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SYNTHESIS AND SPECIAL FEATURES OF THE STRUCTURE OF 6(7)-AMINOPERIMIDINE DERIVATIVES

A. V. Aksenov[1]*, A. S. Lyakhovnenko[1], N. C. Karaivanov[1], and I. I. Levina[2]

A method of synthesizing 6(7)-aminoperimidines has been developed based on the electrophilic amination of perimidines with sodium azide in PPA. The corresponding amides were synthesized by acylation and were also obtained by the Schmidt reaction from 6(7)-acetyl(or benzoyl)perimidines. A special feature of the structure of the 2-substituted amines and amides is the presence of annular tautomerism slow in NMR time.

Keywords: sodium azide, 6(7)-aminoperimidines, perimidine, PPA (polyphosphoric acid), amination, Schmidt reaction.

Aromatic amines serve as important synthetic building blocks. The standard method of synthesizing them is sequential nitration and then reduction of the nitro compound formed at the first stage [1]. Direct one-step amination is known, however it proceeds only in low yield [1, 2], since in many cases the initial aromatic compound is used as solvent. Hydroxylamine [3, 4], alkylhydroxylamines [5], hydroxylamine O-sulfonic acid [6], and hydrazoic acid [7] in the presence of a Lewis acids are used as aminating reagents. More recently Olah has used hydrazoic acid [8] and trimethylsilyl azide [9] in the presence of a superacid for these purposes. The latter system is the most efficient, the yield was ~90% calculated on azide, but as a result of using a large excess of aromatic compound the degree of conversion of the latter does not exceed 10%.

In the present work we propose a method of aminating perimidines based on a new reactant system, sodium azide – PPA (for preliminary communication see [10]).

We have proposed that the PPA azide **1** will be formed as a result of the reaction of sodium azide with PPA, which may be protonated both at the nitrogen atom *a* and also *b* with the formation of two tautomeric cations **2**. As the result of azocoupling of the latter with perimidines **3a-c** the intermediates **4a-c** will be formed, the hydrolysis of which leads to a mixture of tautomers of amines **5a-c** and **6a-c**.

* To whom correspondence should be addressed, e-mail: biochem-org@stavsu.ru.

[1]Stavropol State University, Stavropol 355009, Russia.
[2]N. M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Moscow 119991, Russia; e-mail: iilevina@rambler.ru.

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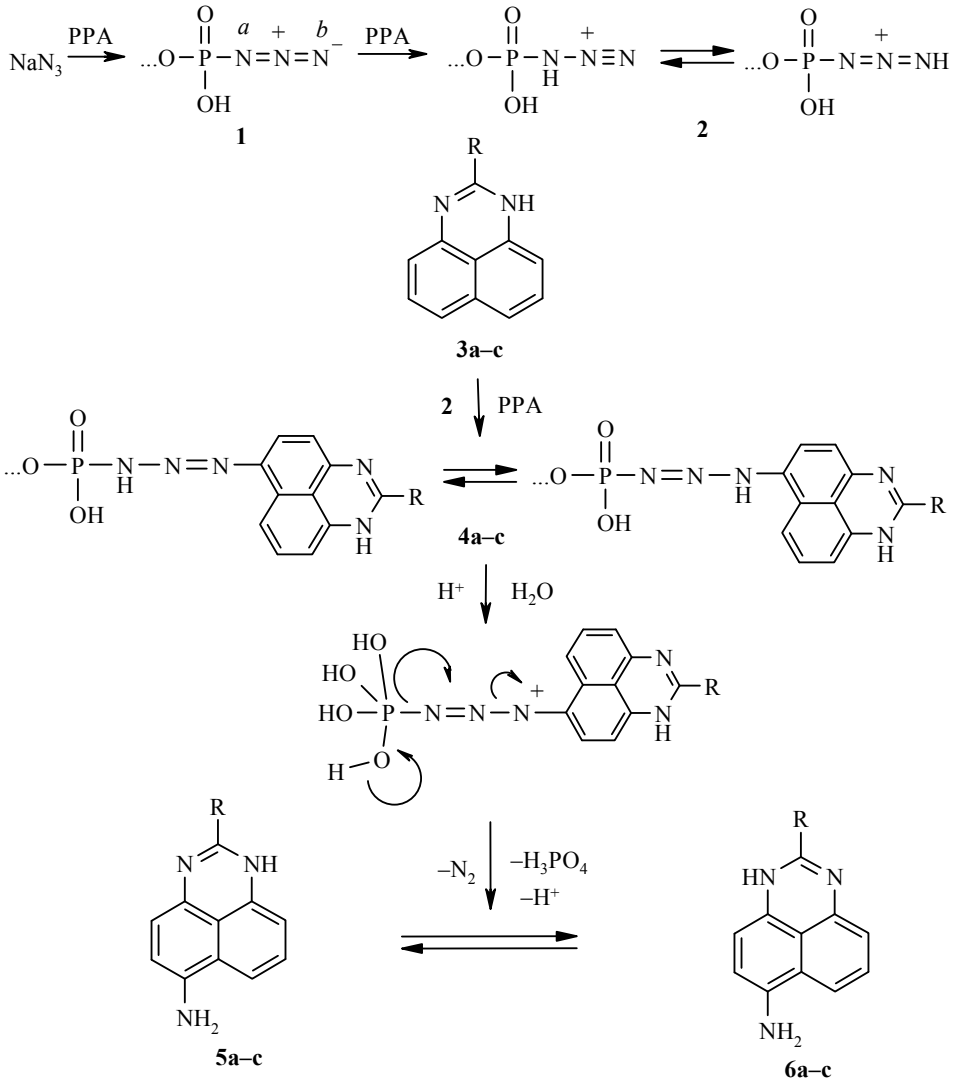


