REACTION OF PYRYLIUM SALTS WITH HETEROCYCLIC AMINES

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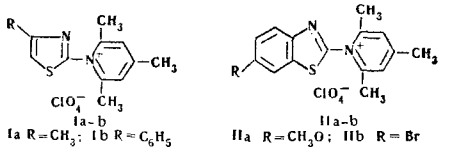
It has been established that in the reaction of 2,4,6-trimethylpyrylium perchlorate with 2-, 3-, and 4-aminopyridines, cytosine, adenine, guanine, and the corresponding nucleosides, and also with 2-amino-1-methylbenzimidazole, 2-amino-4-methylthiazole, 2-amino-4-phenylthiazole, 2-amino-6-bromobenzothiazole, and 2-amino-6-methoxybenzothiazole, either the corresponding quaternary pyridinium salt is formed or the pyrylium ring opens, depending on the basicity of the amino group.

The capacity of pyrylium salts for readily reacting with primary amines of the aliphatic and aromatic series is widely used to obtain quaternary pyridinium compounds [1]. We have shown that the brief boiling of 2,4,6-trimethylpyrylium perchlorate (TMPP) with equimolecular amounts of 2-amino-4-methylthiazole, 2-amino-4-phenylthiazole, 2-amino-6-methoxybenzothiazole, and 2-amino-6-bromobenzothiazole in ethanol of glacial acetic acid forms almost quantitative yields of quaternary pyridinium salts which, on the basis of elementary analysis and IR spectroscopy (presence of strong absorption bands of pyridinium ring at 1640–1655 and 1560–1575 cm^{-1} and also bands of the ClO_4^- anion in the 1100-cm^{-1} region) are ascribed structures I and II.



Ia-b

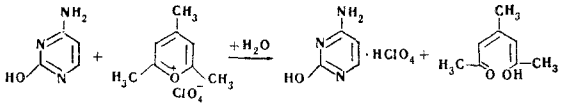
Ia R=CH_3; Ib R=C_6H_5

IIa-b

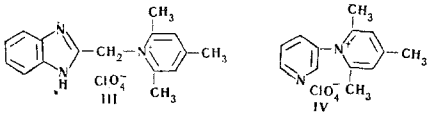
IIa R=CH_3O; IIb R=Br

When weakly basic heterocyclic amines (3-amino-1,2,4-triazole, 5-aminotetrazole, 1-aminocollidinium perchlorate [2]) were used in the reaction, only the starting materials were recovered.

In view of the previously observed [3] capacity of pyrylium salts for causing chromosomal rearrangement, experiments were instituted concerning the reaction of TMPP with the aminopurines and aminopyrimidines present in nucleic acids (cytosine, cytidine, adenine, adenosine, guanine, and guanosine). In contrast to 5-aminopyrimidines, the amino group of which is readily blocked by pyrylium salts with the formation of quaternary pyridinium salts [4], the nitrogen bases and nucleosides mentioned above do not form condensation products with TMPP (even on prolonged boiling in water, ethanol, glacial acetic acid, or dimethylformamide) but split off the anion from the pyrylium salt, and cause a concomitant opening of the pyrylium ring.



The reaction of 2- and 3-aminopyridine and 2-amino-1-methylbenzimidazole takes place in the same way, but 2-aminomethylbenzimidazole and 3-aminopyridine (which, like 5-aminopyrimidines, resembles aromatic amines) form quaternary pyridinium salts (III, IV).



III

IV

The results obtained are in harmony with the results of quantum-mechanical calculations, according to which in adenine the most basic atom is N_1, in guanine N_7, and in cytosine N_3 [5]. These atoms are reaction centers in reactions with electrophilic agents (addition of a proton [6,7] and alkylation [8,9]. In addition to this, the methylation of 2-aminopyridine [10] and 2-aminobenzimidazole [11] takes place at a ring nitrogen atom. On the basis of these facts, we

may assume that in the reaction of TMPP with the designated heterocyclic amines there is no formation of a quaternary pyridinium salt because the electrophilic attack of the pyrylium cation does not take place on the conjugated primary amino group but on the heterocyclic nitrogen atom. Consequently, pyrylium salts are incapable of reacting directly with the nucleic acids, and the chromosomal rearrangements which they induce [3] result from reaction with the proteins [12] of the chromosomes or with enzyme systems.

