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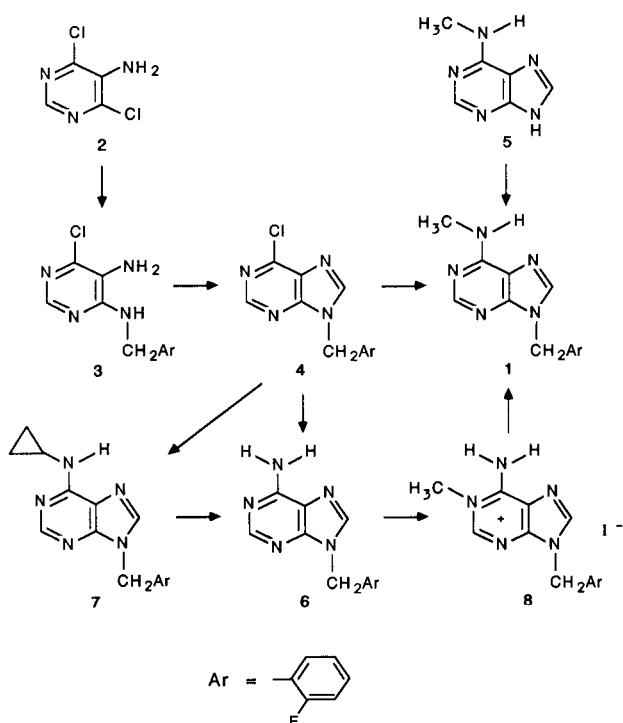
Synthesis of 9-(2-fluorobenzyl)-6-methylamino-9H-purine (**1**) from nine different precursors is reported. Compound **1** was prepared by methylation of 6-chloro-9-(2-fluorobenzyl)-9H-purine (**4**), by alkylation of 6-methylaminopurine (**5**) or form 9-(2-fluorobenzyl)-1-methyladeninium iodide (**8**) via the Dimroth rearrangement. Selective 2-step methylation of 6-aminopurine **6** was accomplished by hydride reduction of 6-formamidopurine **9**, 6-dimethylaminomethyleneaminopurine **10** or 6-phenylthiomethyl purine **11** to give **1**. Compound **1** was also prepared by dethiation or reductive dechlorination of 2-methylthiopurine **16** or 8-chloropurine **19**, respectively, or by hydrolysis of 6-N-methylformamidopurine **12**, which was prepared from 6-dimethylaminopurine **13** by selective oxidation.

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The 9-benzylpurine **1** is a new anticonvulsant agent with potent activity against maximal electroshock-induced seizures in rats and mice [1]. Amongst commonly used anticonvulsants, **1** represents a unique structure type [2]. Although numerous methods for the preparation of 9-substituted purines have been reported [3], the most common entry to the 9-benzylpurines is by alkylation of 6-chloropurine [4,5]. Since this approach necessitates the separation of 7- and 9-isomers by column chromatography, several alternative synthetic routes to **1** were investigated (Schemes 1-3).

The intermediate, 6-chloropurine **4**, was prepared by modification of a literature method [6,7] that obviates the need for chromatography separation of isomers. Amination of **2** (Scheme 1) with 2-fluorobenzylamine gave diami-

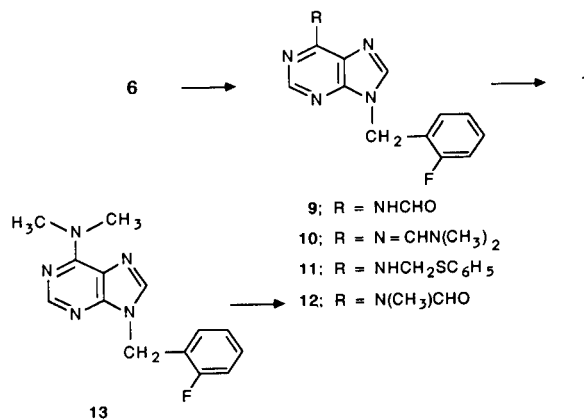
Scheme 1



nopyrimidine **3**. Condensation of **3** with ethanesulfonic acid and triethylorthoformate [8,9] afforded 6-chloropurine **4**. Reaction of **4** with 40% aqueous methylamine in ethanol at ambient temperature gave **1**. Alternatively **4** was reacted with ammonia to give adenine **6**. Compound **6** was also prepared from cyclopropylaminopurine **7** by a novel bromine mediated dealkylation reaction [10]. The cyclopropyl substituent of **7** was cleaved in the presence of bromine; this occurred faster than bromination at the 8-position [11]. Methylation of **6** with methyl iodide gave **8**, which was smoothly converted to **1** via the Dimroth rearrangement [12]. Compound **1** was also prepared by alkylation of the sodium salt of 6-methylaminopurine (**5**) [13] with 2-fluorobenzyl bromide followed by flash column chromatography purification [14].