3–6 a R = H, **b** R = Me, **c** R = Ph

In fact the reaction of perimidines **3a-c** with a threefold excess of sodium azide in PPA* leads to a mixture of the tautomeric amines **5a-c** and **6a-c** in 62-76% yield.

The special feature of the structure of 2-substituted amines is the presence of annular tautomerism slow in NMR time. In the ^{1}H NMR spectrum of a mixture of tautomers **5b** and **6b** of 6(7)-amino-2-methylperimidine the signals of the protons in positions 4 and 6 have one broadened signal, which on heating to 100°C is converted into two doublets. In the presence of the more bulky phenyl substituent the signals of both tautomers **5c** and **6c** (see Fig. 1) were observed in the ^{1}H NMR spectrum at 50°C. On heating to 70°C the signals were broadened, but at 100°C four averaged signals were observed. A similar phenomenon was observed previously for 2-trifluoromethylperimidine-6(7)-carbaldehydes [12] and is linked with the presence of electron-withdrawing substituents. In our opinion the presence of a bulky substituent in position 2, which prevents cleavage of proton by the solvent, is most important. A donor or acceptor substituent in position 6(7) may either reduce the basicity (increase the acidity) or increase the basicity (reduce the acidity) and hinder transfer of proton in this way.

*PPA with a 86% content of P_2O_5 was used; obtained by the procedure of [11].

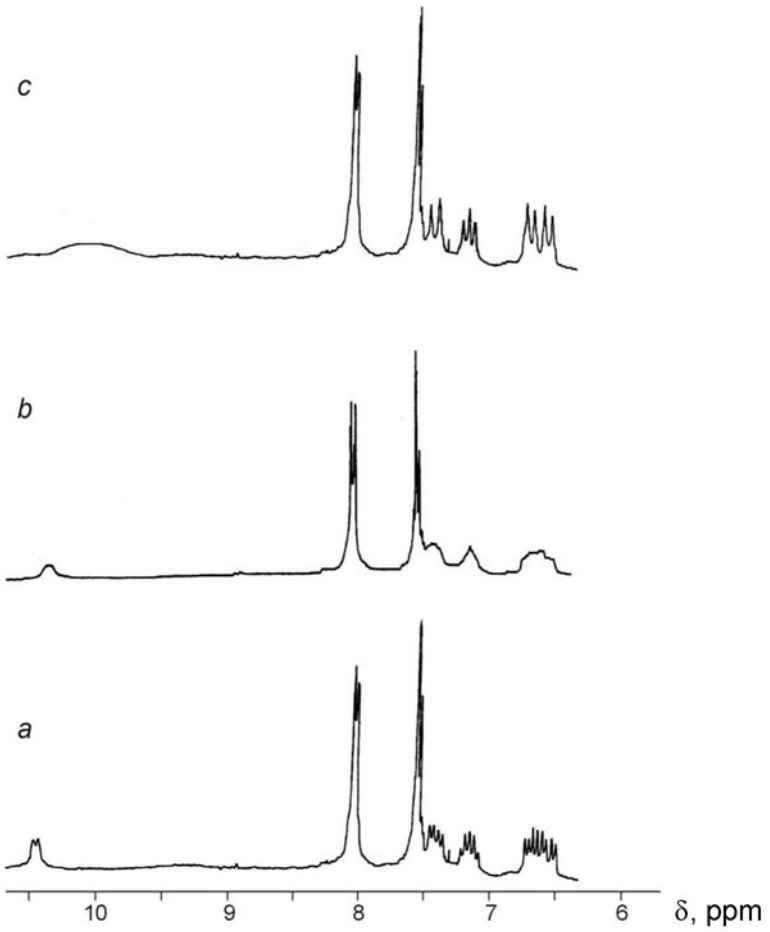
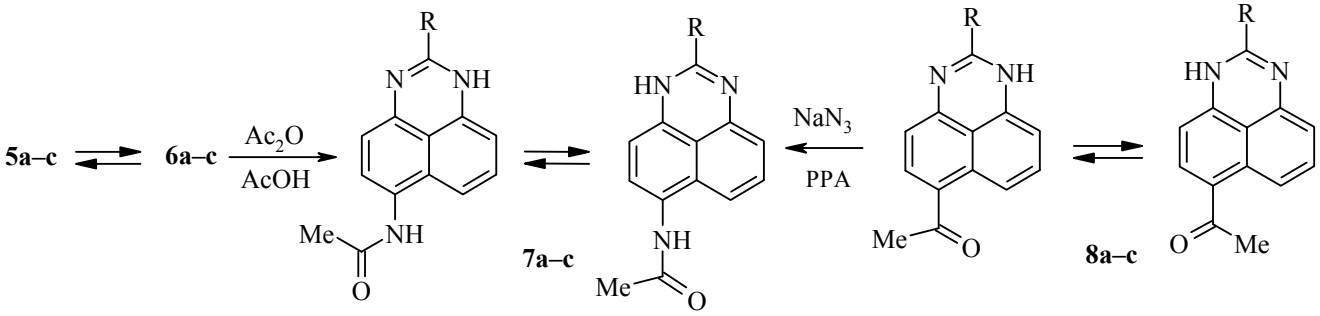


