Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2197–2202

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

REACTIONS OF 7- AND 9-AMINOADENINES WITH 2,4-PENTANEDIONE. FORMATION OF NEW RING SYSTEMS, PYRIDAZINO[6,1-*f*]PURINE AND PYRIDAZINO[1,6-*e*]PURINE

Toyo Kaiya, Tetsuya Saga, Yuriko Yamagata,[a] and Kohfuku Kohda*

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabedori, Mizuho-ku, Nagoya 467, Japan and [a]Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka, Suita, Osaka 565, Japan

Received 16 June 1998; accepted 13 July 1998

Abstract: Reactions of 7-aminoadenines with 2,4-pentanedione yielded pyridazino[6,1-*f*]purines and 5-pyrazolylpyrimidines. The structure of the latter was identified by X-ray analysis. Reaction of 9-amino-N^6-methyladenine with 2,4-pentanedione gave pyridazino[1,6-*e*]purine and Schiff base products. Possible reaction mechanisms are discussed.

INTRODUCTION

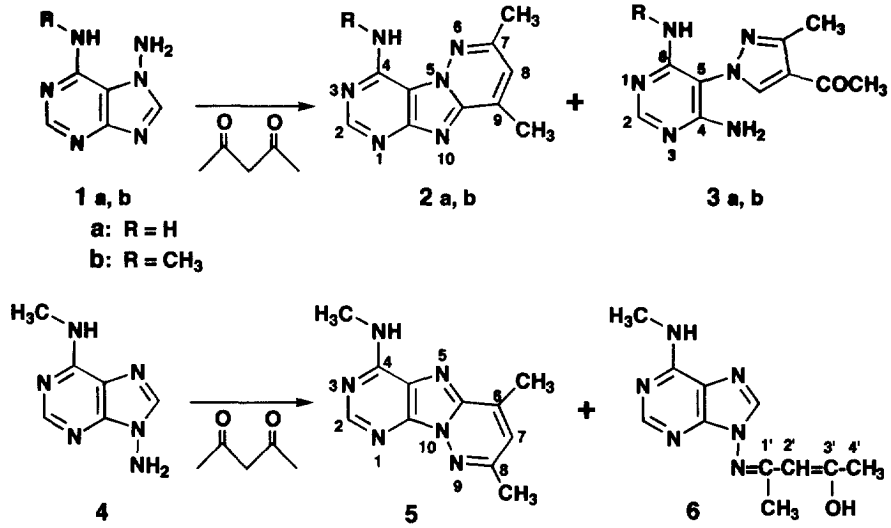
We have carried out extensive studies on simple electrophilic amination of nucleic acid components in connection with chemical carcinogenesis by arylaminating carcinogens.[1-14] So far, we have obtained ring-nitrogen mono aminated bases and nucleosides of all nucleic acid components.[2,4,7,11] We also have examined the chemical characteristic,[4,6,7,9,11,13] reactivity[3,5,8,10,12] and bioactivity[14] of *N*-aminated derivatives. This study was carried out to obtain compounds with new three ring systems by utilizing the *N*-amino group. N7- and N9-aminoadenines were used as starting materials and were allowed to react with 2,4-pentanedione. The reaction gave pyridazinopurines, the new three ring system compounds, and pyrazolylpyrimidines and Schiff base products. The pyridazinopurines and the pyrazolylpyrimidines may be formed by ring closure of the Schiff base and by ring closure and subsequent imidazole ring opening, respectively.

