A Convenient Synthesis of Tricyclic Purine Derivatives

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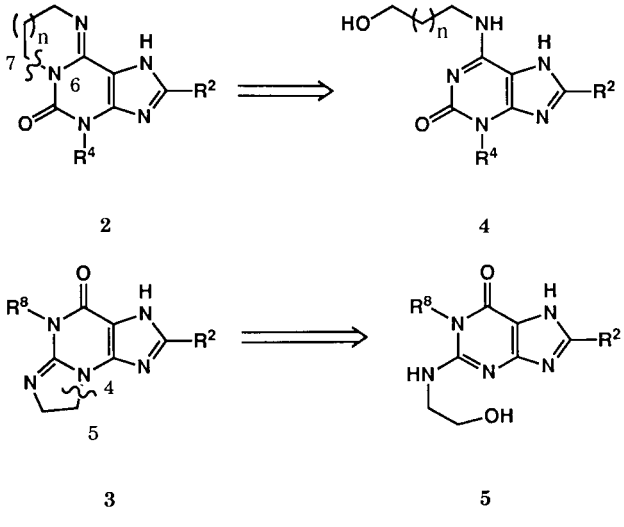
Received June 1, 1992

A convenient synthesis of new heterocycles such as 7,8-dihydro-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-ones (**2**, n = 0) and 5,6-dihydro-1*H*-imidazo[2,1-*b*]purin-9(8*H*)-ones (**3**) was described. The syntheses of **2** and **3** were accomplished by treatment of 6-methylthio-7*H*-purin-2(3*H*)-ones **7** or 2-benzylthio-1-methyl-9-triphenylmethyl-9*H*-purin-6(1*H*)-one (**15**) with appropriate aminoalcohol followed by dehydrative cyclization using thionyl chloride. Compound **15** was efficiently prepared by benzylation of 6-hydroxy-2-mercaptopurine (**12**) followed by tritylation and *N*-methylation.

J. Heterocyclic Chem., **30**, 241 (1993).

Xanthines show interesting and diverse pharmacological activities owing to their interactions with enzymes and receptors [1]. Theophylline (**1**), used in the treatment of asthma [2], possesses a very low margin of safety [3] due to its multiple pharmacological activities and much effort has been directed toward the development of new xanthine derivatives with potent bronchodilator activity and fewer side effects. We postulated that the diverse pharmacological actions of theophylline might be based on multiple biochemical mechanisms. Previous work suggested that an increase in lipophilicity at the xanthine skeleton enhances one of these biochemical activities to some degree [4-5]. Thus, new heterocycles such as 7,8-dihydro-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-ones **2** (n = 0) and 5,6-dihydro-1*H*-imidazo[2,1-*b*]purin-9(8*H*)-ones **3** were designed (Scheme 1) [6].

Scheme 1



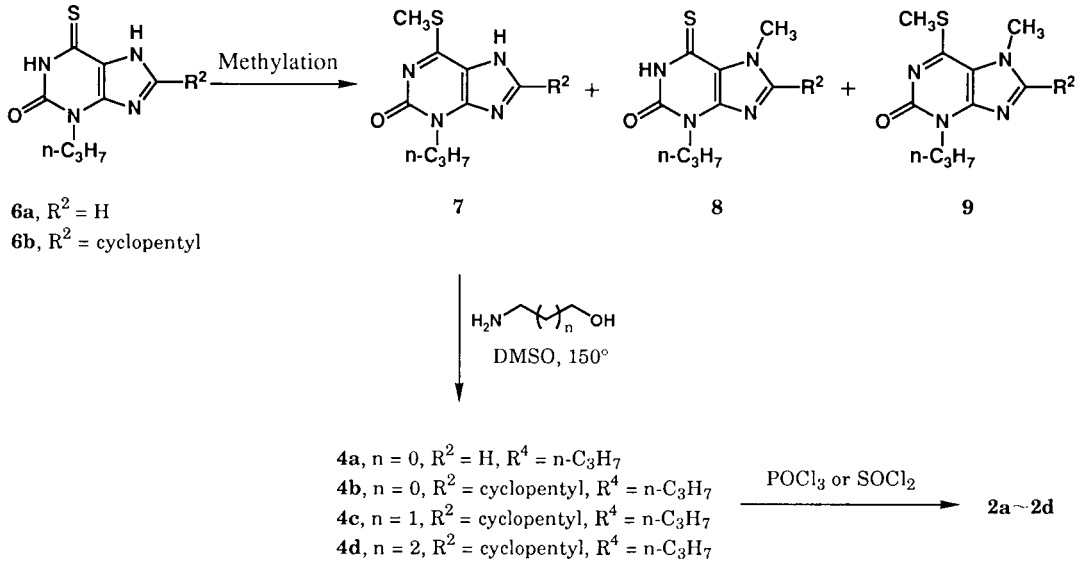
In this paper, we wish to report convenient syntheses of novel imidazo-fused tricyclic purine derivatives from the requisite substituted purines [7].