Fig. 1. Fragments of the ^{1}H NMR spectra of mixtures of tautomers of 6-amino- (**5c**) and 7-amino-2-phenylperimidine (**6c**) obtained at *a* – 50, *b* – 70, and *c* – 100°C.

We further synthesized the acetyl derivatives **7** by reacting amines **5(6)** with acetic anhydride in acetic acid, and also from 6(7)-acetylperimidines **8a-c** by the Schmidt reaction.



a R = H, **b** R = Me, **c** R = Ph

Broadening of the signals of protons in positions 4 and 9 was observed in the ^{1}H NMR spectra of compounds **7b,c** at room temperature. In the ^{13}C NMR spectrum of amide **7b** the signals of the C-4 and C-9 atoms were absent. On heating to 100°C the broadened signal was converted into two doublets and signals of the corresponding carbon atoms appeared.

In the presence of an acetamide group, which is less donating than an amino group, the tautomerism is therefore slowed to a lesser extent.

EXPERIMENTAL

The NMR spectra were recorded on Bruker instruments, WP 200 (200 MHz) for compounds **5(6)a-c** and JNM-ECX 400 (^{1}H and ^{13}C, 400 and 100 MHz respectively) for compounds **7a-c** in DMSO-d_6, internal standard was TMS. A check on the progress of reactions and the homogeneity of the synthesized compounds was carried out on Silufol UV-254 plates in the system ethyl acetate–alcohol, 3:1.

Amination of Perimidines (General Method). A mixture of perimidine **3a-c** (1 mmol) and sodium azide (0.13 g, 2 mmol) in PPA (2-3 g) was heated for 2 h at 70-80°C with vigorous stirring. If all the starting material had not reacted (check by TLC) then further sodium azide (0.65 g, 1 mmol) was added and the mixture heated for 2 h more. The mixture was then poured into water (50 ml), neutralized with ammonia solution, the precipitated solid was filtered off, dried, and purified by recrystallization from ethyl acetate.

6(7)-Aminoperimidine (5(6)a). Yield 0.114 g (62%); mp 261-262°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.30 (2H, br. s, NH_2); 6.35 (1H, d, *J* = 7.9, H-4(9)); 6.40 (1H, d, *J* = 7.3, H-9(4)); 7.07 (1H, dd, *J* = 8.6, *J* = 7.3, H-8(5)); 7.27 (1H, s, H-2); 7.32 (1H, d, *J* = 7.9, H-5(8)); 7.96 (1H, d, *J* = 8.6, H-7(6)); 10.44 (1H, br. s, NH). Found, %: C 72.68; H 4.37; N 22.95. $C_{11}H_9N_3$. Calculated, %: C 72.51; H 4.43; N 23.06.

6(7)-Amino-2-methylperimidine (5(6)b). Yield 0.136 g (69%); mp 274-275°C (ethyl acetate). Dihydrochloride: mp >310°C [13]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (3H, s, CH_3); 3.40 (2H, br. s, NH_2); 6.35 (2H, br. m, H-4(9), 9(4)); 7.05 (1H, dd, *J* = 8.8, *J* = 7.3, H-8(5)); 7.31(1H, d, *J* = 7.6, H-5(8)); 7.91 (1H, d, *J* = 8.8, H-7(6)); 10.43 (1H, br. s, NH). Found, %: C 73.22; H 5.58; N 21.20. $C_{12}H_{11}N_3$. Calculated, %: C 73.07; H 5.62; N 21.31.

