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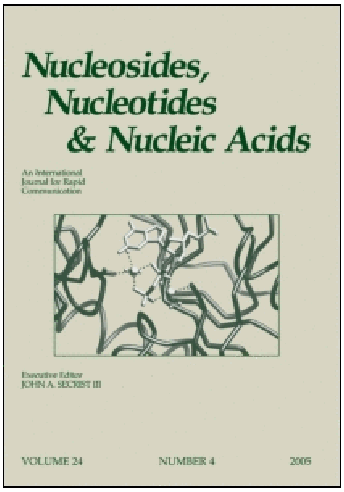

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Method for the Synthesis of Uric Acid Derivatives

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METHOD FOR THE SYNTHESIS OF URIC ACID DERIVATIVES

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ABSTRACT: A general procedure to obtain tetra-substituted uric acid by stepwise *N*-alkylation is described. 2,6-Dichloropurine (**1**) was condensed with 1-propanol by Mitsunobu reaction to give 9-propyl congener (**2**). Treatment of **2** with ammonia gave adenine derivative (**4a**), which was converted to the 8-oxoadenine (**5b**) in 3 steps. Methylation of **5b** proceeded site-specifically to give 6-amino-2-chloro-7,8-dihydro-7-methyl-9-propylpurin-8-one (**6**) as a sole product. Compound **6** was successively treated with $NaNO_2$ and iodomethane to give 2-chloro-1,6,7,8-tetrahydro-1,7-dimethyl-9-propylpurin-6,8-dione (**9**) accompanied by the O^6-methyl product (**8**) in 75% and 6.9%, respectively. After nucleophilic substitution of **9** with NaOAc, the product (**11**) was reacted with iodomethane to give the uric acid (**12**) and the 2-methoxy product (**13**) in 46% and 15.5%, respectively. However, the reaction of **11** with the benzylating agents gave only *O*-benzyl products (**14a,b**).

Introduction

Purine nucleotides and nucleosides are, after metabolically converted to xanthine, oxidized to uric acid. This compound has four protons changeable to the alkyl group, and some *N*-alkyl derivatives have interesting biological properties. Fraisse *et al.*[1] reported that long-chain derivatives of uric acid exhibit oxygen radical induced lipid peroxydation in bovine heart mitochondria. Another interesting oxidation is observed in DNA which contains 8-oxoguanine. It is reported that single-stranded DNA oligomers containing a 8-oxoguanine residue have high reactivity toward $KMnO_4$,[2] and *N*-alkylated derivatives of 8-oxoguanosines have been shown to be small-molecule immunostimulants.[3] Synthesis of

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uric acid derivatives usually starts from caffeine or theophilline.[4] Also, a ring closure of 5,6-diaminouridine and urea is popular.[5] Mehrotra *et al.*[6] reported that the reaction of fervenulane with *t*-butyl bromoacetate caused a ring reduction to form uric acid. However, there has been no report on the stepwise synthesis of 1,3,7,9-tetra-substituted derivatives of uric acid. This background prompted us to develop a general procedure to prepare *N*-substituted derivatives of 8-oxoguanine and/or uric acid. In this report, we describe a general procedure for the synthesis of tetra-substituted uric acid by stepwise *N*-alkylation.

Results and Discussion

2,6-Dichloropurine (**1**) was condensed with 1-propanol using Mitsunobu reaction[7] to afford 9-propyl analog (**2**) as a major product (71% yield). The UV spectrum of a minor product **3** was different from **1** and **2**, indicating 7-isomer. Nucleophilic substitution of **2** with ammonia in MeOH gave the adenine (**4a**), of which UV spectrum was similar to that of 2-chloroadenosine.[8] Compound **4a** was treated with bromine-water at pH 4[9] to give 8-bromo congener (**4b**), then the product was subjected to nulcoephilic substitution. A trial using NaOAc in DMF recovered the starting material. Also purin-2,8-dione derivative (**5c**) was the major product when treated with NaOAc in Ac_2O-AcOH, suggesting both chlorines at 2-carbon as well as 8-carbon were replaced by acetate anion. Reaction of **4b** with Ac_2O and AcOH gave the desired 6-acetamide-2-chloro-7,8-dihydro-9-propylpurin-8-one (**5a**) in good yield. Then **5a** was treated with ammonia in MeOH to give 6-amino-2-chloro-7,8-dihydro-9-propylpurin-8-one (**5b**). The UV spectrum of **5b** was similar to that of 6-amino-7,8-dihydro-9-(β-D-ribofuranosyl)purin-8-one[11] and different from 6-amino-2,3-dihydro-9-(β-D-ribofuranosyl)purine-2-one[10]. Treatment of **5b** with iodomethane in DMF in the presence of K_2CO_3 afforded **6**. To determine the structure of **6**, 8-OMe-adenine (**4c**) was prepared from **4b** by the treatment with NaOMe. The UV spectrum of **4c** was compared with that of **6**. 8-OMe-Adenine (**4c**) shows an absorption maximum at 267 nm and compound **6** at 278 nm. These results strongly suggest that **6** is an 7-Me structure. To introduce the third alkyl group at N1, **6** was deaminated by $NaNO_2$ in $AcOH-H_2O$, and then treated with iodomethane in a similar manner to **5b** to give two products in 75% and 6.9% yields, respectively. Molecular-ion peaks of **8** and **9** appeared