Several methods for introducing a 6-N-methyl substituent into **6** are depicted in Scheme 2. Selective formylation of **6** with acetic-formic anhydride gave **9**, which was reduced with lithium aluminum hydride to yield **1**. Condensation of **6** with dimethylformamide dimethylacetal [15]

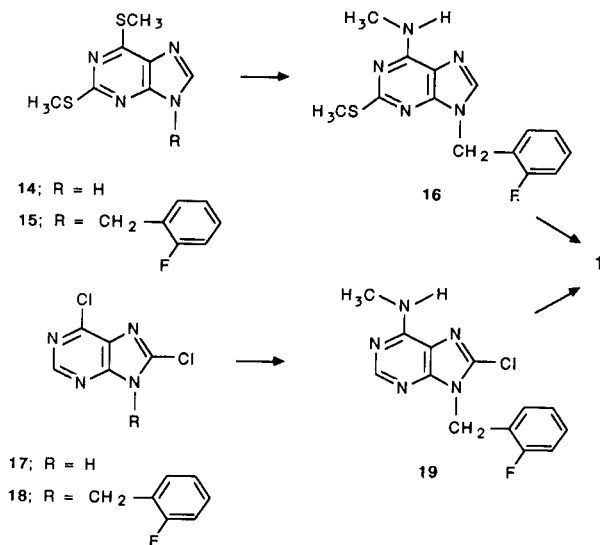
Scheme 2



or with benzenethiol and aqueous formaldehyde [16] gave **10** and **11**, respectively. Both **10** and **11** generated **1** when

treated with sodium borohydride. Compound **1** was also prepared from amide **12** by base hydrolysis. The latter compound was formed by selective oxidation [17] of one of the *N*-methyls in **13**.

Scheme 3



Preparation of **1** by dethiation or reductive dechlorination is illustrated in Scheme 3. Alkylation of 2,6-bis(methylthio)purine (**14**) [18] with 2-fluorobenzyl bromide gave **15**, which was converted to **16** with 40% aqueous methylamine. Desulfuration of **16** with Raney nickel gave **1**. Alkylation of 6,8-dichloropurine (**17**) [19] gave **18**, which was aminated to afford **19**. Dechlorination of **19** with palladium on carbon gave **1**.

The preferred route of preparation of **1** is from 5-amino-4,6-dichloropyrimidine (**2**) as illustrated in Scheme 1. This method gives high yields and is easily adapted to the preparation of analogues from readily available starting materials.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian XL-100-15-FT, a Varian FT-80A, a Varian T-60 or a Hitachi Perkin-Elmer R-24 spectrometer with tetramethylsilane as an internal standard. Ultraviolet absorption spectra were measured on a Unicam SP 800 or Cary 118 UV-vis spectrophotometer. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on tlc. Tlc's were developed on Whatman 200 μ MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography [14] was performed on Silica Gel 60 (40-63 μ m, E. Merck No. 9385). The analytical samples gave combustion values for C, H, N within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc. The 5-amino-4,6-dichloropyrimidine was purchased from Pacific Chemical Laboratories, Inc. and 2-fluorobenzylamine was purchased from Fairfield Chemical Company, Inc.

5-Amino-4-chloro-6-(2-fluorobenzylamino)pyrimidine (**3**).

A mixture of **2** (12.6 g, 76.8 mmoles), 2-fluorobenzylamine (96%) (10.0 g, 76.7 mmoles), 1-butanol (150 ml) and triethylamine (8.0 g, 79.2 mmoles) was refluxed with stirring for 24 hours. The dark solution was cooled to give a solid that was collected on a Buchner funnel and washed with cyclohexane. The white solids were dispersed in water (50 ml), collected and dried to give 15.97 g (82%) of **3**, mp 218-221°. Recrystallization of a portion from ethanol gave the analytical sample, mp 220-223°; uv (0.1*N* hydrochloric acid + 10% ethanol): λ max 305 nm (ϵ 12800); (pH 7 + 10% ethanol or 0.1*N* sodium hydroxide + 10% ethanol): λ max 263 nm (ϵ 9450), 268 nm (ϵ 9200), 292 nm (ϵ 9400); nmr (DMSO-*d*₆): δ 7.77 (s, 1H, pyrimidine H), 7.27 (complex m, 5H, aromatic H and NH), 5.08 (br s, 2H, NH₂), 4.68 (d, collapsed to s with deuterium oxide, 2H, CH₂).