As shown in Scheme 1, retrosynthetic analysis of **2** and **3** suggested that simple disconnection of the single bond (N(6)–C(7)) in **2** to **4** [8] or that of the single bond (N(4)–C(5)) in **3** to **5**, respectively, might be appropriate.

Reaction of 6-thioxanthine (**6a**) [9] with methyl iodide (1.5 equivalents) in the presence of sodium hydride (1.2 equivalents) in DMF gave a mixture of *N*- and *S*-alkylated products: **7a**, 43%; **8a**, 14%; **9a**, 29% yield (Scheme 2). In contrast to this result, methylation of 8-cyclopentyl-6-thioxanthine (**6b**) under above condition occurred predominantly at the sulfur atom to give **7b** in 75% yield and **9b** in 2.6% yield. The presence of the substituent (R^2) on the imidazole ring greatly influenced the regioselectivity of methylation under these conditions. When **6** was treated with methyl iodide (1.5 equivalents) in aqueous alkaline solution, selective monomethylation at sulfur [10] occurred to afford **7a** and **7b** (78 and 84% yield respectively). Treatment of 6-methylthio-7*H*-purin-2(3*H*)-one derivatives **7a** and **7b** with excess ethanolamine (5 equivalents) in DMSO at 150° gave corresponding 6-(2-hydroxyethyl)amino-7*H*-purin-2(3*H*)-ones **4a** and **4b** in good yields. The amino alcohols **4a** and **4b** were then cyclized to 7,8-dihydro-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-ones **2a** and **2b** with phosphorus oxychloride at reflux temperature [11] for 30 minutes in 29 and 23% yields. Compound **4b** was also cyclized to **2b** with thionyl chloride at room temperature [12] and the yield was improved to 78% yield for **2b**. To confirm the structure of **2a**, it was methylated to give **10**, which was identical with that prepared from **9a**.

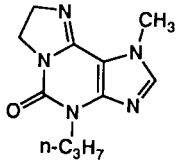
6-(3-Hydroxypropyl)- or 6-(4-hydroxybutyl)amino-7*H*-purin-2(3*H*)-ones **4c** and **4d** prepared as above was next subjected to the cyclization reaction. Treatment of **4c** with phosphorus oxychloride at reflux temperature gave only trace amounts of the cyclized compound **2c**. On the other hand, **2c** and **2d** were obtained in 44 and 35% yields by treatment with thionyl chloride at 50°, respectively. Compounds **4c** and **4d** were cyclized with more difficulty than **4a** and **4b** presumably because cyclization to a 6- or 7-membered ring was kinetically a more unfavorable reaction than that to a 5-membered ring. Griengl *et al.* [12b] reported that treatment of 6-[*N*-(4-hydroxybutyl)-*N*-methyl]aminopurine with thionyl chloride gave only the 4-chlo-

Scheme 2



robutyl compound, which was cyclized in alkaline medium to the C(6)-N(7) bridged compound **11** (Scheme 2). During cyclization of **4d**, such a bridged compound was not found.

Next, synthesis of **3** was investigated. The chemical issues to be explored were: (a) the two selective alkylations of N(1) and S[C(2)] of **12** to afford **15**; and (b) the intramolecular cyclization of **5** to **3** [13].



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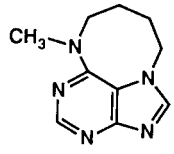

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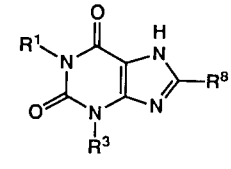
Treatment of **12** with benzyl bromide in aqueous alkaline solution [14] gave **13** in a 45% yield as the sole product (Scheme 3). Owing to more favorable solubility in organic solvents, a benzyl group was preferred for *S*-alkylation instead of a methyl group [15]. Tritylation of **13** at N-9 (54% yield) and methylation of **14** at N-1 (58% yield) under the usual conditions gave **15**. In these reactions, none of other regioisomers was observed. The NOE between the methylene protons of the benzyl group and those of the 1-methyl group, and the lack of an observation of long range couplings between the 1-methyl group and C-4, and long range coupling based on long range selective proton decoupling experiments ($^3J_{C(5)-H[C(8)]}$ = 11.2 Hz and $^3J_{C(4)-H[C(8)]}$ = 5.3 Hz) confirmed the chemical structure of **15** as shown in Scheme 3. The alkylation selectivities are consistent with results reported by Montgometry *et al.*, where allylation of hypoxanthine using potassium *tert*-butoxide, followed by methylation with methyl tosylate afforded 9-allyl-1-methylhypoxanthine [16]. In general, the allyl protecting group is more difficult to remove under mild acidic conditions than the trityl group [17].