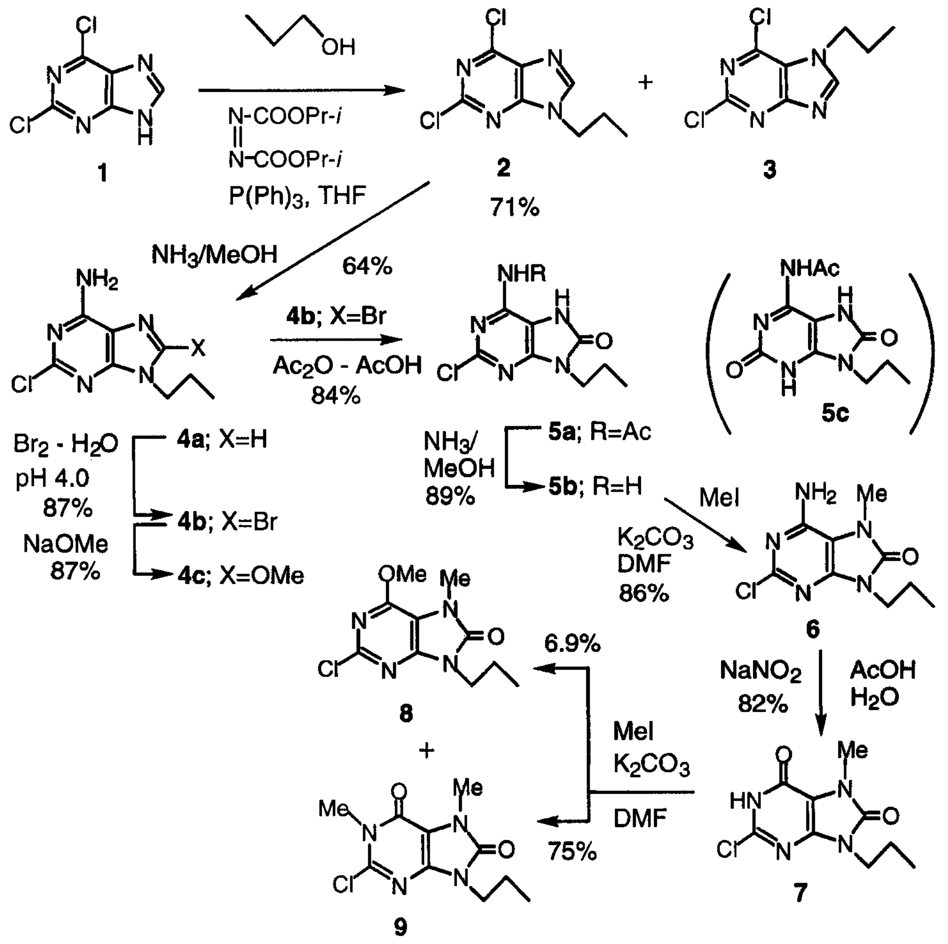

Chart 1

at 256 and 258 in the mass spectroscopy. However, their UV spectra were different from each other. The main product (**9**) was converted to 2-amino-1,6,7,8-tetrahydro-1,7-dimethyl-9-propylpurin-6,8-dione (**10**), of which the UV specturm was almost identical to that of 2-amino-1,6,7,8-tetrahydro-1,7-dimethyl-9-(β-D-ribofuranosyl)purin-6,8-dione.[12] This evidence supports that the structure of **9** is a 1-methyl derivative and consequently a minor product **8** is a 6-OMe derivative. Compound **9** was subjected to nucleophilic substitution with NaOAc in AcOH to give the derivative of uric acid (**11**). Then **11** was treated with iodomethane again. The minor product (**13**) was identical in