Anal. Calcd. for C₁₁H₁₀ClFN₄: C, 52.28; H, 3.99; N, 22.17. Found: C, 52.39; H, 3.99; N, 22.07.

6-Chloro-9-(2-fluorobenzyl)-9H-purine (**4**).

A mixture of **3** (12.55 g, 49.7 mmoles), triethylorthoformate (100 ml) and ethanesulfonic acid (90 mg) was stirred at ambient temperature for 41 hours. The solution was spin evaporated *in vacuo*. The residual solid was dissolved in ethyl acetate (200 ml) and washed sequentially with 5% aqueous sodium bicarbonate (50 ml), water (4 \times 50 ml), brine (50 ml) and then dried (magnesium sulfate). The solution was spin evaporated *in vacuo* to a residue that was collected and washed with cyclohexane to give 12.41 g (95%) of **4**, mp 96-98°. Recrystallization from cyclohexane-ethyl acetate gave the analytical sample, mp 97-99°; uv (pH 7 + 10% ethanol): λ max 264-268 (plateau) (ϵ 10200); nmr (DMSO-*d*₆): δ 8.78 (s, 2H, purine Hs), 7.34 (complex m, 4H, Ar), 5.65 (s, 2H, CH₂).

Anal. Calcd. for C₁₂H₈ClFN₄: C, 54.87; H, 3.07; N, 21.33. Found: C, 54.96; H, 3.04; N, 21.15.

6-Amino-9-(2-fluorobenzyl)-9H-purine (**6**).

Amination of **4**.

A mixture of **4** (10.00 g, 38.07 mmoles) and ammonia saturated ethanol (300 ml) in a glass lined, stainless steel reaction vessel was heated (120°) for 48 hours. The reaction mixture was cooled, and the solids were collected on a Buchner funnel. Recrystallization from ethanol gave 7.11 g (76%) of **6**, mp 243-245°; uv (0.1*N* hydrochloric acid): λ max 261 nm (ϵ 16000); (pH 7.4 buffer): λ max 262 nm (ϵ 16600); nmr (DMSO-*d*₆): δ 8.20 (s, 1H, purine H), 8.16 (s, 1H, purine H), 7.5-7.0 (complex m, 6H, Ar + NH₂), 5.48 (s, 2H, CH₂).

Anal. Calcd. for C₁₂H₁₀FN₅: C, 59.25; H, 4.14; N, 28.79. Found: C, 59.19; H, 4.15; N, 28.76.

Dealkylation of **7**.

Bromine (2 ml) was added to a solution of **7** (5.00 g, 17.6 mmoles), 0.5 *N* sodium acetate pH 4 buffer (100 ml) and tetrahydrofuran (100 ml). After 10 minutes 2 ml more of bromine was added. The reaction was stirred for 20 minutes, and a slurry of sodium sulfite (12 g) in water was added to reduce the excess bromine. The solution was extracted with ethyl acetate (3 \times 400 ml). The combined extracts were washed with brine, dried (magnesium sulfate) and spin evaporated *in vacuo*. The residue was combined with the product from a separate reaction of **7** (6.20 g, 21.9 mmoles) and dissolved in methanol. This solution was added to Silica Gel 60 (20 g) and spin evaporated *in vacuo*. The residual solids were introduced on a column (20 cm \times 40 cm) of Silica Gel 60 wetted with 1% methanol in chloroform. The column was successively eluted with 1% methanol in dichloromethane (2 liters), 2% methanol in dichloromethane (1 liter) and 3% methanol in dichloromethane using flash chromatography. The fractions that contained product were combined, spin evaporated *in vacuo* and recrystallized from ethanol to give 5.00 g (52%) of **6**, mp 237.5-238.5°.

Anal. Calcd. for C₁₂H₁₀FN₅: C, 59.25; H, 4.14; N, 28.79. Found: C, 59.11; H, 4.01; N, 28.78.

6-Cyclopropylamino-9-(2-fluorobenzyl)-9H-purine (**7**).