EXPERIMENTAL

1-(4'-Methylthiazol-2'-yl)collidinium perchlorate (Ia). A mixture of 1.14 g (0.01 mole) of 2-amino-4-methylthiazole and 2.23 g (0.01 mole) of TMPP in 10 ml of glacial acetic acid was boiled for 30 min. The cooled reaction mixture was diluted with a threefold volume of ether, and the light colored crystals were filtered off. Yield 2.7 g (85%), mp 148° C (from ethanol). Found, %: C 44.91; H 5.01; Cl 11.40; S 10.05. Calculated for $C_{12}H_{15}ClN_2O_4S$, %: C 45.21; H 4.74; Cl 11.12; S 10.05.

1-(4'-Phenylthiazol-2'-yl)collidinium perchlorate (Ib). In a manner similar to the preparation of Ia, 1.76 g (0.01 mole) of 2-amino-4-phenylthiazole and 2.23 g (0.01 mole) of TMPP in 15 ml of glacial acetic acid yielded 3.2 g (84%) of a crystalline product with mp 195° C (from ethanol). Found, %: C 53.30; H 4.32; Cl 9.12; S 8.15. Calculated for $C_{17}H_{17}ClN_2O_4S$, %: C 53.61; H 4.23; Cl 9.31; S 8.42.

1-(6'-Methoxybenzothiazol-2'-yl)collidinium perchlorate (IIa). A mixture of 0.52 g (~3 mM) of 2-amino-6-methoxybenzothiazole and 0.56 g (2.5 mM) of TMPP in 5 ml of ethanol was boiled for 3 hr. When the cooled solution was diluted with ether, a crystalline product separated out. Yield 0.9 g (94%), mp 154° C (from ethanol). Found, %: C 50.22; H 4.62; Cl 9.22; S 8.13. Calculated for $C_{16}H_{17}ClN_2O_5S$, %: C 49.93; H 4.45; Cl 9.21; S 8.33.

1-(6'-Bromobenzothiazol-2'-yl)collidinium perchlorate (IIb). A mixture of 1.14 g (5 mM) of 2-amino-6-bromobenzothiazole and 1.12 g (5 mM) of TMPP in 5 ml of acetic acid was boiled for 1 hr 30 min. After standing for a day at room temperature, the reaction mixture was filtered from the unchanged TMPP. On dilution with ether, the filtrate deposited a syrup, which crystallized in the course of a day, giving 0.6 g (27%) of product. Light colored needles, mp 190° C (from ethanol). Found, %: C 41.32; H 3.51; Cl 8.17; S 7.11. Calculated for $C_{15}H_{14}ClBrN_2O_4S$, %: C 41.07; H 3.25; Cl 8.17; S 7.39.

Benzimidazol-2'-ylmethylcollidinium perchlorate (III). A mixture of 1.47 g (0.01 mole) of 2-aminomethylbenzimidazole and 2.23 g (0.01 mole) of TMPP was boiled in 15 ml of glacial acetic acid for 20 min. When the reaction mixture was diluted with ether a syrup deposited, which crystallized giving 3.4 g (96%) of a product with mp 210° C (from water). Found, %: C 54.93; H 5.42; Cl 9.99. Calculated for $C_{16}H_{18}ClN_3O_4$, %: C 54.62; H 5.15; Cl 10.07.

1-(Pyridin-3'-yl)collidinium perchlorate (IV). A solution of 0.9 g (~0.01 mole) of 3-aminopyridine in 6 ml of glacial acetic acid was treated with 2.23 g (0.01 mole) of TMPP, and the mixture was boiled for 30 min. The cooled solution was filtered from a resin and was highly diluted with ether. The syrup that deposited was dissolved in 5 ml of water and the solution was acidified with $HClO_4$ and extracted with ether. The aqueous solution was evaporated under vacuum. The residual syrup was dissolved in hot ethanol and, on cooling, colorless needles deposited. The yield of IV was 0.7 g (23%), mp 208° C (from ethanol). Found, %: C 52.34; H 4.78; Cl 12.25. Calculated for $C_{13}H_{15}ClN_2O_4$, %: C 52.26; H 5.06; Cl 11.86.

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