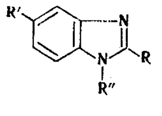
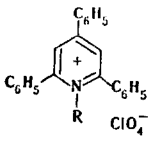
*See display after Table 1 at top of next page.

TABLE 1. Basicity Constants of N-Hetarylpyridinium Perchlorates



VIII



IX

Compound	R	R′	R″	pK$_a$ (25 ± 0.1 °C) in acetonitrile
VIIIa	H	Y*	CH_3	10,79
VIIIb	H	Z†	CH_3	10,36
VIIIc	CH_2Y*	H	H	8,76
VIIId	CH_2Z†	H	H	8,91
VIIIe	$(CH_2)_2Z$†	H	H	11,47
VIIIf	$(CH_2)_3Z$†	H	H	12,65
VIIIg	Z†	H	H	<5
VIIIh	Z†	H	C_2H_5	<5
VIIIi	Z†	H	C_9H_{19}	<5
IXa	2-pyridine	—	—	<5
IXb	4-pyridine	—	—	7,92

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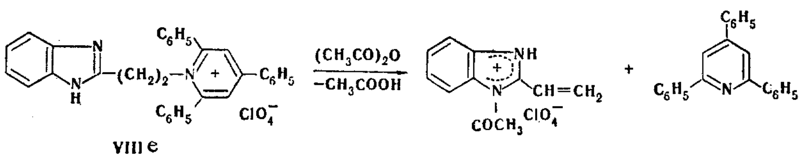
*Y = N-(2,4,6-trimethylpyridinia) perchlorate.

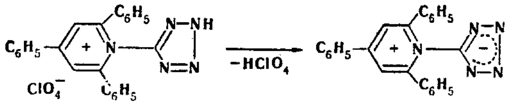
†Z = N-(2,4,6-triphenylpyridinia) perchlorate.



VIIIe

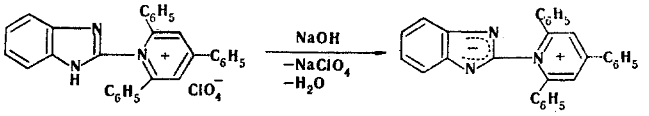
Compound VIIIf undergoes acylation at the NH group to give N-(1-acetyl-2-benzimidazolyl-3-prophy)-2,4,6-triphenylpyridinium perchlorate in 40% yield, 2,4,6-triphenylpyridine (30%), and 2-propenylbenzimidazolium perchlorate (31%).

The synthesis of N-tetrazolyl-2,4,6-triphenylpyridinium perchlorate (X) also yielded its ylid (XI), which is probably formed from X with splitting out of a molecule of perchloric acid:



X XI

We were also able to obtain ylid XII from VIIIg by refluxing it in alcoholic alkali:



VIIIg XII

Compound VIIId does not form an ylid.

EXPERIMENTAL

The pK$_a$ values were measured by potentiometric titration in absolute acetonitrile at 25 ± 0.1°C. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer.

1,6-Hexamethylenebis(N,N′-2,4,6-triphenylpyridinium) Diperchlorate (Ia). This compound was obtained by refluxing perchlorate IV and hexamethylenediamine in a molar ratio of 2 : 1 in absolute ethanol. The substance that precipitated when the mixture was cooled was removed by filtration to give a product with mp 286-287°C (from acetic acid with nitromethane) in 62% yield. Found: C 69.6; H 5.2; Cl 7.7; N 3.2%. $C_{52}H_{46}Cl_2N_2O_8$. Calculated: C 69.6; H 5.2; Cl 7.9; N 3.1%.

1,6-Hexamethylenebis(N,N′-1,3-dimethyl-6,7-dimethoxyisoquinolinium) Diperchlorate (II). This compound, with mp 300-303°C (from acetic acid with nitromethane), was obtained in 8% yield. Found: C 53.2; H 6.4; Cl 9.7; N 4.3%. $C_{32}H_{42}Cl_2N_2O_{12}$. Calculated: C 53.6; H 5.9; Cl 9.9; N 3.9%.

p-Phenylenebis(N,N'-2,4,6-triphenylpyridinium) Diperchlorate (Ic). This compound was obtained by a similar method, but DMF was used as the solvent. The product was obtained in quantitative yield and had mp > 360°C (from nitromethane). Found: C 69.8; H 4.8; Cl 8.6; N 3.6%. $C_{52}H_{38}Cl_2N_2O_8$. Calculated: C 70.2; H 4.3; Cl 8.0; N 3.2%.