Treatment of **15** with excess of ethanolamine at 160° gave **5a**, the precursor for cyclization. Since **5a** was not stable, partly purified material was immediately reacted with thionyl chloride at room temperature as mentioned above to afford the desired cyclized product **3a**. Acidic cyclization was followed by removal of the trityl protecting group. This scheme presents new methodology for the synthesis of a variety of N^2,3-cyclized guanine derivatives using appropriate hydroxyalkylamines instead of ethanolamine.



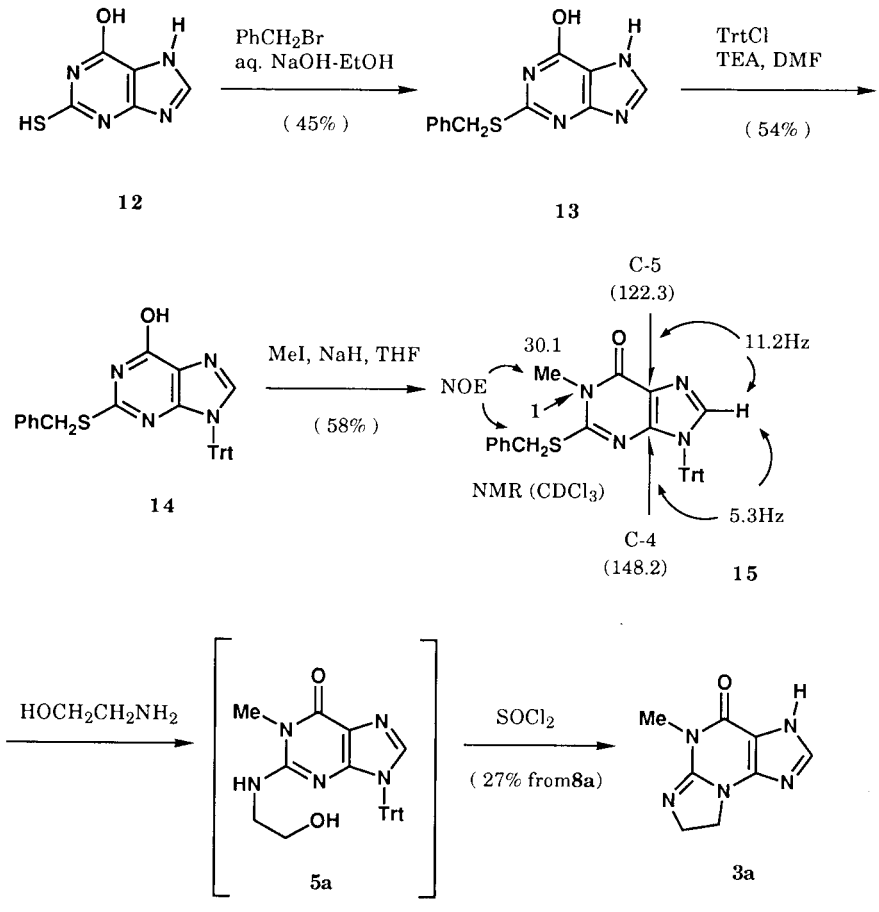
1, $R^1 = R^3 = CH_3$, $R^8 = H$

Some of these heterocycles exhibited potent bronchodilator activities which will be published elsewhere. In conclusion, the synthesis of several tricyclic purine derivatives **2** and **3** was accomplished by treatment of 6- or 2-alkylthio-substituted purines **7** and **15** with the appropriate amino-alcohol followed by dehydrative cyclization using thionyl chloride.

EXPERIMENTAL

Melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. Infrared (ir)

Scheme 3



spectra were measured on a JASCO IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were measured on a Hitachi R-90H or a JEOL JNM GX-270 spectrometer with tetramethylsilane (TMS) as an internal standard. The ^{13}C nmr spectra were recorded on a JEOL JNM GX-270 or a Bruker AMX400 spectrometer. Values of the chemical shift and coupling constant (J) are given in δ (ppm) and Hz. Mass spectra (ms) were determined on a JEOL JMS-D300 instrument at an ionization potential of 70 eV. Microanalysis was performed on a Perkin-Elmer 2400CHN. For column chromatography, Silica gel 60 (E. Merck, 0.063-0.200 mm) was used. Silica gel preparative thin layer chromatography was performed with Merck Kieselgel $F_{254}S$. Standard workup refers to chloroform extraction washed successively with water and brine, dried over anhydrous sodium sulfate and concentrated by a rotary evaporator.

6-Methylthio-3-propyl-7*H*-purin-2(3*H*)-one Hydrate (**7a**).

(A) Methylation using Sodium Hydride.