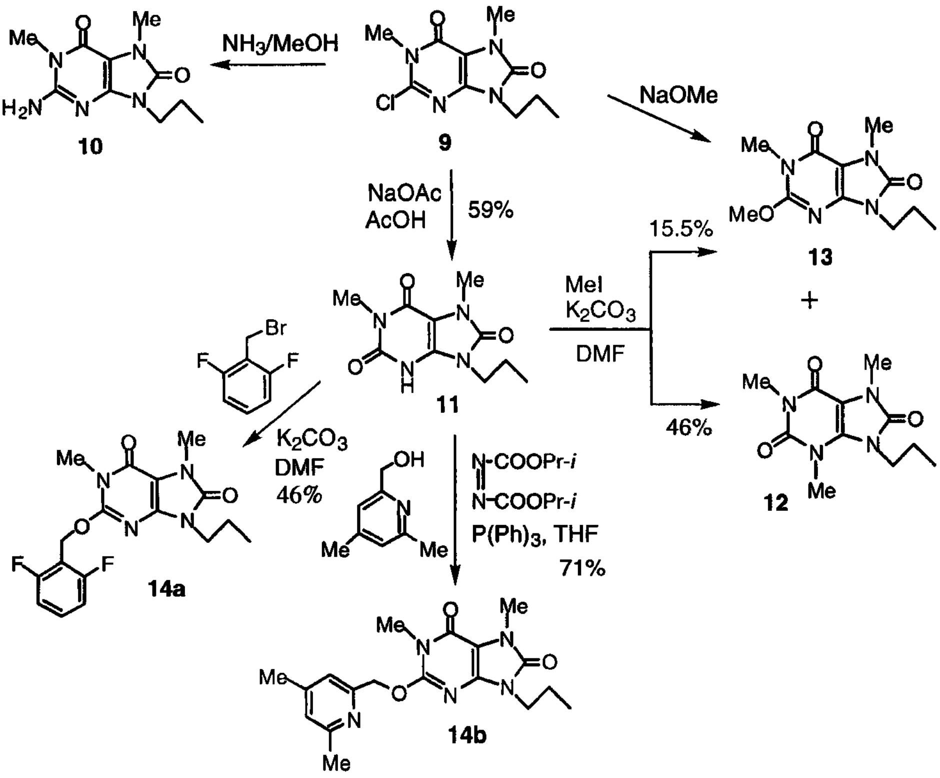

Chart 2

any respect to the sample that was obtained by treatment of **9** with NaOMe, indicating that **13** is the 2-OMe product. The HMBC Spectrum of **12** shows a correlation between 3-methyl protons and C2 and C4. Consequently, the major product (**12**) was identified as a tetra-substituted uric acid. However, the ratio of the OMe product (15.5%) to the *N*-Me one (46%) increased to more than one fourth. The intramolecular steric hinderance between 9-isopropyl and 3-methyl explains this result.[13] When **11** was condensed with aralkyl alcohol by Mitsunobu reaction or reacted with 2,6-difluorobenzyl bromide, only the OCH_2Ar products (**14a,b**) were obtained.

We developed a general procedure to prepare tetra-substituted uric acid by stepwise alkylation. However, the problem derived from steric hinderance still remains in the last N^3-alkylation.

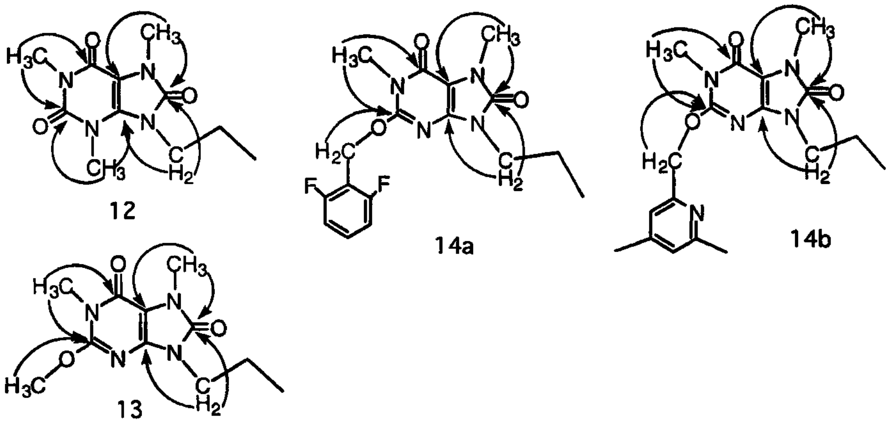

FIG. 1. HMBC correlations of compounds **12, 13 and 14a,b**

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low resolution mass spectra were obtained on a Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60-200 mesh) was employed for column chromatography.

