Regioselective Electrophilic Reactions on Substituted Purines. Predominant Intermediacy of 6- or 8-Purinyl Carbanions

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6-Iodo-9-(tetrahydropyran-2-yl)purine (1) was found to undergo reaction with *n*-butyllithium in THF to produce, depending upon the time and temperature of the reaction, either 6-lithio- or 8-lithio-9-(tetrahydropyran-2-yl)purine in predominance. Shorter reaction time and lower temperature were necessary for the utilization of the 6-lithio derivative, while longer reaction time and higher operating temperature favored the equilibration to the 8-lithio isomer. These carbanions were treated with a variety of electrophiles to produce the corresponding 6- or 8-substituted compounds (**3** or **4**). 6-Chloro-9-(tetrahydropyran-2-yl)purine (**7**) was treated similarly with *n*-butyllithium in THF at −78 °C and was then caused to react with various electrophiles to give 8-substituted 6-chloro-9-(tetrahydropyran-2-yl)purines (**8**). The chloro substituent in **8** was removed by hydrogenolysis or displaced with NH_3 to give the correspondingly substituted purines (**4**) or adenines (**9**).

The direct formation of 6-alkylpurines remains incompletely explored despite indications of the biological activity of some of these derivatives.[1,2] To date, the methods of carbon–carbon bond formation at the 6 position of intact purines involve the reaction of suitable leaving groups with phenyllithium,[3] sodiomalonic esters,[3,4] cuprous cyanide,[5] and various alkylidenephosphoranes.[6,7] In addition, the Eschenmoser sulfide contraction[8] has been applied to appropriately substituted purines.[9]

Until recently, few effective methods have been reported for the direct formation from parent purines of 8-alkylpurines,[10,11] compounds which are produced in photoreactions of purines with alcohols, ethers, amines, and amino acids.[12] As examples, 8-(2-hydroxy-2-propyl)-adenine and 8-(2-hydroxy-2-propyl)guanine have been obtained from the irradiation of DNA in the presence of 2-propanol with ultraviolet light,[13,14] with acetone as a photosensitizer or organic peroxide as an initiator. 8-Substituted purines may in fact be important consequences of protein–nucleic acid photointeractions.[15] A promising approach, recently described,[16] is the direct alkylation of protected adenosine derivatives at the 8 position by lithiation followed by reaction with an alkyl halide.

We describe here the use of a common purinyl precursor to produce at will, by time and temperature control of the reaction, different series of substituted purine derivatives. This approach provides facile synthetic methodology for obtaining purine compounds of potential biological interest that would otherwise be difficult to synthesize.

On the basis of our previous experience with the formation and use of pyrimidine carbanions,[17] a halogen–metal exchange reaction between *n*-butyllithium and an appropriately N-protected halopurine was envisaged as a general route to the desired purinyl carbanions. Operation at low temperature was directed in order to avoid diversionary attacks on the heterocyclic ring. The tetrahydropyran-2-yl group (Thp) was selected as the N-9 protecting moiety because of its stability toward base and its favorable influence on solubility. Specifically, 6-iodo-9-(tetrahydropyran-2-yl)purine (**1**)[18] demonstrated satisfactory solubility properties and was readily available in a two step reaction sequence from 6-chloropurine.

When compound **1** was subjected to an initial set of reaction conditions (THF, −100 °C, nitrogen atmosphere, *n*-butyllithium, and treatment with an electrophile), a mixture of three products was obtained upon workup. Following chromatographic isolation, spectroscopic analyses provided identification of the products as 9-(tetrahydropyran-2-yl)purine (**2**) and the 6- and 8-substituted isomers (**3** and **4**) resulting from the reaction of a purinyl carbanion with the electrophile. Differentiation between the latter two products was possible on the basis of the deuterium-exchange reaction in refluxing D_2O observed for the 8 position of purines.[19,20] Although products **2** and **3** were readily explained in terms of the reaction of a 6-purinyl carbanion with a proton source and the electrophile, respectively, the appearance of the 8-substituted purine product **4** raised a question as to the precursor sequence.

