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Synthesis of 9-Aryl-6-aminopurines from 5-Amino-1-aryl-1*H*-imidazole-4-carbonitriles

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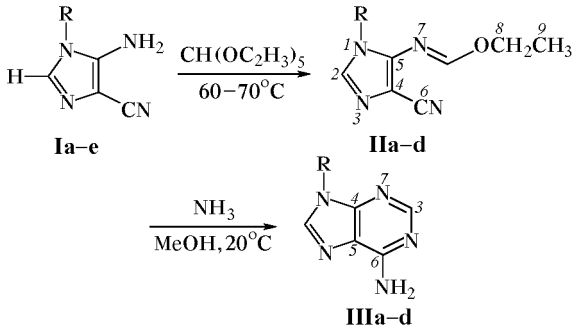
Abstract—5-Amino-1-aryl-1*H*-imidazole-4-carbonitriles were converted into 9-aryl-6-aminopurines via imidates formation at treating with $CH(OEt)_3$ and Ac_2O followed by reaction with ammonia.

Purine, purines nucleosides, and their analogs are valuable antitumor medicines [1–4]. In 1964 Robins considered in a review the antitumor activity of the purine and purine nucleosides from the viewpoint of a structure–activity relation [5]. Several reviews on this problem were published later [6–9]. The chemotherapeutic application of purines and their analogs encouraged the growth of research on their synthesis both in theoretical aspect and in pharmaceutical industry.

1-Amino-6-iminopurines and 6-hydrazinopurines are potential chemotherapeutical agents which are poorly understood up till now [10, 11]. We used the transformations shown further in the synthesis of 9-arylpurines.



Ia–e **IIa–d** **IIIa–d**

R = 2-$ClC_6H_4CH_2$ (**a**), 3,4-$(CH_3O)_2C_6H_3CH_2$ (**b**), 3,4-$(CH_3O)_2C_6H_3$ (**c**), 4-$CH_3OC_6H_4$ (**d**).

The initial stage involved the conversion of 5-amino-1*H*-imidazole-4-carbonitriles [12, 13] into the corresponding ethoxyimidates **IIa–d**. This was performed with the use of procedure [14, 15] modified by heating the appropriate cyanoamine with triethyl orthoformate for several hours.

After complete consumption of the initial reagent (TLC monitoring) the solution obtained was evaporated in a vacuum, the residue was treated with a mixture of ethyl ether–hexane, 1 : 1, and thus imidate **II** was prepared in good yield. Compound **IIa** was used in the next stage without additional purification; all the other imidates **II** were recrystallized from ethyl ether–hexane (1 : 1).

In all cases (again except compound **IIa**) the results of microanalysis and mass spectrometry were satisfactory. In the IR spectra of compounds **IIb–d** the absorption bands of stretching vibrations of C≡N and C=N groups were observed at 2210–2220 and 1630–1650 cm^{-1} respectively.

In the ^1H NMR spectra of ethoxyimidates **IIb–d** the signal of proton H^2 from the imidazole ring appeared in the region δ 7.26–8.28 ppm, that of proton H^7 at δ 8.28–8.66 ppm. The accurate quartet and triplet from CH_2 and CH_3 groups of the ethoxy substituent were observed respectively as expected at 4.31–4.50 and 1.32–1.55 ppm.The other signals were in conformity with the assumed structures of compounds **IIb–d**. The ^{13}C NMR spectra of imidazoles **IIb–d** also contained the expected set of signals: peak from carbon C^2 of the imidazole ring appeared at 135–140.9, of carbon C^7 at 159.9–165.5, and of carbon C^4 at 98.9–103.0 ppm.

Imidates **IIa–d** were converted into the corresponding 6-amino-9-arylpurines **IIIa–d** by treating with ammonia in a minimum amount of methanol. The reactions were carried out at room temperature under argon atmosphere. Within the first 20 min of reaction started precipitation of a white solid. In 2–3 h TLC monitoring revealed the absence of the initial reagent, The reaction mixture was filtered to isolate the powder product in 67–93% yield. Purines **IIIa–d** were characterized by microanalysis and spectral methods. The elemental analyses and mass spectra of 6-amino-9-arylpurines **IIIa–d** were adequate.