1,6-Hexamethylenebis(N,N'-2,4-dimethyl-6-phenylpyridinium) Diperchlorate (Ib). This compound was obtained by refluxing 2 mmole of 2,4-dimethyl-6-phenylpyrylium perchlorate and 1 mmole of hexamethylenediamine in glacial acetic acid for 15 min. The mixture was cooled, and the salt was precipitated by the addition of ether and recrystallized from acetic acid to give a product with mp 253-254°C in 35% yield. Found: C 59.1; H 6.0; Cl 11.1; N 3.8%. $C_{32}H_{38}Cl_2N_2O_8$. Calculated: C 59.2; H 5.9; Cl 10.9; N 4.3%.

3-(2,4,6-Triphenyl-1-pyridinia)propionic Acid Perchlorate (VIa). A mixture of perchlorate IV and β-alanine in a molar ratio of 1:4 was refluxed for 30 min in 85% aqueous ethanol, after which the solvent was removed by evaporation, and the dry residue was treated with hot acetone. The acetone solution was cooled to give VIa, with mp 169-172°C (from ethanol), in 83.5% yield. Found: C 65.4; H 4.9; Cl 7.4; N 2.6%. $C_{26}H_{22}ClNO_6$. Calculated: C 65.1; H 4.6; Cl 7.4; N 2.9%. IR spectrum: 1100 (ClO_4^-), 1570, 1605, 1630, 1730, and 1750 cm^{-1}.

4-(2,4,6-Triphenyl-1-pyridinia)butyric Acid Perchlorate (VIb). This compound, with mp 215°C (from aqueous ethanol), was obtained in 78% yield. Found: C 65.6; H 5.2; Cl 7.3; N 2.7%. $C_{27}H_{24}ClNO_6$. Calculated: C 65.6; H 4.9; Cl 7.2; N 2.8%. IR spectrum: 1105, 1570, 1630, 1715, 1750 cm^{-1}.

3-(N-Collidinia)propionic Acid Perchlorate. Equimolar amounts of perchlorate III and β-alanine were refluxed for 30 min in glacial acetic acid, after which the mixture was cooled and treated with ether, and the liberated oil was washed with ether, during which it solidified. The yield of product with mp 166-168°C (from ethanol) (mp 150-152°C), was 95%. Found: C 44.6; H 5.9; Cl 11.8; N 4.9%. $C_{11}H_{16}ClNO_6$. Calculated: C 45.0; H 5.5; Cl 12.1; N 4.8%. IR spectrum: 1100, 1575, 1645, 1725 cm^{-1}.

4-(N-Collidinia)butyric Acid Perchlorate. This compound, with mp 65-67°C (from acetone with chloroform), was obtained in 63% yield. Found: C 46.5; H 6.1; Cl 11.5; N 4.2%. $C_{12}H_{18}ClNO_6$. Calculated: C 46.8; H 5.9; Cl 11.5; N 4.6%. IR spectrum: 1100, 1582, 1650, 1725 cm^{-1}.

N-(2-Benzimidazolyl-3-propyl)-2,4,6-triphenylpyridinium Perchlorate (VIIIf). A 1.24-g (2.5 mmole) sample of acid VIb and 0.27 g (2.5 mmole) of o-phenylenediamine were heated in 6 g of PPA to 150°C for 4 h, after which the mixture was cooled below 100°C and poured into a mixture of ice and water. The aqueous mixture was made alkaline to pH 8 with ammonium hydroxide, and the precipitate was removed by filtration to give 0.81 g (57%) of a product with mp 211-212°C (from acetic acid). Found: C 70.3; H 5.0; Cl 6.2; N 7.0%. $C_{33}H_{28}ClN_3O_4$. Calculated: C 70.0; H 5.0; Cl 6.3; N 7.4%. IR spectrum: 1100, 1575, 1605, 1630 cm^{-1}.

N-(2-Benzimidazolyl-β-ethyl)collidinium Diperchlorate (VIIa). This compound was obtained by refluxing N-collidinia-β-propionic acid perchlorate and o-phenylenediamine in a ratio of 1.5:1 in 5.5 N HCl for 17-19 h. The mixture was cooled, and the precipitate was removed by filtration to give a product with mp 248-250°C (from water) in 43-48% yield. Found: C 43.7; H 4.6; Cl 15.4; N 9.1%. $C_{17}H_{21}Cl_2N_3O_8$. Calculated: C 43.8; H 4.5; Cl 15.2; N 9.0%

N-(2-Benzimidazolyl-γ-propyl)collidinium Diperchlorate (VIIb). This compound, with mp 224-227°C (dec., from ethanol), was similarly obtained in 48% yield. Found: C 45.2; H 5.2; Cl 14.9; N 8.3%. $C_{18}H_{23}Cl_2N_3O_8$. Calculated: C 45.0; H 4.8; Cl 14.8; N 8.8%.