A solution of **4** (3.00 g, 11.4 mmoles), ethanol (35 ml) and cyclopropyl-

amine (8 ml) was stirred at ambient temperature for 64 hours. The reaction was spin evaporated *in vacuo*. The white solids were dispersed in water (100 ml), collected on a Buchner funnel and suction filtered. Recrystallization from cyclohexane gave 2.66 g (82%) of **7**, mp 133-134°; nmr (DMSO-*d*₆): δ 8.24 (s, 1H, purine H), 8.20 (s, 1H, purine H), 7.89 (br d, 1H, NH), 7.50-7.10 (complex m, 4H, Ar), 5.44 (s, 2H, CH₂Ar), 3.08 (br m, 1H, NHCH), 0.77-0.55 (complex m, 4H, CH₂CH₂).

Anal. Calcd. for C₁₅H₁₄FN₅: C, 63.59; H, 4.98; N, 24.72. Found: C, 63.27; H, 5.03; N, 24.75.

9-(2-Fluorobenzyl)-1-methyladeninium Iodide (**8**).

A mixture of **6** (1.00 g, 4.12 mmoles), methyl iodide (1 ml) and dimethylformamide (10 ml) was stirred in the dark for 24 hours at ambient temperature. The reaction mixture was diluted with ethanol (40 ml) and stirred for 3 hours. The white solids were collected on a Buchner funnel and washed with ethanol. Recrystallization from water gave 0.98 g (62%) of **8**, 290° (dec); uv (pH 7.4 + 9.5% ethanol): λ max 259 nm (ε 14600); nmr (DMSO-*d*₆): δ 9.40 (br s, 2H, NH₂), 8.64 (s, 1H, purine H), 8.58 (s, 1H, purine H), 7.4-7.2 (complex m, 4H, Ar), 5.54 (s, 2H, CH₂), 3.76 (s, 3H, CH₃).

Anal. Calcd. for C₁₃H₁₃FIN₅: C, 40.53; H, 3.40; N, 18.18. Found: C, 40.49; H, 3.41; N, 18.10.

9-(2-Fluorobenzyl)-6-formamido-9H-purine (**9**).

To an ice cold solution of anhydrous formic acid (5 ml), acetic anhydride (10 ml) and dichloromethane (50 ml) was added in small portions 4-dimethylaminopyridine (0.75 g, 6.17 mmoles). The solution was allowed to come to ambient temperature while being stirred under nitrogen. To this stirred solution was added **6** (1.50 g, 6.17 mmoles). After 66 hours the reaction was diluted with dichloromethane (400 ml) and washed with water (50 ml), 5% sodium bicarbonate (50 ml), water (50 ml) and dried (magnesium sulfate). The solution was spin evaporated *in vacuo*, and the residue was recrystallized from ethyl acetate-hexanes to give 1.50 g (90%) of **9**, mp 201-202°; uv (0.1N hydrochloric acid + 9.5% ethanol): λ max 267 nm (ε 15000); (pH 7.0 buffer + 9.5% ethanol): λ max 273 nm (ε 18500); (0.1N sodium hydroxide + 9.5% ethanol): λ max 261 nm (ε 15300); nmr (DMSO-*d*₆): δ 11.3-11.1 (d + s, 1H, [11.19, d, J = 9.8 Hz, HNCHO, E isomer and 11.12, s, HNCHO, Z isomer]), 10.05-9.85 (d + s, 1H, [9.96, d, J = 9.8 Hz, NHCHO, E isomer and 9.95, s, HNCHO, Z isomer]), 8.58 (s, 2H, purine Hs), 7.5-7.0 (m, 4H, Ar), 5.56 (s, 2H, CH₂).

Anal. Calcd. for C₁₃H₁₀FN₅O: C, 57.56; H, 3.72; N, 25.82. Found: C, 57.55; H, 3.74; N, 25.82.

6-(Dimethylaminomethyleneamino)-9-(2-fluorobenzyl)-9H-purine (**10**).

A mixture of **6** (2.00 g, 8.22 mmoles) and dimethylformamide dimethylacetal (30 ml) was refluxed with stirring for 1 hour. The reaction mixture was cooled, and the white solids were collected and washed with cyclohexane to give 1.80 g (73%) of **10**, mp 210-212°; nmr (DMSO-*d*₆): δ 8.91 (s, 1H, NCHN(CH₃)₂), 8.40 (s, 1H, purine H), 8.30 (s, 1H, purine H), 7.35-7.13 (complex m, 4H, Ar), 5.48 (s, 2H, CH₂), 3.18 (s, 3H, CH₃), 3.12 (s, 3H, CH₃).