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In the IR spectra the stretching vibrations of NH groups were observed as 3–4 bands in the region 3300–3095 cm^{-1}, and the absorption of C=N bonds appeared in the region 1660–1650 cm^{-1}. In the ^1H NMR spectra the proton signals from NH_2 group were located in the region 5.68–5.94 ppm, the peak of proton H^2 from purine system appeared at 8.18–8.50 ppm, and the proton H^8 gave rise to a singlet at 8.08–8.38 ppm.

EXPERIMENTAL

^1H NMR spectra were registered on spectrometers Hitachi–Perkin–Elmer R24B (60 MHz) or Bruker XL 300 (300 MHz). Coupling constants *J* are given in Hz. ^{13}C NMR spectra (in DEPT 125 mode) were measured on spectrometer Bruker WP80 or Bruker XL 300. IR spectra were recorded on spectrophotometer Shimadzu IR-435. Mass spectra were taken on Kratos Concept instrument. Melting points were measured on a digital device Electrothermal and were reported uncorrected.

1-Aryl-5-[(ethoxymethylidene)amino]-1*H*-imidazole-4-carbonitriles IIa–d. A mixture of 5-amino-1-aryl-4-cyanoimidazole (0.5 g), triethyl orthoformate (1 mol-equiv) and acetic anhydride (6 mol-equiv) was cautiously heated to 60–70°C for several hours under argon atmosphere. On completion of initial product consumption (TLC monitoring) the obtained yellow-brown solution was evaporated in a vacuum. The residue was treated with a mixture of anhydrous ether and hexane (1:1). The separated precipitate was filtered off, washed with the same solvent mixture, and dried in a vacuum.

1-(2-Chlorobenzyl)-5-[(ethoxymethylidene)-amino]-1*H*-imidazole-4-carbonitrile (IIa). On evaporation of the yellow-brown solution in a vacuum an oily compound was obtained which was used in the second stage of reaction without further purification.

1-(3,4-Dimethoxybenzyl)-5-[(ethoxymethylidene)-amino]-1*H*-imidazole-4-carbonitrile (IIb). On recrystallization of the reaction product from a mixture ethyl ether–hexane (1:1) we obtained 0.53 g (87%) of compound **IIb** as pale yellow crystals, mp 87–88°C. IR spectrum, ν, cm^{-1}: 2210 s (C≡N), 1635 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.26 (H^2), 8.30 (H^7), 4.31 (H^8), 1.32 (H^9), 3.78 (2 OMe), 3.80 s (3H, OCH_3), 4.90 s (2H, H^{10}), 6.62 d (1H, H^{16}, $^4J_{12,16}$ 2 Hz), 6.68 d.d (1H, H^{12}, $^3J_{12,13}$ 8, $^4J_{12,16}$ 2 Hz), 6.78 d (1H, H^{13}, $^3J_{13,12}$ 8 Hz). ^{13}C NMR spectrum, δ, ppm: 135.4 (C^2), 98.9 (C^4), 149.5 (C^5), 116.1 (C^6), 159.9 (C^7), 14.0 (C^9), 47.8 (C^{10}), 55.9 and 56.0 (C^{17} and C^{18}), 63.9 (C^8), 110 and 111.4 (C^{13} and C^{16}), 120.4 (C^{12}), 127.5 (C^{11}). Found, %: C 59.8; H 5.5; N 18.4. $C_{16}H_{18}N_4O_3$. Calculated, %: C 60.0; H 5.3; N 18.7. Mass spectrum, *m/z*: 315 $(M + 1)^+$. M_{calc} 314.

1-(3,4-Dimethoxyphenyl)-5-[(ethoxymethylidene)amino]-1*H*-imidazole-4-carbonitrile (IIc). On recrystallization of the reaction product from a mixture ethyl ether–hexane (1:1) we obtained 0.48 g (79%) of compound **IIb** as pale yellow crystals, mp 104–106°C. IR spectrum, ν, cm^{-1}: 2215 s (C≡N), 1630 s (C=N). ^1H NMR spectrum, δ, ppm: 8.28 (H^2), 8.70 (H), 4.50 (H), 1.55 (H), 4.03 s (3H, OMe), 4.05 s (3H, OMe), 7.30 d.d (1H, H^{11}, $^3J_{11,12}$ 8, $^4J_{11,15}$ 2 Hz), 7.38 d (1H, H^{12}, $^3J_{12,11}$ 8 Hz), 7.42 d (1H, H^{15}, $^4J_{15,11}$ 2 Hz). ^{13}C NMR spectrum, δ, ppm: 140.9 (C^2), 103.0 (C^4), 149.6 (C^5), 120.2 (C^6), 165.5 (C^7), 17.9 (C^9), 49.9 (C^{16} and C^{17}), 67.8 (C^8), 113.5 and 115.7 (C^{12} and C^{15}), 121.3 (C^{11}), 131.0 (C^{10}), 152.9 (C^{13} and C^{14}). Found, %: C 59.8; H 5.5; N 18.4. $C_{15}H_{16}N_4O_3$. Calculated, %: C 60.0; H 5.3; N 18.7. Mass spectrum, *m/z*: 301 $(M + 1)^+$. M_{calc} 300.

