[Chem. Pharm. Bull. 30(7)2583—2585(1982)]

Synthesis of 2-Substituted 6-Methyl-9-β-D-ribofuranosylpurines

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(Received December 19, 1981)

A new method for the synthesis of 2-substituted 6-methylpurine ribosides from guanosine is described. Reaction of *N*(2), *O*(2′), *O*(3′), *O*(5′)-tetraacetyl-*O*(6)-*p*-toluenesulfonylguanosine with carbanion from ethylacetoacetate gave the 6-ethoxycarbonylmethyl derivative, which was further converted to 2-amino-6-methylpurine riboside by deacetylation and decarboxylation. Replacement of the amino group of the compound by the fluoro group was achieved by the Schiemann reaction. The fluoro group could easily be replaced by several nucleophiles. As a result, 2-methoxy-, 2-methylthio-, and 2-dimethylamino-6-methyl-9-β-D-ribofuranosylpurines could be effectively prepared.

Keywords——guanosine; nucleophilic substitution; carbanion; ethylacetoacetate; decarboxylation; Schiemann reaction

6-Methyl-9-β-D-ribofuranosylpurine was shown to have an interesting biological activity.[1] However, there have been very few reports on the synthesis or biological activity of 2-substituted 6-methyl-9-β-D-ribofuranosylpurines.[2] Using the *O*(6)-*p*-toluenesulfonylguanosine derivative[3] as the starting material, we have now synthesized several new and interesting 2-substituted 6-methylpurine nucleosides. While three groups reported the synthesis of 6-