Anal. Calcd. for C₁₅H₁₅FN₆: C, 60.39; H, 5.07; N, 28.17. Found: C, 60.29; H, 5.11; N, 28.09.

9-(2-Fluorobenzyl)-6-phenylthiomethylamino-9H-purine (**11**).

A mixture of **6** (0.510 g, 2.10 mmoles), ethanol (15 ml), benzenethiol (0.93 g, 8.48 mmoles) and aqueous formaldehyde 36-38% in water (1 ml) was refluxed with stirring for 23 hours. The reaction was spin evaporated *in vacuo* and dissolved in 50 ml of dichloromethane. This solution was added to Silica Gel 60 (15 g) and evaporated to dryness. The solids were introduced onto a column (4 cm × 18 cm) of Silica Gel 60 wetted with ethyl acetate:cyclohexane (1:1). The column was eluted with ethyl acetate:cyclohexane (2:1) using flash chromatography. The appropriate fractions were combined and evaporated to give an oil, which crystallized in cyclohexane. Recrystallization from cyclohexane-ethyl acetate gave 0.307 g (40%) of **11**, mp 135-135.5°; nmr (DMSO-*d*₆): δ 8.60 (br, s, 1H, NH), 8.29 (s, 1H, purine H), 8.27 (s, 1H, purine H), 7.5-7.0 (m, 9H, 2 Ar), 5.46 (s, 2H, CH₂Ar), 5.15 (br s, 2H, NCH₂S).

Anal. Calcd. for C₁₉H₁₆FN₅S: C, 62.44; H, 4.41; N, 19.17. Found: C, 62.33; H, 4.46; N, 19.16.

9-(2-Fluorobenzyl)-6-(N-methylformamido)-9H-purine (**12**).

A solution of **13** (1.0 g, 3.68 mmoles) in 50% aqueous acetic acid (20 ml) was stirred at ambient temperature while three portions of potassium permanganate (0.582 g, 3.68 mmoles; 0.290 g, 1.84 mmoles; and 0.290 g, 1.84 mmoles) were added at 20 minute intervals. After an additional 30 minutes, the dark slurry was diluted with methanol (60 ml), filtered through a pad of Celite 545 and spin evaporated *in vacuo*. The dark residue was leached with ethyl acetate (150 ml) and filtered to give a light yellow solution that was added to Silica Gel 60. This mixture was spin evaporated *in vacuo*, and the residual solids were added to a column (2.5 cm × 20 cm) of Silica Gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate using flash chromatography. The appropriate fractions were combined and spin evaporated *in vacuo*. The white, solid residue was recrystallized from ethyl acetate-hexanes to give 0.282 g (27%) of **12**, mp 142.5-143.5°; nmr (DMSO-*d*₆): δ 10.32 (s, 1H, CHO), 8.71 (s, 1H, purine H), 8.64 (s, 1H, purine H), 7.35-7.2 (complex m, 4H, Ar), 5.60 (s, 2H, CH₂), 3.44 (s, 3H, CH₃).

Anal. Calcd. for C₁₄H₁₂FN₅O: C, 58.94; H, 4.24; N, 24.55. Found: C, 58.84; H, 4.26; N, 24.50.

6-Dimethylamino-9-(2-fluorobenzyl)-9H-purine (**13**).

A solution of **4** (5.00 g, 19.0 mmoles), ethanol (50 ml) and 40% aqueous dimethylamine was stirred at ambient temperature for 20 hours. The reaction mixture was spin evaporated *in vacuo* to remove the volatile substances. The residue was dispersed in water (75 ml), and the solids were collected. Recrystallization from cyclohexane gave 4.38 g (84%) of **13**, mp 137-139°; uv (0.1N hydrochloric acid + 10% ethanol): λ max 269 nm (ε 18100); 0.1N sodium hydroxide + 10% ethanol): λ max 277 nm (ε 17800); nmr (DMSO-*d*₆): δ 8.22 (s, 2H, purine Hs), 7.4-7.1 (complex m, 4H, Ar), 5.45 (s, 2H, CH₂), 3.43 (s, 6H, N(CH₃)₂).

Anal. Calcd. for C₁₄H₁₄FN₅: C, 61.98; H, 5.20; N, 25.82. Found: C, 62.14; H, 5.19; N, 25.88.

2,6-Bis-methylthio-9-(2-fluorobenzyl)-9H-purine (**15**).