RESULTS AND DISCUSSION

Reaction of 7-aminoadenine (**1a**) with 2,4-pentanedione in the presence of $ZnCl_2$ under refluxed temperature gave 4-amino-7,9-dimethylpyridazino[6,1-*f*]purine (**2a**) and 5-(4-acetyl-3-methyl)pyrazolyl-4,6-diamino-pyrimidine (**3a**) in 46% and 14% yield, respectively (Scheme 1). Similarly the reaction of 7-amino-N^6-methyladenine (**1b**) with 2,4-pentanedione gave 7,9-dimethyl-4-methylaminopyridazino[6,1-*f*]purine (**2b**) and 5-(4-acetyl-3-methyl)pyrazolyl-4-amino-6-methylaminopyrimidine (**3b**) in 22% and 19% yield, respectively. The structure of compound **2** was determined with spectroscopic data and elemental analysis. The HMBC correlations between ^1H and ^{13}C of compound **2b** are shown in Fig. 1. Since the structure of compound **3** could not be established with ordinary spectroscopic data, X-ray analysis of compound **3b** was carried out. It revealed that the structure of compound **3** was unexpectedly pyrazolylpyrimidine that was formed by imidazole ring-opening, as shown in Fig. 2. HMBC analysis of compound **3b** supports this structure (Fig. 1). Reaction of 9-amino-N^6-methyladenine (**4**) with 2,4-pentanedione in the presence of $ZnCl_2$

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00392-8

Scheme 1. Reactions of *N*-Aminoadenines with 2,4-Pentanedione



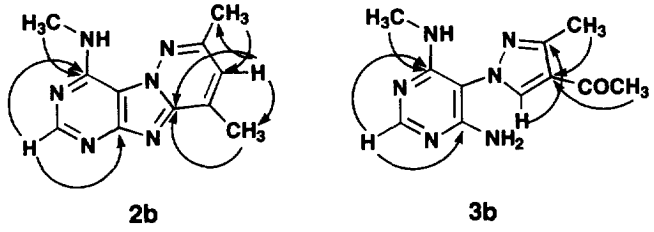


Fig. 1. HMBC correlations of compounds **1b** and **3b**.

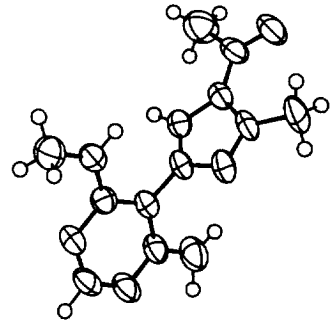
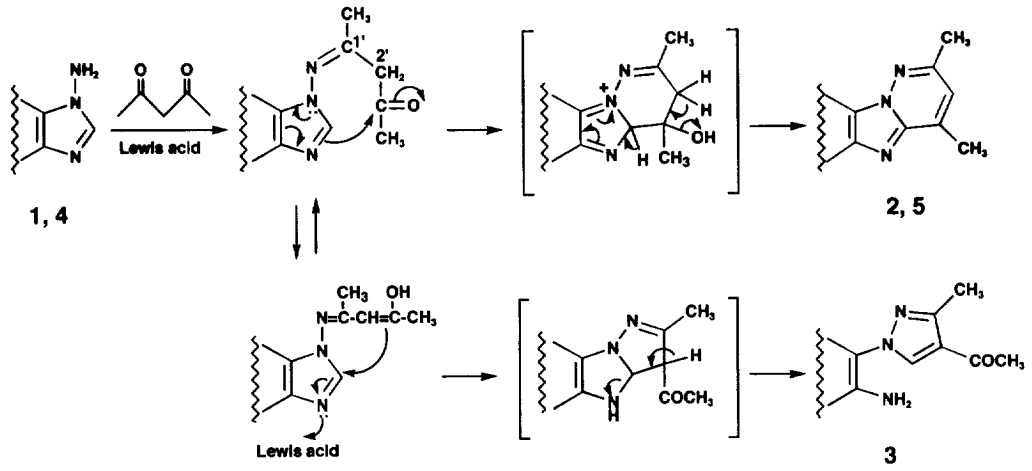


Fig. 2. Crystal structure of compound **3b**.