2,6-Dichloro-9-propylpurine (2). To a mixture of *n*-propanol (4.5 ml, 60mmol) and 2,6-dichloropurine (5.67 g, 30 mmol) in dry THF was added triphenylphosphine (15.75 g, 60mmol) and diisopropyl azodicarboxylate (11.82 ml, 60mmol) and the solution was stirred at 50°C overnight, then concentrated to a small volume. The residual solution was chromatographed on a column of silica gel (4.5 × 52 cm) using a 50-100% AcOEt in hexane to give **2** as white crystals (4.89 g, 71%). mp 49-50°C. *Anal* Calcd for $C_8H_8Cl_2N_4$: C, 41.57; H, 3.49; N, 24.24. Found: C, 41.73; H, 3.33; N, 23.80. MS *m/z*: 230, 232, 234

(M^+). UV λ_{max} (MeOH) nm: 274. ^{1}H-NMR ($CDCl_3$) δ: 8.11 (1H, s, H-8), 4.25 (2H, dd, *J*=7.1, 7.3 Hz, CH_2), 1.88-2.07 (2H, m, CH_2), 1.00 (3H, t, *J*=7.3 Hz, CH_3). Second fraction was evaporated to give the mixture of 2,6-dichloro-7-propylpurine (**3**) and triphenylphosphine oxide. A part of triphenylphosphine was precipitated in the mixture solution of hexane and benzene and the supernatant was applied to the column of silica gel G using 33-50% AcOEt in benzene as eluents to give **3** as white crystals (627 mg, 9.1%). mp 103.4-104.0°C. *Anal* Calcd for $C_8H_8Cl_2N_4$: C, 41.57; H, 3.49; N, 24.24. Found: C, 41.73; H, 3.60; N, 23.43. MS *m/z*: 230, 232, 234 (M^+). λ_{max} (MeOH) nm: 281. ^{1}H-NMR ($CDCl_3$) δ: 8.23 (1H, s, H-8), 4.42 (2H, dd, *J*=7.1, 7.3 Hz, CH_2), 1.9-2.1 (2H, m, CH_2), 1.00 (3H, t, *J*=7.3 Hz, CH_3).

2-Chloro-9-propyladenine (4a). A solution of **2** (4.7 g, 20.3 mmol) in MeOH (30 ml) saturated with ammonia at 0°C was heated in a steel bomb at 120°C overnight, then ice-cooled. The solution was concentrated to a small volume and chromatographed on a column of silica gel (4.5 × 30 cm) using 5% EtOH in CH_2Cl_2 to give **4a** as white crystals (4.89 g, 71%). mp 168-172°C. *Anal* Calcd for $C_8H_{10}ClN_5$: C, 45.40; H, 4.76; N, 33.09. Found: C, 45.40; H, 4.87; N, 32.73. MS *m/z*: 211, 213 (M^+). UV λ_{max} (MeOH) nm: 265. ^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, s, H-8), 6.47 (2H, br s, NH_2) 4.36 (2H, dd, *J*=7.1, 7.3 Hz, CH_2), 1.83-2.00 (2H, m, CH_2), 0.97 (3H, t, *J*=7.3 Hz, CH_3).

8-Bromo-2-chloro-9-propyladenine (4b). To a solution of **4a** (2.5 g, 11.8 mmol) in 0.5 M acetate buffer (pH 4.0, 64 ml) was added acetic acid (65 ml) and bromine water (128 ml) and stirred at room temperature for 2 days, then filtrated to give **4b** as pale brownish crystals (2.97 g, 87%). mp 164-167°C. *Anal* Calcd for $C_8H_9BrClN_5$: C, 33.07; H, 3.12; N, 24.10. Found: C, 32.84; H, 3.24; N, 23.90. MS *m/z*: 289, 291, 293 (M^+). UV λ_{max} (MeOH) nm: 270. ^{1}H-NMR ($CDCl_3$) δ: 7.91 (2H, br s, NH_2) 4.04 (2H, dd, *J*=7.1, 7.3 Hz, CH_2), 1.71-1.82 (2H, m, CH_2), 0.87 (3H, t, *J*=7.3 Hz, CH_3).