A mixture of **14** [18] (3.20 g, 15.1 mmoles), 2-fluorobenzyl bromide (3.14 g, 16.6 mmoles), anhydrous potassium carbonate (2.5 g, 18.3 mmoles) and dimethylformamide (20 ml) was stirred for 66 hours at ambient temperature. The reaction was diluted with water (100 ml) and extracted with ethyl acetate (4 × 100 ml). The ethyl acetate extracts were combined and washed with water (25 ml), dried with magnesium sulfate and spin evaporated *in vacuo*. The residual oil was dissolved in ethyl acetate, added to Silica Gel 60 and spin evaporated *in vacuo*. The residual solids were introduced onto a column of Silica Gel 60 wetted with ethyl acetate:hexanes (1:4). The column was eluted using flash chromatography. Fractions containing the major component were combined and spin evaporated *in vacuo*. Recrystallization from ethyl acetate-hexane gave 2.20 g (45%) of **15**, mp 110-110.5°; uv (0.1N hydrochloric acid + 9.5% ethanol): λ max 262 nm (ε 19900), 311.5 nm (ε 10900); (pH 7.0 buffer + 9.5% ethanol): λ max 261 nm (ε 21000), 308 nm (ε 12500); (0.1N sodium hydroxide + 9.5% ethanol): λ max 260 nm (ε 21000), 308.5 nm (ε 12500); nmr (DMSO-*d*₆): δ 8.38 (s, 1H, purine H), 8.37 (s, 1H, purine H), 7.1-7.5 (m, 4H, Ar), 5.47 (s, 2H, CH₂), 2.64 (s, 3H, CH₃), 2.56 (s, 3H, CH₃).

Anal. Calcd. for C₁₄H₁₃FN₅S₂: C, 52.48; H, 4.09; N, 17.49. Found: C, 52.54; H, 4.11; N, 17.49.

9-(2-Fluorobenzyl)-6-methylamino-2-methylthio-9H-purine (**16**).

A solution of **15** (1.50 g, 4.68 mmoles), 40% aqueous methylamine (30 ml) and water (20 ml) was heated in a 200 ml stainless steel reaction vessel at 130° for 4 hours. The cooled reaction mixture was spin evaporated *in vacuo*, and the residual solid was recrystallized from ethyl acetate-cyclohexanes to give 0.84 g (59%) of **16**, mp 154-155°; uv (0.1N hydrochloric acid): λ max 270 nm; (pH 7.0 buffer and 0.1N sodium hydroxide): λ max 278 nm, 240 nm; nmr (DMSO-*d*₆): δ 8.06 (s, 1H, purine), 7.75 (br s, 1H, NH), 7.40-7.1 (m, 4H, Ar), 5.38 (s, 2H, CH₂), 2.95 (br s, 3H, NCH₃), 2.47 (s, 3H, SCH₃).

Anal. Calcd. for $C_{14}H_{13}FN_5S$: C, 55.61; H, 4.33; N, 23.16. Found: C, 55.18; H, 4.69; N, 22.83.

6,8-Dichloro-9-(2-fluorobenzyl)-9H-purine (18).

A mixture of **17** [19] (3.0 g, 15.9 mmoles), 2-fluorobenzyl bromide (3.0 g, 15.9 mmoles), anhydrous potassium carbonate (3.3 g, 23.9 mmoles) and dimethylformamide (30 ml) was stirred for 18 hours at ambient temperature. The dark solution was diluted with water (400 ml) and extracted with ethyl acetate (6 × 100 ml). The ethyl acetate extracts were combined, dried (magnesium sulfate) and added to Silica Gel 60. This mixture was spin evaporated *in vacuo*, and the residual solids were added to a column (5 cm × 20 cm) of Silica Gel 60 wetted with ethyl acetate:hexane (1:1). The column was eluted with ethyl acetate:hexane (1:1) using flash chromatography. The appropriate fractions were combined and spin evaporated *in vacuo*. The white residue was recrystallized from hexane to give 2.1 g (45%) of **18**, mp 104-105°; uv (0.1N hydrochloric acid + 9.5% ethanol): λ max 268.5 nm (ε 14500); (pH 7.0 buffer + 9.5% ethanol): λ max 269 nm (ε 14500); (0.1N sodium hydroxide): λ max 268.5 nm (ε 13100); nmr (DMSO- d_6): δ 8.83 (s, 1H, purine), 7.95-7.50 (m, 4H, Ar), 5.57 (s, 1H, CH₂).