Scheme 2. Proposed Reaction Mechanisms



under refluxed temperature gave pyridazino[1,6-*e*]purine (**5**) and Schiff base (**6**) in 6% and 31% yield, respectively. The structures of compounds **5** and **6** were esablished with spectroscopic data. The structure of the N^9-substituent of compound **6** was identified as an enol form by ^{1}H NMR spectrum of **6** that showed an H-D exchangeable broad singlet at 11.8 ppm (1H, OH) and a singlet at 5.40 (1H, CH). Measurements of UV spectra of compounds **2a,b** and **5** in aqueous acidic, neutral and alkaline media showed that, under acidic conditions, these compounds have a protonation site. When adenine was allowed to react with 2,4-pentanedione under the same reaction conditions as with compounds **1** and **4**, no reaction occurred. As far as we know, pyridazino[6,1-*f*]purine (**2**) and pyridazino[1,6-*e*]purine (**5**) derivatives that we synthesized are new ring systems.[15]

Proposed reaction mechanisms for formation of compounds **2**, **5** and **3** are shown in Scheme 2 in which Schiff base formation by 2,4-pentanedione at the *N*-amino group is the initial step. Cyclization between the carbonyl carbon of the 2'-acetyl-1'-ethylidene group and the imidazole carbon forms an intermediate, which aromatizes to produce the pyridazinopurines **2** and **5**. Cyclization between the acidic 2'-carbon and the imidazole carbon forms an intermediate and subsequent bond cleavage at the imidazole ring produces pyrazolylpyrimidine **3**. It is not clear why the N9-aminoadenine derivative **4** did not give pyridazinopurine while the N7-aminoadenine derivative **1** gave product **3**. Reaction of 9-amino-O^6-methylguanine with 2,4-pentanedione also gave the corresponding pyridazinopurine and Schiff base (Data not shown). No Schiff base product was isolated in the reaction of compound **1** with 2,4-pentanedione under the conditions employed. This might be due to the high reactivity of the Schiff base that formed in the reaction mixture. Further study on the mechanisms of the reaction with 2,4-pentanedione is under way using a series of 1-aminobenzimidazole (ABI) derivatives as substrates. Preliminary experiments showed that ABI with an electron donating group at the benzene moiety gave mainly a three ring system compound that corresponds to compounds **2** and **5**, while ABI with an electron withdrawing group, gave mainly pyrazolylbenzene that corresponds to compound **3**.

These results strongly suggest that the electron density of the imidazole moiety has a role to determinining the reaction pathway, as we previously reported for the oxidation of a series of ABI derivatives.[16]

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on EX 270, GSX 400 and ALPHA 500 spectrometers (JEOL) and chemical shifts are reported as δ values (ppm) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were obtained with a JMS-DX300 spectrometer (JEOL), UV spectra were recorded on a Shimadzu UV-2100 spectrophotomete and HPLC analyses were carried out using a Shimadzu LC-10AD apparatus equipped with a photodiode array UV detector SPD-M6A. Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Silica gel 60 PF_{254} (Merck) was used for preparative thin-layer chromatography (PLC). 7-Aminoadenine, 7-amino-N^6-methyladenine and 9-amino-N^6-methyladenine were prepared as previously reported.[11]