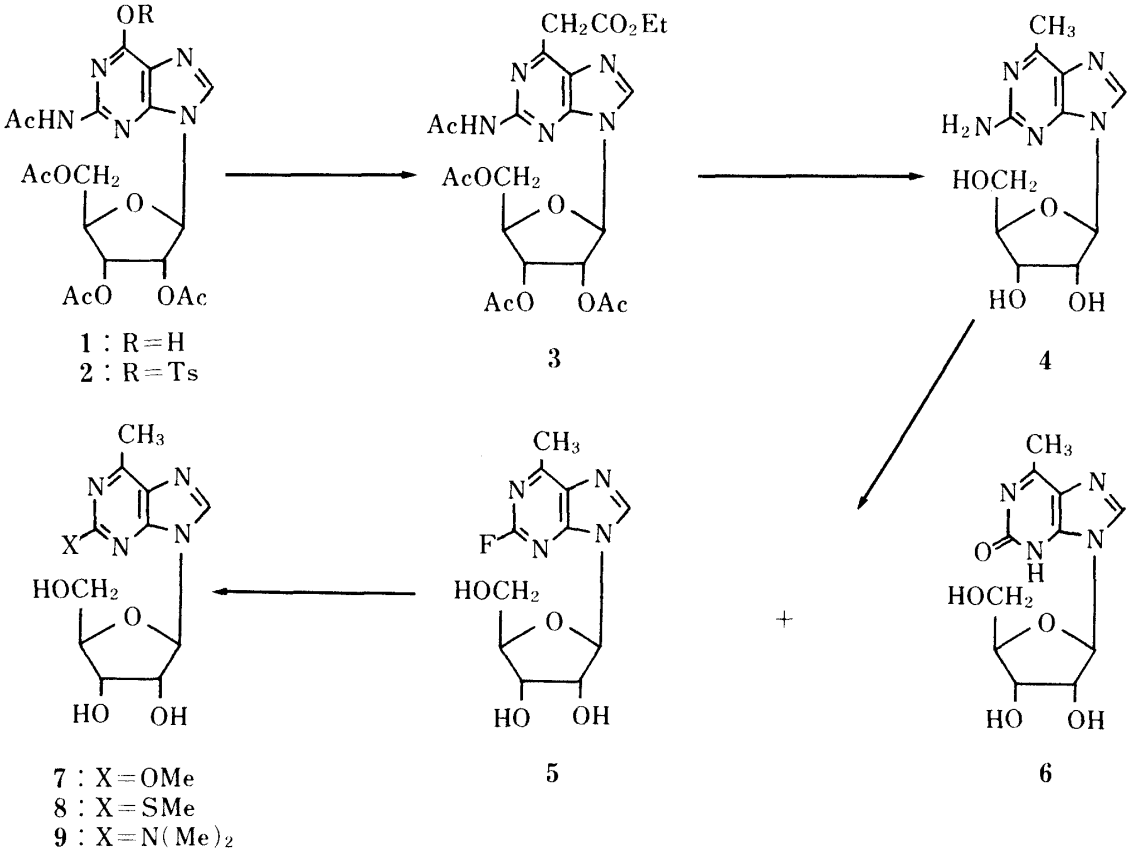

Chart 1

carbon substituted purine nucleosides by nucleophilic displacement of the corresponding 6-methylsulfonyl,[4] 6-chloro[5] and 6-iodo derivatives,[6] we found that the *O*(6)-*p*-toluenesulfonyl group was readily displaced by the carbanion of ethylacetoacetate to give the 6-ethoxycarbonylmethylpurine nucleoside.

N(2), *O*(2′), *O*(3′), *O*(5′)-Tetraacetyl-*O*(6)-*p*-toluenesulfonylguanosine (**2**) was prepared from *N*(2), *O*(2′), *O*(3′), *O*(5′)-tetraacetylguanosine (**1**) according to the method of Reese *et al.*[3b] The compound **2** was treated with 2 equivalents of the carbanion prepared from ethylacetoacetate and sodium hydride in refluxing tetrahydrofuran for 1.5 h. Purification of the product on a silica gel column afforded 2-acetamido-6-ethoxycarbonylmethyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**3**) as a foam in 60% yield. Deacetylation and saponification of **3** with sodium hydroxide in 50% aqueous ethanol at room temperature for 1 d, followed by acidification gave a compound characterized as 2-amino-6-methyl-9-β-D-ribofuranosylpurine (**4**), which has previously been synthesized, though detailed analytical data were not given.[2a,4b] For effective substitution of the amino group of compound **4** with several nucleophilic substituents, we tried to introduce a fluoro group prior to the substitution. The replacement of the amino group by a fluoro group could be performed by diazotization in fluoboric acid;[7] treatment of **4** with sodium nitrite in the presence of 48% fluoboric acid gave both 2-fluoro-6-methyl-9-β-D-ribofuranosylpurine (**5**)[2a] and 6-methyl-9-β-D-ribofuranosylpurine-2-one (**6**) in 55% and 16% yields, respectively. The physical properties of **5** were generally in agreement with those reported for the compound prepared by the coupling of tetra-*O*-acetyl-D-ribofuranose and 2-fluoro-6-methylpurine.[2a] The preparation of 2-methoxy-6-methyl-9-β-D-ribofuranosylpurine (**7**) was accomplished by treating **5** with sodium methoxide in methanol at room temperature for 2 h in an excellent yield. Similarly, reaction of **5** with sodium methylmercaptide or dimethylamine in dimethylformamide readily gave 2-methylthio-6-methyl-9-β-D-ribofuranosylpurine (**8**) or 2-dimethylamino-6-methyl-9-β-D-ribofuranosylpurine (**9**), respectively.

Experimental

The following instruments were used to obtain physical data: melting points, Yanagimoto micro melting point apparatus (recorded uncorrected); ultraviolet (UV) absorption spectra, Hitachi 220 spectrophotometer; ^{1}H nuclear magnetic resonance (NMR) spectra, Hitachi R-20B NMR spectrometer (with tetramethylsilane (TMS) as an internal standard); mass spectra, Hitachi RMU-6E instrument. Mass spectra and elemental analysis were performed by the staff of the Analytical Center of Hokkaido University.