1-(4-Methoxyphenyl)-5-[(ethoxymethylidene)-amino]-1*H*-imidazole-4-carbonitrile (IId). On recrystallization of the reaction product from a mixture ethyl ether–hexane (1:1) we obtained 0.54 g (86%) of compound **IIb** as pale colorless crystals, mp 82–83°C. IR spectrum, ν, cm^{-1}: 2220 s (C≡N), 1650 s (C=N). ^1H NMR spectrum, δ, ppm: 8.10 (H^2), 8.55 (H^7), 4.34 (H^8), 1.38 (H^9), 3.94 (OMe), 7.22 d (2H, H^{12} and H^{14}, $^3J_{12,11}$ 9 Hz), 7.54 d (2H, H^{11} and H^{15}, $J_{11,12}$ 9 Hz). ^{13}C NMR spectrum, δ, ppm: 140.6 (C^2), 102.8 (C^4), 149.5 (C^5), 120.0 (C^6), 165.3 (C^7), 17.7 (C^9), 59.4 (C^{16}), 67.7 (C^8), 118.4 (C^{12} and C^{14}), 130.7 (C^{11} and C^{15}), 131.1 (C^{10}), 163.1 (C^{13}). Found, %: C 62.3; H 5.2; N 20.7. $C_{14}H_{14}N_4O_2$. Calculated, %: C 62.2; H 5.2; N 20.7. Mass spectrum, *m/z*: 271 $(M + 1)^+$. M_{calc} 270.

6-Amino-9-arylpurines IIIa–d. To a stirred solution of 1-aryl-4-cyano-5-[(ethoxymethylene)amino]-imidazole **IIa–d** (0.3 g) in anhydrous methanol (8–10 ml) was added under argon atmosphere at room temperature 1 mol-equiv of ammonia. In 15–20 min the separated precipitate was filtered off, washed with a mixture of anhydrous ethyl ether–hexane (1:1), and dried in a vacuum.

6-Amino-9-(2-chlorobenzyl)purine (IIIa). Along the above procedure compound **IIIa** was obtained as colorless solid. After recrystallization from a mixture of anhydrous ethyl ether with hexane (1:1) we obtained crystalline compound **IIIa** in 67% yield, mp 168–

170°C. IR spectrum, cm^{-1}: 3300 m, 3285 s, 3150 m, 3140 s, 3095 s ν(N–H); 1650 s ν(C=N), 1600 s δ(N–H). ^1H NMR spectrum, δ, ppm: 8.26 (H^2), 8.22 (H^8), 5.68 (H^{10}), 5.94 (NH_2), 7.25 d.d (1H, H^{16}, $^3J_{16,15}$ 7, $^4J_{16,14}$ 1 Hz), 7.63–7.60 d.d.t (2H, H^{14} and H^{15}, $^4J_{14,16}$ 2, $^3J_{14,13}$ 8 Hz), 7.8 d.d (1H, H^{13}, $^3J_{13,14}$ 7, $^4J_{13,15}$ 1 Hz). ^{13}C NMR spectrum, δ, ppm: 152 (C^2), 146 (C^4), 126 (C^5), 158.2 (C^6), 144 (C^8), 48.5 (C^{10}), 131.8 (C^{15}), 133.1 (C^{16}), 133.7 (C^{14}), 133.8 (C^{13}), 136.0 (C^{12}), 138.0 (C^{11}). Found, %: C 55.6; H 4.1; N 27.4; Cl 13.1. $C_{12}H_{10}N_5Cl$. Calculated, %: C 55.6; H 3.9; N 27.0; Cl 13.5. Mass spectrum, *m/z*: $(M + 1)^+$ 260. M_{calc} 259.