To a solution of **6a** [9] (210 mg, 1.0 mmoles) in 5 ml of DMF was added portionwise 48.0 mg (1.2 mmoles) of 60 wt% sodium hydride with ice-cooling. After stirring 30 minutes at 0°, 93 μl (1.5 mmoles) of methyl iodide was added, and the mixture was stirred for further thirty minutes at 0°. Standard workup followed by purification on silica gel column chromatography (eluent: 2-10% methanol/chloroform) afforded **7a**, **8a**, and **9a**.

Compound **7a**.

This compound was obtained in 43% yield, mp 241-243° (acetonitrile); ir (potassium bromide): ν 3400 (br), 1600 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.88 (t, 3H, J = 7.2 Hz, $NCH_2CH_2CH_3$), 1.62-1.80 (m, 3H, $NCH_2CH_2CH_3$), 2.57 (s, 3H, SCH_3), 3.99 (t, 2H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 8.13 (s, 1H, 8-H), 13.54 ppm (br s, 1H, NH); ^{13}C nmr (DMSO-d_6): 11.0 ($NCH_2CH_2CH_3$), 11.3 (SCH_3), 20.6 ($NCH_2CH_2CH_3$), 44.4 ($NCH_2CH_2CH_3$), 112.8 (br, C-5), 149.4 (br), 153.7 (C-8), 160.6 ppm; ms: m/z 224 (M^+).

Anal. Calcd. for $C_9H_{12}N_4OS\cdot H_2O$: C, 44.61; H, 5.82; N, 23.12. Found: C, 44.80; H, 5.94; N, 23.03.

7-Methyl-3-propyl-6-thioxanthine (**8a**).

This compound was obtained in 14% yield, mp 202° (ethanol-water); ir (potassium bromide): ν 1693, 1666, 1587 cm^{-1}; ^{1}H nmr (deuteriochloroform): 0.98 (t, 3H, J = 7 Hz, $NCH_2CH_2CH_3$), 0.55-2.00 (m, 2H, $NCH_2CH_2CH_3$), 4.07 (t, 3H, J = 7 Hz, NCH_2CH_2-CH_3), 4.15 (s, 3H, N-CH_3), 7.61 (s, 1H, 8-H), 9.60 ppm (br s, 1H, NH); ms: m/z 224 (M^+).

Anal. Calcd. for $C_9H_{12}N_4OS$: C, 48.19; H, 5.39; N, 24.98. Found: C, 48.32; H, 5.29; N, 24.94.

7-Methyl-6-methylthio-3-propyl-7*H*-purin-2(3*H*)-one (**9a**).

This compound was obtained in 29% yield, mp 225-226° (acetonitrile); ir (potassium bromide): ν 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): 0.98 (t, 3H, J = 7.2 Hz, $NCH_2CH_2CH_3$), 1.77-1.95 (m, 2H, $NCH_2CH_2CH_3$), 2.71 (s, 3H, SCH_3), 4.01 (s, 3H, N-CH_3), 4.16 (t, 2H, J = 7.0 Hz, $NCH_2CH_2CH_3$), 7.53 ppm (s, 1H,

8-H); ^{13}C nmr (deuteriochloroform): 11.2 ($NCH_2CH_2CH_3$), 12.2 (SCH_3), 21.2 ($NCH_2CH_2CH_3$), 45.0 ($NCH_2CH_2CH_3$), 114.3 (C-5), 143.3 (C-8), 151.6 (C-4), 154.7 (C=O), 160.9 ppm (C-6); ms: m/z 238 (M^+).

Anal. Calcd. for $C_{10}H_{14}N_4OS$: C, 50.40; H, 5.92; N, 23.50. Found: C, 50.30; H, 5.95; N, 23.35.

(B) Methylation in an Aqueous Alkaline Solution.

To a solution of **6a** (105 mg, 0.5 mmole) in 2 ml of 0.5*N* aqueous sodium hydroxide solution and 1 ml of ethanol was added 47 μl (0.75 mmole) of methyl iodide at 0°. After stirring for 2 hours at room temperature, the mixture was neutralized with 1*N* hydrochloric acid and concentrated. The resulting precipitate was collected by filtration and recrystallized from acetonitrile to give 87 mg (78%) of **7a**.

8-Cyclopentyl-3-propyl-6-thioxanthine (**6b**).