***N*(2), *O*(2′), *O*(3′), *O*(5′)-Tetraacetyl-*O*(6)-*p*-toluenesulfonylguanosine** (**2**)——To a solution of *N*(2), *O*(2′), *O*(3′), *O*(5′)-tetraacetylguanosine (**1**) (49.4 g) in 550 ml of $CHCl_3$ were added 109 ml of triethylamine and tosyl chloride (100.0 g), and the mixture was stirred for 1.5 h at room temperature. The solution was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and applied to a silica gel column (silica gel, 1 kg). The eluate with $CHCl_3$–EtOH (99: 1) was concentrated to dryness to afford **2** (62.0 g, 94%) as a foam. UV λ_{max}^{EtOH} nm: 276, 256. λ_{min}^{EtOH} nm: 267, 245. NMR ($CDCl_3$) δ: 8.43 (bs, 1, NH), 8.03 (s, 1, 8-H), 7.99 (d, 2, ArH, J=8.0), 7.35 (d, 2, ArH, J=8.0), 5.7—6.1 (m, 3, 1′-H, 2′-H, 3′-H), 4.41 (m, 3, 4′-H, 5′-H), 2.44 (s, 6, *p*-CH_3, *N*-acetyl), 2.0—2.13 (s × 3, 9, *O*-acetyl).

2-Acetamido-6-ethoxycarbonylmethyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine (**3**)——A solution of 24.8 g of ethylacetoacetate and 6.1 g of 50% NaH in 70 ml of tetrahydrofurane (THF) was added dropwise to a solution of 38.5 g of **2** in 290 ml of THF, and the mixture was refluxed for 2.5 h. After neutralization of the cooled solution with AcOH, the solvent was removed *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed with water, and evaporation of the solvent gave a foam, which was applied to a silica gel column (silica gel, 1.5 kg). The column was eluted with $CHCl_3$–EtOH (99: 1). The eluate was collected and concentrated to leave 20.0 g (60%) of **3** as a foam. UV λ_{max}^{EtOH} nm: 326, 292, 256 (sh). λ_{min}^{EtOH} nm: 306, 267. NMR ($CDCl_3$) δ: 8.35 (br s, 1, NH), 8.04 (s, 1, 8-H), 6.19 (d, 1, 1′-H), J=4.2 Hz), 4.18 (q, 2, $-O\underline{CH_2}-CH_3$), 4.12 (s, 1, 6-CH_2–), 1.26 (t, 3, $-OCH_2\underline{CH_3}$, J=7.0 Hz). MS *m/e*: 521 (M^+), 264 (B+2), 263 (B+1).

2-Amino-6-methyl-9-β-D-ribofuranosylpurine (**4**)——A solution of 16.5 g of **3** in 500 ml of EtOH–1 N NaOH (1: 1) was stirred for 25 h at room temperature. Diaion PK 216 resin (H^+, 330 ml of wet resin) was added to the solution and the mixture was stirred for 2 h. The resin was removed by filtration and washed thoroughly with 1.5 l of 0.15 N NH_4OH. The filtrate and washings were combined and evaporated to dryness, and the residue was crystallized from water to give 4.5 g (51%) of **4**, mp 158—159°C (mp 142—144°C).[4b]

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 1/3H_2O$: C, 45.99; H, 5.50; N, 24.38. Found: C, 45.89; H, 5.24; N, 24.52. UV $\lambda_{max}^{H_2O}$ nm (ε): 298 (7800), 244 (6800). $\lambda_{min}^{H_2O}$ nm (ε): 263 (1300). NMR (DMSO-d_6) δ: 8.14 (s, 1, 8-H), 6.28 (br s, 2, 2-NH_2), 5.78 (d, 1, 1′-H, J=7.2), 2.47 (s, 3, 6-CH_3). MS *m/e*: 281 (M^+), 150 (B+2), 149 (B+1).