6-Amino-9-(3,4-dimethoxybenzyl)purine (IIIb) was obtained as colorless solid. After recrystallization from a mixture of toluene with ethanol (1 : 1) we obtained 0.22 g (83%) of colorless crystals of compound **IIIb**, mp 172–174°C. IR spectrum, cm^{-1}: 3300 s, 3210 m, 3100 s ν(N–H); 1660 ν(C=N), 1605 m δ(N–H). ^1H NMR spectrum, δ, ppm: 8.18 (H), 810 (H), 5.25 (H), 5.72 (H), 3.78 (2 OMe), 6.86 d (1H, H^{13}, $^3J_{13,12}$ 8 Hz), 6.95 d.d (1H, H^{12}, $^3J_{12,13}$ 8, $^4J_{12,16}$ 2 Hz), 7.12 d (1H, H^{16}, $^4J_{16,12}$ 2 Hz). ^{13}C NMR spectrum, δ, ppm: 152 (C^2), 145 (C^4), 126 (C^5), 158.2 (C^6), 143 (C^8), 50.3 (C^{10}), 59.6 (C^{17} and C^{18}), 115.7, 115.9, 124.1 (C^{12}, C^{13} and C^{16}), 133.3 (C^{11}), 152.5 and 152.8 (C^{14} and C^{15}). Found, %: C 58.7; H 5.2; N 24.5. $C_{14}H_{15}N_5O_2$. Calculated, %: C 58.9; H 5.3; N 24.6. Mass spectrum, *m/z*: 286 $(M + 1)^+$. M_{calc} 285.

6-Amino-9-(3,4-dimethoxyphenyl)purine (IIIc) was obtained in the same way as colorless solid. After recrystallization from a mixture of toluene with ethanol (1 : 1) we obtained 0.23 g (85%) of colorless crystals of compound **IIIc**, mp 190–192°C. IR spectrum, cm^{-1}: 3290 m, 3230 s, 3110 m ν(N–H); 1655 s ν(C=N), 1605 m δ(N–H). ^1H NMR spectrum, δ, ppm: 8.26 (H), 8.08 (H), 5.68 (H), 3.78 (2 OMe), 7.08 d (1H, H^{15}, $^4J_{15,11}$ 2 Hz), 7.20 d.d (1H, H^{11}, $^3J_{11,12}$ 8, $^4J_{11,15}$ 2 Hz), 7.28 d (1H, H^{12}, $^3J_{12,11}$ 8 Hz). ^{13}C NMR spectrum, δ, ppm: 152 (C^2), 145 (C^4), 127 (C^5), 160 (C^6), 143 (C^8), 59.8 (C^{16} and C^{17}), 112.1 (C^{15}), 115.9 (C^{12}), 119.8 (C^{11}), 131.6 (C^{10}), 135.0 (C^{13}), 152.1 (C^{14}). Found, %: C 57.5; H 4.8; N 25.4. $C_{13}H_{13}N_5O_{12}$. Calculated, %: C 57.6; H 4.8; N 25.8. Mass spectrum, *m/z*: 272 $(M + 1)^+$. M_{calc} 271.

6-Amino-9-(4-methoxyphenyl)purine (IIId). Along the above procedure compound **IIId** was obtained as colorless solid. After recrystallization from a mixture of anhydrous ethyl ether with hexane (1 : 1) we obtained 0.24 g (93%) of colorless crystals of compound **IIId**, mp 197–199°C. IR spectrum, cm^{-1}: 3310 br, 3260 s, 3185 s, 3120 m ν(N–H); 1650 s ν(C=N), 1600 s δ(N–H). ^1H NMR spectrum, δ, ppm: 8.50 (H), 8.38 (H), 5.82 (H), 3.98 (OMe), 7.20 d (2H, H^{12} and H^{13}, $^3J_{12,11}$ 8.5 Hz), 8.10 d (2H, H^{11} and H^{14}, $^3J_{11,12}$ 8.5 Hz). ^{13}C NMR spectrum, δ, ppm: 153 (C^2), 147 (C^4), 130 (C^5), 163.2 (C^6), 143 (C^8), 59.6 (C^{15}), 118.7 (C^{12} and C^{14}), 129.5 (C^{11} and C^{15}), 132.9 (C^{10}), 166.4 (C^{13}). Found, %: C 59.5; H 4.6; N 28.9. $C_{12}H_{11}N_5O$. Calculated, %: C 59.8; H 4.6; N 29.0. Mass spectrum, *m/z*: 242 $(M + 1)^+$. M_{calc} 241.

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