Reaction of 7-aminoadenine (1a) with 2,4-pentanedione. Formation of 4-amino-7,9-dimethylpyridazino[6,1-*f*]purine (2a) and 5-(4-acetyl-3-methyl)pyrazolyl-4,6-diamino-pyrimidine (3a) 7-Aminoadenine (**1a**, 150 mg, 1 mmol) and $ZnCl_2$ (30 mg) were dissolved in 2,4-pentanedione (20 mL) and the mixture was heated at reflux for 4 h. Solvent was removed by evaporation. After MeOH (about 30 mL) was added to the residue, insoluble material (fraction of **2a**) was removed by filtration. Products in MeOH were separated by PLC (silica gel, $CHCl_3$-MeOH = 9:1, Rf of **2a** was 0.61; Rf of **3a** was 0.55). Yields were; pyridazino[6,1-*f*]purine (**2a**) 99 mg (46%) and pyrazolylpyrimidine (**3a**) 33 mg (14%). Recrystallization from MeOH gave colorless crystals of **2a**: mp >300 °C; ^1H NMR (Me_2SO-*d*6) δ 2.62 (s, 6H, CH_3 x 2), 7.0 and 7.9 (each br s, each 1H, NH_2), 7.42 (s, 1H, 8-H), 8.40 (s, 1H, 2-H); UV λmax nm (pH 1) 249 (ε = 29,600), 300 (9,800), (H_2O and pH 12) 245 (28,000), 307 (7,300); MS *m/z* 214 (M^+). HRMS *m/z* M^+ Calcd for $C_{10}H_{10}N_6$: 214.0967; Found: 214.0964. Anal. Calcd for $C_{10}H_{10}N_6$: C, 56.06; H, 4.71; N, 39.23. Found: C, 55.97; H, 4.75; N, 39.08. Recrystallization from EtOH gave colorless needles of **3a**: mp 296-299 °C; ^1H NMR (Me_2SO-*d*6) δ 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.09 (br s, 4H, NH_2 x 2), 7.85 (s, 1H, 2-H), 8.50 (s, 1H, 5'-H); ^{13}C NMR (Me_2SO-*d*6) δ 14.0 (q, 3'-CH_3), 28.4 (q, $COCH_3$), 99.2 (s, 5-C), 121.6 (s, 3'-C), 139.1 (d, 5'-C), 150.7 (s, 4'-C), 157.3 (d, 2-C), 159.1 (s x 2, 4-C, 6-C), 192.5 (s, $COCH_3$); UV λmax nm, pH 1 219, 239 (sh), H_2O 217, 239 (sh); MS *m/z* 232 (M^+). HRMS *m/z* M^+ Calcd for $C_{10}H_{12}N_6O$: 232.1073; Found: 232.1045.

Reaction of 7-amino-N^6-methyladenine (1b) with 2,4-pentanedione. Formation of 7,9-dimethyl-4-methylaminopyridazino[6,1-*f*]purine (2b) and 5-(4-acetyl-3-methyl)pyrazolyl-4-amino-6-methylaminopyrimidine (3b) 7-Amino-N^6-methyladenine (**1b**, 164 mg, 1 mmol) and $ZnCl_2$ (14 mg) were dissolved in 2,4-pentanedione (5 mL) and the mixture was heated at reflux for 2 h. After solvent was removed by evaporation, the products were separated by PLC (silica gel, $CHCl_3$-MeOH = 93:7, Rf of **2b** was 0.39; Rf of **3b** was 0.34). Yields were; pyridazino[6,1-*f*]purine (**2b**) 50 mg (22%) and pyrazolylpyrimidine (**3b**) 47 mg (19%). Recrystallization from AcOEt gave colorless leaflets of **2b**: mp 231-234 °C; ^1H NMR (Me_2SO-*d*6) δ 2.62 (d, *J* = 1.0 Hz, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.15 (d, *J* = 5.0 Hz, 3H, N-CH_3), 7.40 (s, 2H, 8-H, NH), 8.47 (s, 1H, 2-H); ^{13}C NMR (Me_2SO-*d*6) δ 16.1 (q, 7-CH_3), 20.8 (q, 9-