2-Chloro-8-methoxy-9-propyladenine (4c). To a suspension of **4b** (10 mg, 0.03 mmol) in MeOH (1 ml) was added 5.2M NaOMe (0.1 ml) and stirred at 50°C for 2 hr, then concentrated to a small volume. The residue was partitioned between $CHCl_3$ (10 ml) and water (10 ml). The organic layer was dried over $MgSO_4$, and concentrated to a small volume. The residue was crystallized from 50% EtOH to give **4c** as white crystals (7.2 mg). mp 169-171°C. UV λ_{max} (MeOH) nm: 267.

6-Acetamide-2-chloro-7,8-dihydro-9-propylpurin-8-one (5a). A solution of **4b** (2 g, 6.88 mmol) in acetic acid (40 ml) and acetic anhydride (40 ml) was stirred at 100°C overnight, then evaporated. The residue was crystallized from EtOH to give **5a** as white crystals (1.55 g, 84%). mp 178-182°C. *Anal* Calcd for $C_{10}H_{12}ClN_5O_2$: C, 44.54; H, 4.48; N, 25.97. Found: C, 44.28; H, 4.39; N, 25.53. MS *m/z*: 269, 271 (M^+). UV λ_{max} (MeOH) nm: 299. ^{1}H-NMR (DMSO- d_6) δ: 11.06 (1H, br s, *N*-H), 10.19 (1H, br s, *N*-H), 3.73 (2H, dd, *J*=7.0, 7.3 Hz, N^9-CH_2), 2.13 (3H, s, Ac), 1.61-1.79 (2H, m, CH_2), 0.88 (3H, dd, *J*=7.1, 7.7 Hz, CH_3).

Reaction of 4b with NaOAc in the mixture of Ac_2O and AcOH. A solution of **4b** (100 mg, 0.34 mmol) and anhydrous NaOAc (130 mg, 1.7 mmol) in a mixture of AcOH (5 ml) and Ac_2O (5 ml) was heated under reflux for 1 hr, then evaporated. To the residue was added $CHCl_3$ (5 ml) and water (5 ml) and insoluble solid was collected to give 6-acetamide-2,3,7,8-tetrahydro-9-propylpurin-2,8-dione (**5c**) as white crystals (37 mg). mp >250°C. *Anal* Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.87. Found: C, 47.48; H, 5.15; N, 27.48. MS *m/z*: 251 (M^+). UV λ_{max} (MeOH) nm: 313, 325 (sh). Compound **5a** was observed in the organic layer on thin-layer chromatography (TLC).

6-Amino-2-chloro-7,8-dihydro-9-propylpurin-8-one (5b). A solution of **5a** (1.55 g, 5.75 mmol) in MeOH (45 ml) saturated with ammonia at 0°C was stirred at room temperature overnight, then evaporated. The residue was crystallized from EtOH to give **5b** as white crystals (1.17 g, 89%). mp 252-255°C. *Anal* Calcd for $C_8H_{10}ClN_5O$: C, 42.21; H, 4.43; N, 30.76. Found: C, 42.02; H, 4.46; N, 30.44. MS *m/z*: 227, 229 (M^+). UV λ_{max} (MeOH) nm: 276. ^{1}H-NMR (DMSO-d_6) δ: 10.25 (1H, br s, N^7-H), 6.84 (2H, br s, NH_2), 3.73 (2H, t, *J*=7.1 Hz, N^9-CH_2), 1.56-1.74 (2H, m, CH_2), 0.85 (3H, dd, *J*=7.1, 7.7 Hz, CH_3).

6-Amino-2-chloro-7,8-dihydro-7-methyl-9-propylpurin-8-one (6). To a solution of **5b** (1.15 g, 5.05 mmol) in DMF (120 ml) was added potassium carbonate (1.61 g, 11.6 mmol) and iodomethane and stirred at room temperature for 1.5 hr, then AcOH (1 ml) was added and the solution was concentrated to a small volume. The residue was partitioned between $CHCl_3$ (150 ml) and water (150 ml). The organic layer was evaporated to dryness and crystallized from EtOH to give **6** as white crystals (1.06 g, 86%). mp 178.5-181.5°C. *Anal* Calcd for $C_9H_{12}ClN_5O{\bullet}0.2H_2O$: C, 44.07; H, 5.10; N, 28.55. Found: C, 44.20; H, 4.96; N, 28.59. MS *m/z*: 241, 243 (M^+). UV λ_{max} (MeOH) nm: 278. ^{1}H-NMR (DMSO- d_6) δ: 7.04 (2H, br s, NH_2), 3.68 (2H, t, *J*=7.1 Hz, N^9-CH_2), 3.46 (3H, s, N^7-CH_3), 1.60-1.71 (2H, m, CH_2), 0.84 (3H, dd, *J*=7.3, 7.5 Hz, CH_3).