A mixture of 8-cyclopentyl-3-propylxanthine [18] (14.1 g, 53.8 mmoles) and 19.5 g (87.7 mmoles) of phosphorus pentasulfide in pyridine (280 ml) was refluxed for 4 hours. The reaction mixture was poured into 600 ml of ice water and the precipitate was collected by filtration. The filtrate was concentrated and the precipitate was collected again. The combined precipitate was suspended in 400 ml of 2*N* aqueous sodium hydroxide solution. Insoluble materials were filtered off, and the filtrate was neutralized with concentrated hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol-water to afford 13.5 g (90%) of **6b** as pale yellow prisms, mp 214-216°; ir (potassium bromide): ν 1663 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.87 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.55-2.05 (m, 10H), 3.10-3.30 (m, 1H, -CH-), 3.90 (t, 2H, J = 7.2 Hz, $NCH_2CH_2CH_3$), 12.04 (br s, 1H), 13.03 ppm (br s, 1H); ^{13}C nmr (DMSO-d_6): 10.9 ($NCH_2CH_2CH_3$), 20.7 ($NCH_2CH_2CH_3$), 25.2 (cyclopentyl), 32.0 (cyclopentyl), 38.7 (-CH-, cyclopentyl), 43.8 ($NCH_2CH_2CH_3$), 118.5 (C-5), 145.7, 148.9, 161.5 (C=O), 173.3 ppm (C=S); ms: m/z 278 (M^+).

Anal. Calcd. for $C_{13}H_{18}N_4OS \cdot 0.25C_2H_5OH$: C, 55.93; H, 6.77; N, 19.32. Found: C, 56.17; H, 6.76; N, 19.44.

8-Cyclopentyl-6-methylthio-3-propyl-7*H*-purin-2(3*H*)-one (**7b**).

Compound **7b** was prepared from **6b** in 84% yield following the same procedure as for **7a**. This compound was obtained as a pale yellow powder (toluene), mp 258-259°; ir (potassium bromide): ν 1599 cm^{-1}; ^{1}H nmr (deuteriochloroform): 0.95 (t, 3H, J = 7 Hz, $NCH_2CH_2CH_3$), 1.50-2.50 (m, 10H), 2.10 (s, 3H, SCH_3), 3.15-3.53 (m, 1H, -CH-), 4.24 ppm (t, 2H, J = 7 Hz); ms: m/z 292 (M^+).

Anal. Calcd. for $C_{14}H_{20}N_4OS$: C, 57.51; H, 6.89; N, 19.16. Found: C, 57.77; H, 7.22; N, 19.36.

6-(2-Hydroxyethylamino)-3-propyl-7*H*-purin-2(3*H*)-one (**4a**).

A mixture of **7a** (4.00 g, 17.9 mmoles) and 5.40 ml (89.5 mmoles) of ethanolamine in 18 ml of dimethyl sulfoxide was heated at 150° for one hour. The reaction mixture was directly applied to DIAION® HP-40 (Mitubishi Chemical Industries Co., Ltd.) column chromatography. The product was isolated by eluting with 30% methanol/water to give 3.24 g (77%) of **4a** as white needles. An analytical sample was recrystallized from water, mp 285-286°; ir (potassium bromide): ν 3300, 1650, 1642 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.85 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.50-1.70 (m, 2H, $NCH_2CH_2CH_3$), 3.50-3.60 (m, 4H, NCH_2CH_2-OH), 3.88 (t, 2H, J = 7.4 Hz, $NCH_2CH_2CH_3$), 4.90 (br s, 1H), 7.50 (br s, 1H, NH), 7.88 (s, 1H, C8-H), 12.2 ppm (br s, 1H); ms: m/z 237 (M^+).

Anal. Calcd. for $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.51. Found: C, 50.55; H, 6.70; N, 29.19.

8-Cyclopentyl-6-(2-hydroxyethylamino)-3-propyl-7*H*-purin-2(3*H*)-one (**4b**).

A mixture of **7b** (5.00 g, 17.1 mmoles) and 5.16 ml (85.5 mmoles) of ethanolamine in 18 ml of dimethyl sulfoxide was heated at 150° for one hour. Standard workup followed by purification on silica gel column chromatography (eluent: 5% methanol/chloroform) gave 4.81 g (89%) of **4b** as a white powder. An analytical sample was recrystallized from ethanol-water, mp 221-222°; ir (potassium bromide): ν 3342, 1639, 1619, 1507 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.84 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.50-1.80 (m, 8H), 1.95-2.10 (m, 2H), 3.15-3.60 (m, 5H), 3.85 (t, 2H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 4.96 (br s, 1H), 7.08 (br s, 1H), 11.99 ppm (br s, 1H); ms: m/z 305 (M^+).

Anal. Calcd. for $C_{15}H_{23}N_5O_2$: C, 58.99; H, 7.59; N, 22.93. Found: C, 58.74; H, 7.92; N, 22.61.

8-Cyclopentyl-6-(3-hydroxypropylamino)-3-propyl-7*H*-purin-2(3*H*)-one (**4c**).

Compound **4c** was prepared from **7b** and 3-aminopropanol in 98% yield as white solids following the same procedure as for **4b**. An analytical sample was recrystallized from toluene, mp 130°; ir (potassium bromide): ν 3250, 1708, 1664, 1615 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.90 (t, 3H, J = 7.4 Hz, $NCH_2CH_2CH_3$), 1.50-1.85 (m, 10H), 1.90-2.20 (m, 2H), 3.25-3.80 (m, 5H), 3.89 (t, 2H, J = 7.4 Hz, $NCH_2CH_2CH_3$), 8.51 (br s, 1H), 12.80 ppm (br s, 1H); ms: m/z 319 (M^+).