CH_3), 27.3 (q, N-CH_3), 107.6 (s, 4a-C), 123.0 (d, 8-C), 135.8 (s, 7-C), 142.2 (s, 9-C), 151.5 (s, 4-C), 151.7 (s, 9a-C), 155.1 (d, 2-C), 155.9 (s, 10a-C); UV λmax nm (pH 1) 253 (ε = 22,400), 318 (9,700), (H_2O and pH 12) 229 (25,400), 251 (20,500), 326 (7,100); MS *m/z* 228 (M^+). HRMS *m/z* M^+ Calcd for $C_{11}H_{12}N_6$: 228.1123; Found: 228.1120. Anal. Calcd for $C_{11}H_{12}N_6$: C, 57.88; H, 5.30; N, 36.82. Found: C, 57.94; H, 5.35; N, 36.93. Recrystallization from AcOEt gave colorless needles of **3b**: mp 238 °C (dec); ^1H NMR (Me_2SO-*d*6) δ 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.72 (d, *J* = 4.6 Hz, 3H, *N*-CH_3), 5.99 (br s, 3H, NH_2 and N^6-H), 7.96 (s, 1H, 2-H), 8.49 (s, 1H, 5'-H); ^{13}C NMR (Me_2SO-*d*6) δ 14.0 (q, 3'-CH_3), 27.4 (q, N-CH_3), 28.3 (q, $COCH_3$), 99.3 (s, 5-C), 121.7 (s, 3'-C), 139.3 (d, 5'-C), 150.8 (s, 4'-C), 157.2 (d, 2-C), 158.1 (s, 6-C), 158.5 (s, 4-C), 192.4 (s, *C*OCH_3); UV λmax nm (pH 1) 225 (ε = 33,900), 262 (14,700), (H_2O and pH 12) 223 (40,800); MS *m/z* 246 (M^+). HRMS *m/z* M^+ Calcd for $C_{11}H_{14}N_6O$: 246.1229; Found: 246.1240. Anal. Calcd for $C_{11}H_{14}N_6O$: C, 53.64; H, 5.73; N, 34.13. Found: C, 53.78; H, 5.82; N, 33.69.

Reaction of 9-amino-N^6-methyladenine (4) with 2,4-pentanedione. Formation of 4-amino-6,8-dimethylpyridazino[1,6-*e*]purine (5) and 9-(3-hydroxy-1-methyl-2-butenylidene)amino-6-methylaminopurine (6) 9-Amino-N^6-methyladenine (**4**, 110 mg, 0.67 mmol) and $ZnCl_2$ (30 mg) were dissolved in 2,4-pentanedione (20 mL) and the mixture was heated at reflux for 5 h. After solvent was removed by evaporation, the products were separated by PLC (silica gel, $CHCl_3$-MeOH = 19:1, Rf of **5** was 0.88; Rf of **6** was 0.84). Yields were; pyridazino[1,6-*e*]purine (**5**) 9 mg (6%) and Schiff base (**6**) 51 mg (31%). Recrystallization from MeOH gave yellow crystals of **5**: mp 296-298 °C; ^1H NMR (Me_2SO-*d*6) δ 2.56 (s, 3H CH_3), 2.59 (s, 3H, CH_3), 3.02 (d, 3H, *J* = 4.9 Hz, N-CH_3), 7.27 (s, 1H, 7-H), 8.38 (s, 1H, 2-H); UV λmax nm (pH 1) 254, 320 (sh), (H_2O and pH 12) 257, 340 (sh); MS *m/z* 228 (M^+). HRMS *m/z* M^+ Calcd for $C_{11}H_{12}N_6$: 228.1123; Found: 228.1122. Recrystallization from MeOH gave colorless plates of **6**: mp 201-204 °C; ^1H NMR (Me_2SO-*d*6) δ 1.65 (s, 3H, 1'-CH_3), 2.08 (s, 3H, 4'-CH_3), 2.96 (s, 3H, N-CH_3), 5.40 (s, 1H, 2'-H), 7.87 (br s, 1H, NH), 8.21 and 8.25 (each s, each 1H, 2-H and 8-H), 11.84 (br s, 1H, OH); ^{13}C NMR (Me_2SO-*d*6) δ 17.3 (q, 1'-CH_3), 29.0 (q, N^6-CH_3), 31.3 (q, 4'-CH_3), 97.9 (s, 5-C), 97.9 (d, 2'-C), 136.6 (s, 4-C), 141.0 (d, 8-C), 153.3 (d, 2-C), 154.9 (s, 6-C), 159.9 (s, 1'-C), 196.1 (s, 3'-C); UV λmax nm (pH 1) 262 (ε = 17,700), (H_2O) 275 (18,000), (pH 12) 275 (18,000), 305 (29,600); MS *m/z* 246 (M^+). HRMS *m/z* M^+ Calcd for $C_{11}H_{14}N_6O$: 246.1229; Found: 246.1237. Anal. Calcd for $C_{11}H_{14}N_6O$: C, 53.64; H, 5.73; N, 34.13. Found: C, 53.68; H, 5.67; N, 34.27.