2-Fluoro-6-methyl-9-β-D-ribofuranosylpurine (5)——Compound **4** (3.25 g) was added to 116 ml of 48% aqueous fluoboric acid, and the mixture was stirred for 1 h at −15——−10°C. Sodium nitrite (1.60 g) dissolved in 6 ml of water was added to the mixture over a period of 10 min. After the addition had been completed, the mixture was stirred for 30 min at −15——−10°C and then neutralized (<0°C) to pH 7 with 28% NH_4OH. The solution was applied to a column of Diaion HP-20 resin (500 ml of wet resin), which was then eluted with 10% EtOH in water and the eluate was collected. The eluate was evaporated to dryness and the residue was crystallized from AcOEt–EtOH (3: 1) to give 1.81 g (55%) of **5**, mp 179—180°C (174—176°C).[2a] *Anal.* Calcd for $C_{11}H_{13}N_4O_4F$: C, 46.48; H, 4.61; N, 19.71. Found: C, 46.42; H, 4.68; N, 19.70. UV $\lambda_{max}^{H_2O}$ nm (ε): 264 (8200), 240 (sh, 3600). $\lambda_{min}^{H_2O}$ nm (ε): 227 (2700). NMR (DMSO-d_6) δ: 8.71 (s, 1, 8-H), 5.92 (d, 1, 1′-H, J=5.4 Hz), 2.73 (s, 3, 6-CH_3). MS *m/e*: 284 (M^+), 153 (B+2), 152 (B+1).

6-Methyl-9-β-D-ribofuranosylpurine-2-one (6)——A fraction eluted before the fraction containing **5** from the above-mentioned column was evaporated to dryness, and the residue was crystallized from water to give 551 mg (16%) of **6**, mp 253—254°C. *Anal.* Calcd for $C_{11}H_{14}N_4O_5 \cdot 1/5H_2O$: C, 46.22; H, 5.08; N, 19.60. Found: C, 46.24; H, 4.83; N, 19.84. UV $\lambda_{max}^{H_2O}$ nm (ε): 312 (7300), 238 (sh, 4000). $\lambda_{min}^{H_2O}$ nm (ε): 265 (5000). NMR (DMSO-d_6) δ: 8.27 (s, 1, 8-H), 5.70 (d, 1, 1′-H, J=5.5 Hz), 2.50 (s, 3, 6-CH_3). MS *m/e*: 282 (M^+), 165 (B+2), 164 (B+1), 163 (B).

2-Methoxy-6-methyl-9-β-D-ribofuranosylpurine (7)——To a solution of 200 mg of **5** in 35 ml of MeOH was added 0.36 ml of 28% NaOMe in MeOH, and the mixture was stirred for 2 h at room temperature. The solution was neutralized with AcOH and evaporated to dryness. The residue was crystallized from water to give 196 mg (90%) of **7**, mp 153—154°C. *Anal.* Calcd for $C_{12}H_{16}N_4O_5 \cdot 1/4H_2O$: C, 47.92; H, 5.53; N, 18.63. Found: C, 48.07; H, 5.46; N, 18.91. UV $\lambda_{max}^{H_2O}$ nm (ε): 277 (9400), 235 (3800). $\lambda_{min}^{H_2O}$ nm (ε): 248 (1700), 224 (3300). NMR (DMSO-d_6) δ: 8.46 (s, 1, 8-H), 5.89 (d, 1, 1′-H), J=5.4 Hz), 2.64 (s, 3, 6-CH_3). MS *m/e*: 296 (M^+), 165 (B+2), 164 (B+1), 163 (B).