Anal. Calcd. for $C_{16}H_{25}N_5O_2 \cdot 1.5H_2O$: C, 55.47; H, 8.15; N, 20.21. Found: C, 55.07; H, 7.96; N, 19.94.

8-Cyclopentyl-6-(4-hydroxybutylamino)-3-propyl-7*H*-purin-2(3*H*)-one Hydrochloride (**4d**).

Compound **4d** was prepared from **7b** and 4-aminobutanol in 90% yield following the same procedure as for **4b** as an amorphous powder. Treatment with hydrogen chloride saturated ethyl acetate solution and recrystallization from toluene-2-propanol afforded an analytical sample as a pale yellow powder, mp 146-147°; ir (potassium bromide): ν 3250, 1722, 1673, 1611 cm^{-1}; ^{1}H nmr (DMSO-d_6): 0.89 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.40-1.80 (m, 12H), 1.90-2.15 (m, 2H), 3.20-3.60 (m, 5H), 3.94 (t, 2H, J = 6.8 Hz, $NCH_2CH_2CH_3$), 10.26 (br s, 1H), 13.92 ppm (br s, 1H); ms: m/z 333 (M^+).

Anal. Calcd. for $C_{17}H_{27}N_5O_2 \cdot HCl \cdot H_2O$: C, 52.64; H, 7.79; N, 18.05. Found: C, 52.97; H, 8.01; N, 17.96.

7,8-Dihydro-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one (**2a**).

To a stirred solution of phosphorus oxychloride (15 ml) was portionwise added 3.50 g (14.8 mmoles) of **4a** at 0°. The reaction mixture was heated under reflux for thirty minutes and concentrated. The residue was poured into 100 ml of ice water and neutralized with 2*N* aqueous sodium hydroxide solution. Standard workup, purification on column chromatography (DIAION® HP-40, eluent: 20% methanol-water), followed by recrystallization from water gave 938 mg (29%) of **2a** as colorless needles, mp 283-285°; ir (potassium bromide): ν 1718, 1660 cm^{-1}; ^{1}H nmr (DMSO-d_6-DCl): 0.88 (t, 3H, J = 7.2 Hz, $NCH_2CH_2CH_3$), 1.60-1.80 (m, 2H, $NCH_2CH_2CH_3$), 3.85-4.12 (m, 6H), 7.70 ppm (s, 1H); ^{13}C nmr (DMSO-d_6): 10.7 ($NCH_2CH_2CH_3$), 20.6 ($NCH_2CH_2CH_3$), 44.1, 45.2, 45.3, 100.3 (C-9b), 143.9 (C-2), 146.7, 149.1, 151.0 ppm; ms: m/z 219 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.54; H, 6.05; N, 32.15.

2-Cyclopentyl-7,8-dihydro-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one Hydrate (**2b**).

To a stirred solution of thionyl chloride (30 ml) was portionwise added 1.58 g (5.18 mmoles) of **4b** at 0°. The reaction mixture was stirred for 3 hours at room temperature and concentrated. To the residue was added aqueous saturated sodium bicarbonate solution. Standard workup, purification on silica gel chromatography (eluent: 10% methanol/chloroform) followed by recrystallization from dioxane gave 1.23 g (78%) of **2b** as a white powder, mp 215-216°; ir (potassium bromide): ν 1712, 1670 cm^{-1}; ^1H nmr (DMSO-d_6): 0.90 (t, 3H, J = 7.4 Hz, $NCH_2CH_2CH_3$), 1.60-1.90 (m, 8H), 2.00-2.20 (m, 2H), 3.25-3.40 (m, 1H, -CH-), 3.90-4.12 (m, 4H), 4.16-4.28 ppm (m, 2H); ms: m/z 287 (M^+).

Anal. Calcd. for $C_{15}H_{21}N_5O \cdot H_2O$: C, 59.00; H, 7.59; N, 22.93. Found: C, 59.19; H, 7.12; N, 22.66.

2-Cyclopentyl-4-propyl-1,7,8,9-tetrahydropyrimido[2,1-*i*]purin-5(4*H*)-one Hydrochloride (**2c**).