2-Chloro-1,6,7,8-tetrahydro-7-methyl-9-propylpurin-6,8-dione (7). To a solution of **6** (575 mg, 2.37 mmol) in AcOH (17 ml) was added dropwise to 0.73 M $NaNO_2$ (5.75 ml) and the solution was stirred at room temperature for 30 min, then concentrated to a small volume. The residue was crystallized from H_2O to give **7** as white crystals (0.47 g, 82%). mp 168.5-173°C. *Anal* Calcd for $C_9H_{11}ClN_4O_2$: C, 44.55; H, 4.57; N, 23.09. Found: C, 44.47; H, 4.57; N, 22.87. MS *m/z*: 242, 244 (M^+). UV λ_{max} (MeOH) nm: 263, 300 (sh). ^{1}H-NMR (DMSO- d_6) δ: 3.71 (2H, dd, *J*=7.0, 7.1 Hz, N^9-CH_2), 3.43 (3Hs, N^7-CH_3), 1.61-1.72 (2H, m, CH_2), 0.86 (3H, dd, *J*=7.3, 7.5 Hz, CH_3).

Methylation of 7. To a solution of **7** (242 mg, 1 mmol) in DMF (26 ml) was added potassium carbonate (0.35 g, 2.5 mmol) and iodomethane (0.155 ml, 2.5 mmol) and stirred at room temperature for 1 hr, then AcOH (1 ml) was added and the solution was concentrated to a small volume. The residue was partitioned between $CHCl_3$ (60 ml) and water (50 ml). The organic layer was dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel (2.6 × 50 cm) using a 33-66% AcOEt in hexane. From the first fraction 2-chloro-6-methoxy-7-methyl-7,8-dihydro-9-propyl-purin-8-one (**8**) was obtained as white crystals (18 mg, 6.9%). mp 115-119°C. *Anal* Calcd for $C_{10}H_{13}ClN_4O_2$: C, 46.79; H, 5.10; N, 21.83. Found: C, 46.87; H, 5.17; N, 21.61. MS *m/z*: 256, 258 (M^+). UV λ_{max} (MeOH) nm: 275. ^{1}H-NMR ($CDCl_3$) δ: 4.09 (3H, s, OCH_3), 3.88 (2H, dd, *J*=7.3, 7.7 Hz, N^9-CH_2), 3.56 (3H, s, N^7-CH_3), 1.64-1.86 (2H, m, CH_2), 0.95 (3H, t, *J*=7.3 Hz, CH_3). Second fraction was evaporated to give 2-chloro-1,6,7,8-tetrahydro-1,7-dimethyl-9-propylpurin-6,8-dione (**9**) as white crystals (192 mg, 75%). mp 151-155°C. *Anal* Calcd for $C_{10}H_{13}ClN_4O_2$: C, 46.79; H, 5.10; N, 21.83. Found: C, 46.86; H, 5.13; N, 21.71. MS *m/z*: 256, 258 (M^+). UV λ_{max} (MeOH) nm: 263, 300. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (2H, dd, *J*=7.0, 7.7 Hz, N^9-CH_2), 3.73 (3H, s, CH_3), 3.63 (3H, s, CH_3), 1.72-1.83 (2H, m, CH_2), 1.02 (3H, dd, *J*=7.3, 7.7 Hz, CH_3).

2-Amino-1,6,7,8-tetrahydro-1,7-dimethyl-9-propylpurin-6,8-dione (10). A solution of **9** (15 mg, 0.17 mmol) in MeOH (4 ml) saturated with ammonia at 0°C was heated in a steel bomb at 100°C overnight, then ice-cooled. The solution was concentrated to a small volume. The residue was crystallized from EtOH to give **10** as a solid (10.8 mg). MS *m/z*: 237 (M^+). UV λ_{max} (MeOH) nm: 253, 296.