2-Methylthio-6-methyl-9-β-D-ribofuranosylpurine (8)——To a solution of 200 mg of **5** in 35 ml of dimethylformamide (DMF) was added 0.7 ml of 15% NaSMe in water, and the mixture was stirred for 2 h at room temperature. The solution was neutralized with AcOH, and evaporated to dryness. The residue was crystallized from water to give 163 mg (73%) of **8**, mp 147°C. *Anal.* Calcd for $C_{12}H_{16}N_4O_4S$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.87; H, 5.23; N, 18.06. UV $\lambda_{max}^{H_2O}$ nm (ε): 296 (7900), 258 (10900). $\lambda_{min}^{H_2O}$ nm (ε): 276 (4500), 243 (6000). NMR (DMSO-d_6) δ: 8.52 (s, 1, 8-H), 5.93 (d, 1, 1′-H, J=5.6), 2.67, 2.57 (s, 3+3, 6-CH_3 and *S*-CH_3). MS *m/e*: 312 (M^+), 181 (B+2), 180 (B+1), 179 (B).

2-Dimethylamino-6-methyl-9-β-D-ribofuranosylpurine (9)——To a solution of 200 mg of **5** in 35 ml of DMF was added 1 ml of 10% dimethylamine in DMF, and the mixture was stirred for 4.5 h at room temperature. The solution was evaporated to dryness and the residue was crystallized from water to give 184 mg (84%) of **9**, mp 223°C. *Anal.* Calcd for $C_{13}H_{19}N_5O_4$: C, 50.48; H, 6.19; N, 22.64. Found: C, 50.45; H, 6.08; N, 22.64. UV $\lambda_{max}^{H_2O}$ nm (ε): 324 (6200), 257 (13100). $\lambda_{min}^{H_2O}$ nm (ε): 280 (1100), 240 (6600). NMR (DMSO-d_6) δ: 8.16 (s, 1, 8-H), 5.82 (d, 1, 1′-H, J=5.6 Hz), 3.13 (s, 6, $N(CH_3)_2$), 2.52 (s, 3, 6-CH_3). MS *m/e*: 309 (M^+), 178 (B+2), 177 (B+1), 176 (B).

Acknowledgement We wish to express our thanks to Dr. T. Ueda, professor of Hokkaido University, for his valuable advice and encouragement. Thanks are also due to Dr. K. Ikeda, the Analytical Center of Hokkaido University, for elemental analysis and mass spectral measurements.

References

1) H.P. Schnebli, D.L. Hill, and L.L. Bennett, Jr., *J. Biol. Chem.*, **242**, 1997 (1967).
2) *a*) J.A. Montgomery and K. Hewson, *J. Med. Chem.*, **11**, 48 (1968); *b*) L.F. Christensen, P.D. Cook, R.K. Robins, and R.B. Meyer, Jr., *J. Carbohyd. Nucleosides. Nucleotides*, **4**, 175 (1977).
3) *a*) P.K. Bridson, W.T. Markiewicz, and C.B. Reese, *J. Chem. Soc. Chem. Commun.*, **1977**, 447; *b*) P.K. Bridson, W.T. Markiewicz, C.B. Reese, *ibid.*, **1977**, 791; *c*) H.P. Daskalov, M. Sekine, and T. Hata, *Bull. Chem. Soc. Jpn.*, **54**, 3070 (1981).
4) *a*) A. Yamane, A. Matsuda, and T. Ueda, *Chem. Pharm. Bull.*, **28**, 150 (1980); *b*) H. Inoue, S. Nomura, and T. Ueda, *Nucleic Acids Res. Symposium Series*, **10**, 19 (1981).
5) T. Miyasaka, H. Suemune, and K. Arakawa (the late), *Nucleic Acids. Res. Symposium Series*, **5**, 273 (1978).
6) J.D. Westover, G.R. Revankar, R.K. Robins, R.D. Madsen, T.R. Ogden, J.A. North, R.W. Mancuso, R.J. Rousseau, and E.L. Stephen, *J. Med. Chem.*, **24**, 941 (1981).
7) J.F. Gerster and R.K. Robins, *J. Am. Chem. Soc.*, **87**, 3752 (1965).