Crystal data for 3b Formula, $C_{11}H_{14}N_6O$; *M* = 246.28; crystal system, triclinic; space group, $P\bar{1}$; cell parameters, *a* = 15.357(3), *b* = 10.535(2), *c* = 8.034(2) Å; α = 91.80(2), β = 100.16(2), γ = 101.84(2)°; *V* = 1249.1(5) $Å^3$; *Z* = 4; *Dc* = 1.310 g/cm^3; 2663 reflections (2571 unique, R_{int} = 0.042) were measured on a Rigaku AFC-5R diffractometer. Final *R* = 0.071 for 2378 observed with $I > 2\sigma(I)$.

Acknowledgement: We would like to thank Professor Emeritus Y. Kawazoe of Nagoya City University for helpful advice and encouragement.

References and Notes

1. Kawazoe, Y.; Huang, G.-F. (Kohda, K.) *Chem. Pharm. Bull.* **1972**, *20*, 2073-2074.
2. Huang, G.-F. (Kohda, K.); Maeda, M.; Okamoto, T.; Kawazoe, Y. *Tetrahedron* **1975**, *31*, 1363-1367.
3. Kohda, K.; Baba, K.; Kawazoe, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2298-2301.
4. Kohda, K.; Yasuda, M.; Ukai, H.; Baba, K.; Yamagata, Y.; Kawazoe, Y. *Tetrahedron* **1989**, *45*, 6367-6374.
5. Kohda, K.; Baba, K.; Kawazoe, Y. *Tetrahedron* **1990**, *46*, 1531-1540.
6. Yamagata, Y.; Tomita, K.; Kohda, K.; Kawazoe, Y. *Acta Cryst.* **1992**, *C48*, 318-320.
7. Kohda, K.; Kobayashi, I.; Itano, K.; Asano, S.; Kawazoe, Y. *Tetrahedron* **1993**, *49*, 3947-3958.
8. Kaiya, T.; Ohta, M.: Kohda, K. *Tetrahedron* **1993**, *49*, 8795-8804.
9. Hasebe, K.; Kohda, K. *Nucleic Acids Sympo. Ser.* **1993**, *No.29*, 27-28.
10. Asano, S.; Itano, K.; Yamagata, Y.; Kohda, K. *Nucleosides & Nucleotides* **1994**, *13*, 1453-1465.
11. Saga, T.; Kaiya, T.; Kohda, K. *Nucleosides & Nucleotides* **1996**, *15*, 219-233.
12. Asano, S.; Itano, K.; Yamagata, Y.; Kohda, K. *J. Heterocyclic Chem.* **1996**, *33*, 1115-1121.
13. Wu, W.; Saga, T.; Terashima, I.; Saeki, K.; Kohda, K.; Kawazoe, Y. *Heterocycles* **1997**, *45*, 157-162.
14. Asano, S.; Yokoyama, Y.; Kohda, K. *Anticancer Res.* **1997**, *17*, 823-826.
15. Although the structure of pyridazino[6,1-*f*]purine was shown in *Ring Systems Handbook* (American Chemical Society, 1984 edition), exact examples could not be found.
16. Kaiya, T.; Aoyama, S.; Kohda, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 625-630.