1-(1-Acetylbenzimidazolyl-2-methyl)-2,4,6-triphenylpyridinium Perchlorate. A 0.52-g (1 mmole) sample of perchlorate VIIId was refluxed for 30 min in 2 ml of acetic anhydride, after which the mixture was cooled, and the resulting precipitate was removed by filtration to give 0.36 g (62%) of the perchlorate with mp 227-229°C (from acetic anhydride). Found: C 68.5; H 4.7; Cl 6.0; N 7.0%. $C_{33}H_{26}ClN_3O_5$. Calculated: C 68.3; H 4.5; Cl 6.1; N 7.2%. IR spectrum: 1100, 1570, 1600, 1630, 1730 cm^{-1}.

Perchlorate VIIIe was similarly acylated to give 1-acetyl-2-vinylbenzimidazolium perchlorate, with mp 286-287°C (from DMF), in 43% yield. Found: C 45.8; H 4.2; Cl 12.2%. $C_{11}H_{11}ClN_2O_3$. Calculated: C 46.1; H 3.9; Cl 12.4%. IR spectrum: 1100, 1535, 1585, 1630, 1660 cm^{-1}. Perchlorate VIIIf was similarly acylated. After the mixture was cooled, it was treated with ether to liberate a viscous oil. A small amount of acetone was added, and the insoluble material was removed by filtration to give 2-propenylbenzimidazolium perchlorate, with mp 201-202°C (from acetic acid), in 31% yield. Found: C 46.8; H 4.6; Cl 13.2%. $C_{10}H_{11}ClN_2O_4$. Calculated: C 46.4; H 4.3; Cl 13.7%. IR spectrum: 1115, 1560, 1580, 1615 cm^{-1}. Treatment of the acetone solutions with ether precipitated N-(1-acetyl-2-benzimidazolyl-3-propyl)-2,4,6-triphenylpyridinium perchlorate, with mp 190-193°C (from methanol), in 40% yield. Found: C 68.7; H 5.1; Cl 5.7%. $C_{35}H_{30}ClN_3O_5$. Calculated: C 69.1; H 5.0; Cl 5.8%. IR spectrum: 1100, 1575, 1605, 1630, 1735 cm^{-1}.

1-(5-Tetrazolyl)-2,4,6-triphenylpyridinium Ylid (XI). A suspension of perchlorate X was refluxed briefly in water, after which it was worked up to give betaine XI, with mp 274-275°C (from ethanol), in 88% yield. Found: C 76.7; H 4.9; N 18.7%. $C_{24}H_{17}N_5$. Calculated: C 76.8; H 4.6; N 18.7%. IR spectrum: 1560, 1620 cm^{-1}.

1-(2-Benzimidazolyl)-2,4,6-triphenylpyridinium Ylid (XII). A mixture of perchlorate VIIIg and an equivalent amount of methanolic KOH was refluxed for 30 min, after which it was cooled, and the $KClO_4$ was removed by filtration. The filtrate was evaporated, and the dry residue was recrystallized successively from aqueous methanol and benzene to give the orange-red betaine, with mp 149-150°C, in 96% yield. Found: C 82.1; H 5.7%. $C_{30}H_{21}N_3 \cdot H_2O$. Calculated: C 81.6; H 5.3%. IR spectrum: 1563, 1605, 1630 cm^{-1}.

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REACTION OF PENTACHLOROPYRIDINE WITH SODIOACETOACETIC ESTER

S. D. Moshchitskii, A. F. Pavlenko,
and G. A. Zalesskii

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Ethyl tetrachloro-4-pyridylacetoacetates and tetrachloro-2-pyridylacetoacetates were synthesized by reaction of pentachloropyridine with sodioacetoacetic ester. Hydrolysis of ethyl tetrachloro-2-pyridylacetoacetate gives 3,4,5,6-tetrachloro-2-pyridylacetic acid rather than the corresponding acetone derivative.

Continuing our study of the reactions of pentachloropyridine with carbanions [1, 6], we investigated the reaction of pentachloropyridine with sodioacetoacetic ester. In ethanol this reaction leads to the formation of ethyl 2,3,5,6-tetrachloro-4-pyridylacetoacetate (I) (60%) and 4-ethoxy-2,3,5,6-tetrachloropyridine (20%). According to the results of gas–liquid chromatography (GLC), ethyl 3,4,5,6-tetrachloro-2-pyridylacetoacetate (II) (65%) is primarily obtained in dioxane, along with ester I (20%).

The observed differences are explained by increased dissociation of the sodioacetoacetic ester in alcohol, owing to which the carbanion attacks the 4 position, which is most sensitive to nucleophiles. Alcohol

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