1,7-Dimethyl-9-propyluric acid (11). A mixture of **9** (784 mg, 3 mmol) and NaOAc (2.04 g, 24.9 mmol) in AcOH (80 ml) was heated at 140°C for 3 days, then concentrated to a small volume. The residue was partitioned between CH_2Cl_2 (50 ml) and water (50 ml). The aqueous layer was extracted with CH_2Cl_2 (50 ml × 4) and the combined organic layer was dried over $MgSO_4$, concentrated to a small volume, and crystallized from MeOH to give **11** as white crystals (591 mg, 81%). mp 238.5-243°C. *Anal* Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.22; H, 6.01; N, 23.41. MS *m/z*: 238 (M^+). UV λ_{max} (MeOH) nm: 290. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (2H, dd, *J*=7.3, 7.7 Hz, N^9-CH_2), 3.58 (3H, s, CH_3), 3.38 (3H, s, CH_3), 1.67-1.82 (2H, m, CH_2), 1.02 (3H, t, *J*=7.3 Hz, CH_3).

Methylation of 11. To a solution of **11** (150 mg, 0.63 mmol) in DMF (10 ml) was added potassium carbonate (182 mg, 1.3 mmol) and iodomethane (0.08 ml, 1.3 mmol) and stirred at room temperature for 1.5 hr, then AcOH (0.5 ml) was added and the solution was concentrated to a small volume. The residue was partitioned between $CHCl_3$ (60 ml) and water (60 ml). The organic layer was dried over $MgSO_4$, concentrated to a small volume, and chromatographed on a column of silica gel (1.8 × 35 cm) using 0-10% EtOH in CH_2Cl_2. Evaporation of the first fraction gave 1,3,7-trimethyl-9-propyluric acid (**12**) as white crystals (73 mg, 46%). mp 133-135.5°C. *Anal* Calcd for $C_{11}H_{16}N_4O_3$: C, 52.37; H, 6.39; N, 22.21. Found: C, 52.67; H, 6.51; N, 22.20. MS *m/z*: 252 (M^+). UV λ_{max} (MeOH) nm: 294. ^{1}H-NMR ($CDCl_3$) δ: 4.00 (2H, t, *J*=7.7 Hz, N^9-CH_2), 3.39, 3.59 and

3.69 (each 3H, s, N^1-CH$_3$, N^3-CH$_3$ and N^7-CH$_3$), 1.69-1.80 (2H, m, CH$_2$), 0.96-1.04 (3H, m, CH$_3$). From the second fraction, 1,6,7,8-tetrahydro-2-methoxy-1,7-dimethyl-9-propylpurin-6,8-dione (**13**) was obtained as white crystals (24 mg, 15%). MS *m/z*: 252 (M$^+$). UV λ_{max} (MeOH) nm: 250, 287. ^{1}H-NMR (CDCl$_3$) δ: 4.05 (3H, s, OCH$_3$), 3.80 (2H, t, *J*=7.1 Hz, N^9-CH$_2$), 3.60 (3H, s, N^7-CH$_3$), 3.44 (3H, s, N^1-CH$_3$), 1.75-1.81 (2H, m, CH$_2$), 0.94 (3H, t, *J*=7.4 Hz, CH$_3$). Reaction of **9** (5 mg, 0.02 mmol) with 1M NaOMe (0.6 ml) at 50°C overnight also gave **13** (3.6 mg) as a solid, of which UV spectrum and R*f* value on TLC was identical with the former sample.

2-(2,6-Difluorobenzyl)oxy-1,6,7,8-tetrahydro-1,7-dimethyl-9-propyl-purin-6,8-dione (14a). To a solution of **11** (100 mg, 0.42 mmol) in DMF (10 ml) was added potassium carbonate (140 mg, 1 mmol) and 2,6-difluorobenzyl bromide (207 mg, 1 mmol) and stirred at room temperature for 1.5 hr, then AcOH (0.5 ml) was added and the solution was concentrated to a small volume. The residue was partitioned between CHCl$_3$ (60 ml) and water (60 ml). The organic layer was dried over MgSO$_4$, concentrated to a small volume, and chromatographed on a column of silica gel G (2.3× 43 cm) using 0-66% AcOEt in hexane to give **14a** as white crystals (70 mg, 46%). mp 119-119.5°C. *Anal* Calcd for C$_{17}$H$_{18}$F$_2$N$_4$O$_3$: C, 56.04; H, 4.98; N, 15.38. Found: C, 56.33; H, 5.08; N, 15.39. MS *m/z*: 364 (M$^+$). UV λ_{max} (MeOH) nm: 252, 288. ^{1}H-NMR (CDCl$_3$) δ: 6.92-7.45 (3H, m, Ph), 5.55 (2H, s, N^3-CH$_2$), 3.82 (2H, dd, *J*=7.0, 7.7 Hz, N^9-CH$_2$), 3.42 and 3.59 (each 3H, s, N^1-CH$_3$ and N^7-CH$_3$), 1.68-1.86 (2H, m, CH$_2$), 0.93-1.00 (3H, m, CH$_3$).