6(7)-Amino-2-phenylperimidine (5(6)c). Yield 0.197 g (76%); mp 288-289°C (ethyl acetate). Found, %: C 78.92; H 4.98; N 16.10. $C_{17}H_{13}N_3$. Calculated, %: C 78.74; H 5.05; N 16.21.

6-Amino-2-phenylperimidine (6c). ^{1}H NMR spectrum, δ, ppm (*J*, Hz); 3.40 (2H, br. s, NH_2); 6.57 (1H, d, *J* = 7.7, H-9); 6.64 (1H, d, *J* = 8.0, H-4); 7.12 (1H, dd, *J* = 8.8, *J* = 7.7, H-8); 7.42 (1H, d, *J* = 8.0, H-5); 7.54 (3H, m, 3,4,5-C_6H_5); 8.03 (3H, m, 2,6-C_6H_5, H-7); 10.47 (1H, br. s, NH).

7-Amino-2-phenylperimidine (6c). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.40 (2H, br. s, NH_2); 6.50 (1H, d, *J* = 7.7, H-4); 6.71 (1H, d, *J* = 7.8, H-9); 7.18 (1H, dd, *J* = 8.8, *J* = 7.7, H-5); 7.35 (1H, d, *J* = 7.8, H-8); 7.54 (3H, m, 3,4,5-C_6H_5); 8.03 (3H, m, 2,6-C_6H_5, H-7); 10.43 (1H, br. s, NH).

Synthesis of Amides 7a-c (General Method). A. Acetic anhydride (0.153 g, 1.5 mmol) in acetic acid (3 ml) was added to a solution of amine **5(6)** (1mmol) in acetic acid (5 ml). The mixture was left for 1 h at room temperature, after which it was poured into water (50 ml), neutralized with ammonia solution, and extracted with butyl alcohol (3×30 ml). The solvent was evaporated, and the residue purified by recrystallization.

B. A mixture of acetylperimidine **8a-c** (1 mmol) and sodium azide (0.13 g, 2 mmol) in PPA (2-3 g) was heated at 50-60°C with vigorous stirring for 1 h, poured into water (50 ml), neutralized with ammonia solution, and extracted with butyl alcohol (3×30 ml). The solvent was evaporated, and the residue purified by recrystallization.

6(7)-Acetylaminoperimidine (7a). Yield 94% (A), 86% (B); mp 225-226°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (3H, s, $COCH_3$); 6.43 (2H, m, H-4(9), 9(4)); 7.03 (1H, d, *J* = 8.5, H-7(6)); 7.15 (1H, dd, *J* = 8.5, *J* = 7.3, H-8(5)); 7.24 (1H, d, *J* = 8.1, H-7(6)); 7.32 (1H, s, H-2); 9.21 (1H, br. s, NHCO); 10.61 (1H, br. s, NH). Found,%: C 69.45; H 4.86; N 18.61. $C_{13}H_{11}N_3O$. Calculated, %: C 69.32; H 4.92; N 18.65.

6(7)-Acetylamino-2-methylperimidine (7b). Yield 95% (A), 88% (B); mp 247-248°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3); 2.07 (3H, s, $COCH_3$); 6.43 (2H, br. m, H-4(9),

9(4)); 7.02 (1H, d, *J* = 8.2, H-7(6)); 7.15 (1H, dd, *J* = 8.2, *J* = 7.3, H-8(5)); 7.24 (1H, d, *J* = 8.3, H-7(6)); 9.14 (1H, br. s, NHCO); 10.5 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.34, 23.41, 107.59, 107.63, 114.41, 114.64, 121.92, 125.14, 126.29, 128.75, 141.55, 154.58, 162.79, 169.22. Found, %: C 70.43; H 4.42; N 17.52. $C_{14}H_{13}N_3O$. Calculated, %: C 70.28; H 5.48; N 17.56.

6(7)-Acetylamino-2-phenylperimidine (7c). Yield 93% (A), 84% (B); mp 302-303°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.09 (3H, s, $COCH_3$); 6.67 (2H, br. m, H-4(9), 9(4)); 7.11 (1H, d, *J* = 8.4, H-7(6)); 7.21 (1H, dd, *J* = 8.4, *J* = 7.3, H-8(5)); 7.34 (1H, d, *J* = 8.0, H-7(6)); 7.54 (3H, m, 3,4,5-C_6H_5); 8.03 (2H, d, *J* = 7.7, 2,6-C_6H_5); 9.19 (1H, br. s, NHCO); 10.5 (1H, br. s, NH). Found, %: C 75.91; H 4.98; N 13.89. $C_{19}H_{15}N_3O$. Calculated, %: C 75.73; H 5.02; N 13.94.

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