To a stirred solution of thionyl chloride (13 ml) was portionwise added 1.00 g (3.13 mmoles) of **4c** at 0°. The reaction mixture was heated under reflux for 30 minutes and concentrated. To the residue was added aqueous saturated sodium bicarbonate solution. Standard workup followed by purification on silica gel chromatography (eluent: 5% methanol/chloroform) gave 704 mg (75%) of **2c** (free base) as an amorphous powder. Treatment with hydrogen chloride saturated ethyl acetate solution and recrystallization from toluene afforded an analytical sample (470 mg, 60% from free base) as a pale yellow powder, mp 190-196°; ir (potassium bromide): ν 1706, 1662 cm^{-1}; ^1H nmr (deuteriochloroform): 1.06 (t, 3H, J = 7.4 Hz, $NCH_2CH_2CH_3$), 1.70-2.20 (m, 8H), 2.25-2.40 (m, 4H), 3.35-3.45 (m, 1H, -CH-), 3.70-3.90 (m, 2H), 4.20-4.35 (m, 4H), 11.6 (br s, 1H), 13.9 ppm (br s, 1H); ^{13}C nmr (deuteriochloroform): 10.9 ($NCH_2CH_2CH_3$), 19.1, 20.9, 25.2 (cyclopentyl), 32.1 (cyclopentyl), 38.6, 39.8 (-CH-), 41.7, 45.8, 100.9 (C-10b), 145.0, 147.9, 149.7, 162.8 ppm; ms: m/z 301 (M^+).

Anal. Calcd. for $C_{16}H_{23}N_5O \cdot HCl$: C, 56.88; H, 7.15; N, 20.72. Found: C, 56.47; H, 7.29; N, 20.44.

2-Cyclopentyl-4-propyl-7,8,9,10-tetrahydro-1*H*-diazepino[2,1-*i*]-purin-5(4*H*)-one Dihydrochloride (**2d**).

Compound **2d** was prepared from **4d** in 35% yield as a white solid following the same procedure as for **2c**, mp 217-218° dec; ir (potassium bromide): ν 1716, 1678 cm^{-1}; ^1H nmr (deuteriochloroform): 1.00 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.60-2.40 (m, 14H), 3.25-3.40 (m, 1H, -CH-), 3.65-3.80 (m, 4H), 4.12 (t, 2H, J = 7.2 Hz, $NCH_2CH_2CH_3$), 11.34 (br s, 1H), 11.54 (br s, 1H), 14.02 ppm (br s, 1H); ^{13}C nmr (deuteriochloroform): 11.1 ($NCH_2CH_2CH_3$), 21.1, 25.4, 25.6, 29.5, 32.3, 39.9 (-CH-), 42.4, 44.2, 45.5, 102.0 (C-11b), 145.0, 150.1, 150.8, 163.9 ppm; ms: m/z 315 (M^+).

Anal. Calcd. for $C_{17}H_{25}N_5O \cdot 2HCl$: C, 52.58; H, 7.01; N, 18.03. Found: C, 52.58; H, 7.01; N, 18.03.

7,8-Dihydro-1-methyl-4-propyl-1*H*-imidazo[2,1-*i*]purin-5(4*H*)-one (**10**).

Compound **10** was prepared by reaction of **9a** and ethanolamine followed by the dehydrative cyclization in 26% overall yield following the same procedure as for **4a** and **2a**. This compound was obtained as a white powder (toluene), mp 110-112°; ir (potassium bromide): ν 1685, 1657 cm^{-1}; ^1H nmr (deuteriochloroform): 0.97 (t, 3H, J = 7.3 Hz, $NCH_2CH_2CH_3$), 1.70-1.90 (m, 2H, $NCH_2CH_2CH_3$), 3.90-4.05 (m, 4H), 3.95 (s, 3H, N-CH_3), 4.05-4.15 (m, 2H), 7.43 ppm (s, 1H, C8-H); ms: m/z 233 (M^+).

Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.49; H, 6.57; N, 30.23.

To a stirred solution of **2a** (22 mg, 0.1 mmole) in 0.5 ml of *N,N*-dimethylformamide was added 4.4 mg (0.12 mmole) of 60 wt% sodium hydride under ice cooling. After stirring for ten minutes at 0°, 8.5 μl (0.15 mmole) of methyl iodide was added, and the mixture was stirred for thirty minutes at room temperature. Standard workup followed by purification on silica gel preparative thin layer chromatography afforded 11.2 mg (53%) of **10**. This material was identical with that obtained above on tlc and ^1H nmr.

2-Benzylthio-6-hydroxypurine (**13**).

6-Hydroxy-2-mercaptopurine (**12**) [14] (2.0 g, 12 mmoles) was dissolved in a mixture of 10 ml of ethanol, 11 ml of 2*N* aqueous sodium hydroxide solution, and 15 ml of water. Under ice cooling with stirring, 2.1 ml (18 mmoles) of benzyl bromide was added to the solution, followed by stirring at room temperature for thirty minutes. Again under ice cooling, the mixture was neutralized with 2 *N* hydrochloric acid, and 30 ml of *n*-hexane was added to the mixture. The resulting precipitate was collected by filtration, washed with ethyl acetate, and dried to afford 1.3 g (45%) of **13** as white crystals. An analytical sample was recrystallized from 2-propanol, mp >300°; ir (potassium bromide): ν 1689 cm^{-1}; ^1H nmr (DMSO-d_6): 4.47 (s, 2H, benzyl CH_2), 7.20-7.55 (m, 6H, amido NH and phenyl protons), 8.06 (s, 1H, 8-H), 12.50 ppm (br s, 1H, imidazole NH); ms: m/z 258 (M^+).

Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.92; H, 3.69; N, 21.50.

2-Benzylthio-6-hydroxy-9-triphenylmethyl-9*H*-purine (**14**).

To a solution of **13** (1.0 g, 3.9 mmoles) in 20 ml of *N,N*-dimethylformamide was added 0.92 ml (5.8 mmoles) of triethylamine. Under ice cooling, 1.6 g (5.8 mmoles) of triphenylmethyl chloride was added to the solution followed by stirring at room temperature for 12 hours. After 400 ml of water was added, the resulting precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol to give 1.1 g (54%) of **14** as white crystals, mp 267-270°; ir (potassium bromide): ν 1683 cm^{-1}; ^1H nmr (deuteriochloroform): 4.38 (s, 2H, benzyl CH_2), 6.75-7.61 (m, 21H, amido NH and phenyl protons), 7.76 ppm (s, 1H, 8-H).

Anal. Calcd. for $C_{31}H_{24}N_4OS$: C, 74.38; H, 4.83; N, 11.19. Found: C, 74.33; H, 4.87; N, 11.30.

2-Benzylthio-1-methyl-9-triphenylmethyl-9*H*-purin-6(1*H*)-one (**15**).

To a solution of **14** (0.50 g, 0.10 mmole) in 20 ml of tetrahydrofuran was added 0.080 g (0.20 mmole) of 60 wt% sodium hyride under ice cooling. After stirring for thirty minutes at room temperature, 0.13 ml (0.20 mmole) of methyl iodide was added, and the mixture was stirred for 2 hours at 50°. Standard workup followed by purification on silica gel column chromatography (eluent: chloroform) afforded 0.30 g (58%) of **15** as white crystals. An analytical sample was recrystallized from 2-propanol-water, mp 255-258°; ir (potassium bromide): ν 1700 cm^{-1}; ^1H nmr (deuteriochloroform): 3.48 (s, 2H benzyl CH_2), 3.49 (s, 3H, CH_3), 6.94-6.98 and 7.07-7.46 (m, 20H, phenyl protons), 7.64 ppm (s, 1H, 8-H); ^{13}C nmr (deuteriochloroform): 29.7 (CPh_3), 30.1 (CH_3), 36.6 ($PhCH_2S$), 122.3 (C-5), 140.2 (C-8), 148.2 (C-4), 157.1 and 157.7 ppm (C-2 and C-6).

Anal. Calcd. for $C_{32}H_{26}N_4OS$: C, 74.68; H, 5.09; N, 10.89. Found: C, 75.00; H, 5.11; N, 10.96.

5,6-Dihydro-8-methyl-1*H*-imidazo[2,1-*b*]purin-9(8*H*)-one Hydrochloride (**3a**).

A suspension of **15** (4.5 g, 8.7 mmoles) in 25 ml (41 mmoles) of ethanolamine was stirred for 30 minutes at 160°. Standard work-up followed by purification on silica gel column chromatography (eluent: 5% methanol/chloroform) afforded 0.42 g of 2-(2-hydroxyethylamino)-1-methyl-9-triphenylmethyl-9*H*-purin-6(1*H*)-one (**5a**). Due to instability, 8.0 ml of thionyl chloride was immediately added to this compound and stirred at room temperature for 30 minutes. The solvent (thionyl chloride) was evaporated under reduced pressure and ethanol was added to the residue. The resulting precipitate was collected by filtration and recrystallized from ethanol-2-propanol to give 0.45 g (27% from **15**) of **3a** as white crystals, mp 308-310°; ir (potassium bromide): ν 1646 cm^{-1}; ^1H nmr (DMSO-d_6): 3.41 (s, 3H, CH_3), 4.00 (dd, 2H, 6-H, J = 7, 5.5 Hz), 4.43 (dd, 2H, 5-H, J = 7, 5.5 Hz), 8.17 ppm (s, 1H, 2-H); ms: m/z 191 (M^+).

Anal. Calcd. for $C_8H_9N_5O \cdot HCl \cdot 0.2C_2H_5OH$: C, 42.59; H, 4.77; N, 29.57. Found: C, 42.14; H, 4.44; N, 29.57.

Acknowledgement.

We thank M. Takahashi and E. Tsuchiya for technical assistance, H. Ueno, T. Yasuzawa, and A. Nakamura for their help in obtaining the nmr spectra.

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