2-[(4,6-Dimethylpyridin-2-yl)methyl]oxy-1,6,7,8-tetrahydro-1,7-dimethyl-9-propylpurin-6,8-dione (14b). To an ice-cooled mixture of **11** (100 mg, 0.42 mmol) and 4,6-dimethy-2-pyridylcarbinol (110 mg, 0.8 mmol) in dry THF was added triphenylphosphine (250 mg, 1 mmol) and diisopropyl azodicarboxylate (0.2 ml, 1 mmol) and the solution was stirred at 50°C overnight, then concentrated to a small volume. The residual solution was chromatographed on a column of silica gel (2.3 × 40 cm) using a gradient of hexane-AcOEt =1:1 (500 ml) to AcOEt-MeOH=9:1 (500 ml) to give **14b** as white crystals (107 mg, 71%). mp 120-121°C. *Anal* Calcd for C$_{18}$H$_{23}$N$_5$O$_3$•0.3H$_2$O: C, 59.59; H, 6.56; N, 19.30. Found: C, 59.55; H, 6.72; N, 19.11. MS *m/z*: 357 (M$^+$). UV λ_{max} (MeOH) nm: 256, 288. ^{1}H-NMR ([^{2}H$_6$]-DMSO) δ: 7.17 and 7.05 (each 1H, s, Py), 5.43 (2H, s, N^3-

CH_2), 3.65 (2H, t, J=7.0 Hz, N^9-CH_2), 3.406 and 3.413 (each 3H, s, N^1-CH_3 and N^7-CH_3), 2.29 and 2.42 (each 3H, s, 4'-CH_3 and 6'-CH_3), 1.54-1.65 (2H, m, CH_2), 0.73-0.81 (3H, m, CH_3).

REFERENCES AND FOOTNOTES

1) Fraisse, L.; Verlhac, J. B.; Roche, B.; Rascle, M. C.; Rabion, A.; Seris, J. L. *J. Med. Chem.*, **1993**, *36*, 1465-1473.
2) a) Koizume, S.; Inoue, H.; Kamiya, H.; Ohtsuka, E. *Chem. Commun.*, **1996**, 265-266. b) *idem, ibid.*, **1998**, *26*, 3599-3607.
3) Reitz, A. B.; Goodman, M. G.; Pope, B. L.; Argentieri, D. C.; Bell, S. G.; Burr, L. E.; Chourmouzis, E.; Come, J.; Goodman, J. H.; Klaubert, D. H.; Maryanoff, B. E.; McDonell, M. E.; Rampulla, M. S.; Schott, M. R.; Chen, R. *J. Med. Chem.*, **1994**, *37*, 3561-3578.
4) a) Brodie, B. B.; Axelrod, J.; Shore, P. A.; Udenfriend, S. *J. Biol. Chem.*, **1954**. *208*, 741-750. b) El'tsov, A. V.; Krivozheiko, K. M.; Kolesova, M. B. *Zu. Org. Khim.*, **1967**, *3*, 1518-1528. c) Mossehli, M. A.; Pfeiderer, W. *J. Heterocycl. Chem.*, **1993**, *30*, 1221-1228.
5) Nathan, A. H; Bogert, M. T. *J. Am. Chem. Soc.*, **1941**, *63*, 2567-2569.
6) Mehrotra, M. M.; Sternbach, D. D.; Rutkowske, R. D. *J. Org. Chem.*, **1995**, *60*, 7063-7065.
7) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn*, **1967**, *40*, 2380.
8) Davoll, J. *J. Am. Chem. Soc.*, **1952**, *74*, 1563.
9) a) Ikehara, M.; Uesugi, S.; Kaneko, M. "*Nucleic Acid Chemistry*", ed. by Townsend, L. B.; Tipson, R. S. John Wiley & Sons, New York, **1978**; pp 837 - 841. b) Ikehara, M.; Kaneko, M. *Tetrahedron*, **1970**, *26*, 4251.
10) Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.*, **1965**, *87*, 1772-1776.
11) Davoll, J. *J. Am. Chem. Soc.*, **1951**, *73*, 3174-3176.
12) Rizkalla, B. H.; Robins, R, K.; Broom, A. D., *Biochem. Biophys. Acta*, **1969**, *195*, 285-293.
13) Brown, D. J.; Hoerger, E.; Mason, S. F., *J. Chem. Soc.*, **1955**, 211

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