Anal. Calcd. for $C_{14}H_7Cl_2FN_4$: C, 48.51; H, 2.37; N, 18.86. Found: C, 48.53; H, 2.39; N, 18.86.

8-Chloro-9-(2-fluorobenzyl)-6-methylamino-9H-purine (19).

A mixture of **18** (1.50 g, 5.04 mmoles), 40% aqueous methylamine (5 ml) and ethanol (15 ml) was stirred in a sealed flask for 2 hours at ambient temperature. The reaction mixture was combined with material from a similar reaction (1.5 mmole scale) and spin evaporated *in vacuo*. The residual solid was dissolved in ethyl acetate:methanol, added to Silica Gel 60 and spin evaporated *in vacuo*. The dry solids were added to a column (5 cm × 25 cm) of Silica Gel 60 wetted with ethyl acetate:hexane (1:3). The column was eluted with ethyl acetate:hexanes (1:3) using flash chromatography. The appropriate fractions were combined and spin evaporated *in vacuo*. Recrystallization of the white solid from ethyl acetate:hexanes gave 0.80 g (42%) of **19**, mp 181.5-182°; uv (0.1N hydrochloric acid + 9.5% ethanol): λ max 267 nm (ε 21900); (pH 7.0 buffer + 9.5% ethanol): λ max 268 nm (ε 19200); (0.1N sodium hydroxide + 9.5% ethanol): λ max 268 nm (ε 19200); nmr (DMSO- d_6): δ 8.25 (s, 1H, purine), 7.85 (br d, 1H, J = 4 Hz, NH), 7.45-7.00 (m, 4H, Ar), 5.43 (s, 2H, CH₂), 2.98 (d, 3H, J = 4 Hz, CH₃).

Anal. Calcd. for $C_{15}H_{11}ClFN_5$: C, 53.53; H, 3.80; N, 24.01. Found: C, 53.41; H, 3.84; N, 23.93.

9-(2-Fluorobenzyl)-6-methylamino-9H-purine (1).

Methylation of 4.

A solution of **4** (5.00 g, 19.0 mmoles), ethanol (40 ml) and 40% aqueous methylamine (10 ml) was stirred at ambient temperature for 15 hours. The reaction mixture was spin evaporated to remove the volatiles. The residue was dispersed in water (70 ml), and the solids were collected and dried to give 4.65 g (94%) of **4** that moved as a single spot on tlc (ethyl acetate). Recrystallization from ethyl acetate gave 2.86 g (58%) of **1**, mp 151-153°; uv (0.1N hydrochloric acid + 10% ethanol): λ max 263 nm (ε 16700); (0.1N sodium hydroxide + 10% ethanol): λ max 268 nm (ε 15300); nmr (DMSO- d_6): δ 8.27 (s, 1H, purine H), 8.22 (s, 1H, purine H), 7.67 (q, 1H, J = 4 Hz, NH), 7.4-7.1 (complex m, 4H, Ar), 5.47 (s, 2H, CH₂), 3.02 (d, 3H, J = 4 Hz, CH₃).

Anal. Calcd. for $C_{15}H_{12}FN_5$: C, 60.69; H, 4.70; N, 27.22. Found: C, 60.83; H, 4.67; N, 27.25.

Alkylation of 5.

To a stirred dispersion of sodium hydride (60.2% dispersion in mineral oil) (0.129 g, 3.23 mmoles) in dry dimethylsulfoxide (10 ml) was added **5** [7] (0.442 g, 2.96 mmoles). The reaction mixture was stirred at ambient temperature for 1 hour, and 2-fluorobenzyl bromide (98%) (0.575 g, 2.98 mmoles) was added. The solution was stirred for 24 hours, then diluted with water (100 ml) and extracted with dichloromethane (4 × 25 ml). The combined extracts were washed with water (5 × 20 ml), filtered through

glass wool and spin evaporated *in vacuo*. The residue was dissolved in dichloromethane (25 ml) and added to Silica Gel 60 (15 g). This mixture was spin evaporated *in vacuo*, and the residual solid was introduced onto a column of Silica Gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate using flash chromatography. The fractions that contained product were combined and spin evaporated *in vacuo* to give 0.340 g (44%) of crude **1**, mp 145-148°. These solids were dispersed in 3 ml of ethyl acetate and collected to give 0.170 g (22%) of **1**, mp 150-152°, which was identical to that prepared from **4**.

Dimroth Rearrangement of 8.

A mixture of **8** (0.20 g, 0.52 mmole) and 10% sodium hydroxide in methanol (60 ml) was stirred at ambient temperature for 2.5 days. The reaction was spin evaporated to remove the volatile substances. The residue was dispersed in ice water (100 ml) and stirred for 2 hours. The white solids were collected, washed with water and dried *in vacuo* to give 0.11 g (83%) of **1**, mp 151-153°, which was identical to that prepared from **4**.

Lithium Aluminum Hydride Reduction of 9.

To a slurry of lithium aluminum hydride (0.040 g, 1.05 mmole) in tetrahydrofuran (20 ml) under nitrogen was added a slurry of **9** (0.203 g, 0.75 mmole) in tetrahydrofuran (20 ml). The reaction was stirred at ambient temperature for 20 minutes and then refluxed for 2 hours. The reaction was cooled, quenched with water (3 ml) and 1 N sodium hydroxide (5 ml) and then stirred for 30 minutes. The solids were removed by filtration and washed with water (20 ml) and ethanol (20 ml). The filtrates and washes were combined and spin evaporated *in vacuo*. The residue was dissolved in ethyl acetate (150 ml), washed with water (3 × 20 ml), dried (magnesium sulfate) and spin evaporated *in vacuo*. The white residue was recrystallized from ethyl acetate:hexanes to give 0.039 g (20%) of **1**, mp 151-153°; it was identical to that prepared from **4**.

Borohydride Reduction of 10.

A solution of **10** (0.150 g, 0.50 mmole), dimethylsulfoxide (6 ml), methanol (6 drops) and sodium borohydride (0.045 g, 1.19 mmoles) was heated with stirring at 100° for 2 hours. The reaction solution was cooled, diluted with ice water (25 ml) and stirred in an ice bath for 1 hour. The white solids were collected and washed with water. Recrystallization from ethyl acetate-cyclohexane gave 0.084 g (65%) of **1**, mp 151-153°, which was identical to that prepared from **4**.

Borohydride Reduction of 11.

A solution of **11** (0.275 g, 0.75 mmole), sodium borohydride (0.072 g, 2.0 mmoles) and 1,2-dimethoxyethane (25 ml) was refluxed for 2 hours. The cooled reaction was diluted with methanol (10 ml), acetone (3 ml) and acetic acid (0.5 ml). The volatiles were removed by spin evaporation *in vacuo*. The residue was dissolved in ethyl acetate (150 ml) and washed with water (30 ml), 5% sodium hydrogen carbonate (2 × 20 ml), water (20 ml); it was then dried (magnesium sulfate) and spin evaporated *in vacuo*. The residue was recrystallized from ethyl acetate-cyclohexane to give 0.107 g (55%) of **1**, mp 154-155°, which was identical to that prepared from **4**.

Hydrolysis of 12.

A solution of **12** (0.20 g, 0.70 mmole), methanol (10 ml) and 1 N aqueous sodium hydroxide (5 ml) was stirred at ambient temperature for 2.5 hours. The reaction mixture was spin evaporated to remove the volatiles, and the residue was dispersed in water (10 ml) and stirred for 15 hours. The white solids were collected, washed with water and recrystallized from ethyl acetate-cyclohexane to give 0.156 g (86%) of **1**, mp 153-154°, which was identical to that prepared from **4**.

Dethiation of 16.

A mixture of **16** (0.100 g, 0.31 mmole), Raney nickel catalyst (4.0 g) and ethanol (10 ml) was refluxed for 18 hours. The mixture was filtered, and the catalyst was washed with ethanol (75 ml) and water (75 ml). The filtrate and washes were combined and spin evaporated *in vacuo*. The white residue was recrystallized from ethyl acetate-cyclohexane to give 0.033 g

(41%) of **1**, mp 153-154°, which was identical to that prepared from **4**.
Dechlorination of **19**.

A mixture of **19** (0.200 g, 0.69 mmole), anhydrous sodium acetate (0.125 g, 1.52 mmoles), 5% palladium on carbon (30 mg) and ethanol (25 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for 4 hours. The reaction mixture was filtered, and the filtrates were spin evaporated *in vacuo*. The white residue was dissolved in ethyl acetate (50 ml), washed with water (3 × 20 ml) and dried (magnesium sulfate). The ethyl acetate solution was spin evaporated, and the residue was recrystallized from ethyl acetate-hexanes to give 0.103 g (58%) of **1**, mp 152.5-154°, which was identical to that prepared from **4**.

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