The apparent relocation of the carbanion from the 6 to the 8 position, leading to 9-tetrahydropyran-2-yl products substituted at the 8 position (e.g., **4**), could occur by at least three routes. One would involve the initial 8-deprotonation of 6-iodo-9-(tetrahydropyran-2-yl)purine (**1**); however, the preferential exchange of lithium for iodine at the 6 position, even at lower operating temperature (−130 °C, see below), and the absence of 6,8-disubstituted purine prod-

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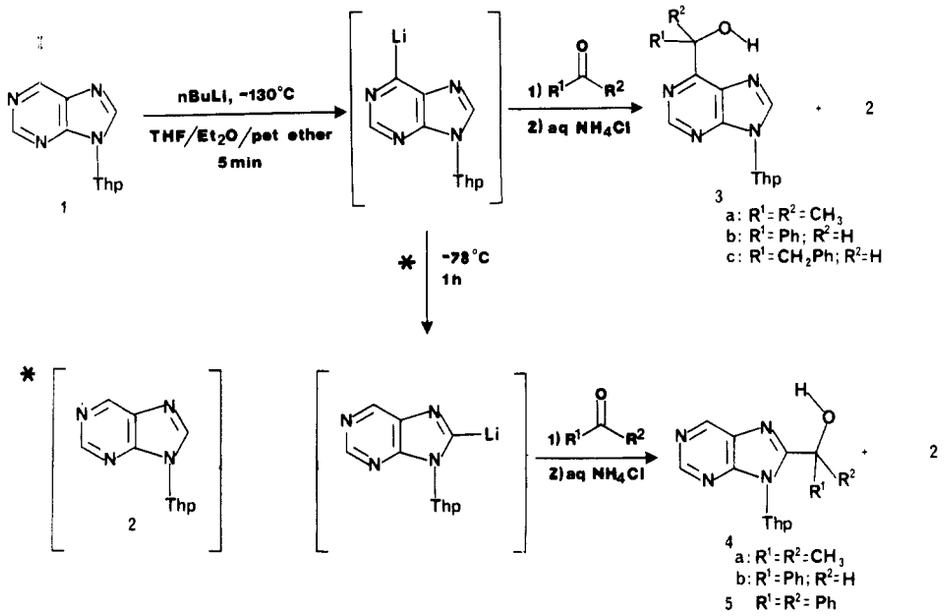

ucts in the mixture do not support this route. Another route would involve the initial formation of the 6-carbanion and interchange of the 8-proton via 6,8-dilithio-9-(tetrahydropyran-2-yl)purine in a catalytic manner. The absence of 6,8-disubstituted purine products disfavors this route since no such product was detected even when a large excess of alkyllithium (100%) and of nonprotic electrophiles (>600%) was used, unless selective proton abstraction by the reaction product of dicarbanion with 1 molar equiv of nucleophile were to occur. The relocation route involving hydrogen abstraction by the 6-carbanion initially formed from **1**, leading to 9-(tetrahydropyran-2-yl)purine (**2**) as an intermediate, is valid. When pure compound **2** was treated with *n*-butyllithium at −80 °C in THF followed by an electrophile, reaction occurred only at the 8 position, corresponding to abstraction of the more acidic proton and generation of the 8-carbanion intermediate.[21-23] Compound **2** was observed as a concomitant product in all of the reactions of **1** with *n*-butyllithium followed by an electrophile.

For these reactions of **1**, the supposition of the initial formation of the 6-purinyl carbanion, along with the postulate of an equilibrium process between the 6-carbanion and the 8-carbanion, suggested that manipulation of the reaction conditions would guide the predominant formation of products derived either from the kinetically favored 6-carbanion or from the thermodynamically preferred 8-carbanion. We found that selective reaction of the 6-carbanion could be realized when the reaction temperature was lowered to −130 °C[24] and the time interval between the introduction of the *n*-butyllithium and the addition of the electrohpile was minimized. These conditions sufficiently diminished the rate of equilibration, 6- to 8-carbanion, and decreased the time available for equilibration so that with the subsequent workup, only 9-(tetrahydropyran-2-yl)purine (**2**) and the 6-substituted product (**3**) were obtained, with no evidence of the 8-substituted product. This was the result when the added electrophile was acetone, benzaldehyde, or phenylacetaldehyde. When the reaction mixture of compound **1** and *n*-butyllithium was warmed to −75 °C over a period of 1 h prior to the addition of the electrophile, the rate and time for the equilibration were increased and the 8-substituted product **4** was formed predominantly, along with only small amounts of **2** and **3**. This was exemplified with the electrophiles acetone and benzaldehyde. Thus, variation of the reaction temperature and time provides position selectivity in purines for the attachment of side chains. The protecting group at **9** was readily removable by hydrolysis with acetic acid.

Despite these useful positive results, some problems remain in the synthetic utilization of 6-purinyl carbanions. At the very low temperatures required for selectivity, a different behavior was encountered with less active electrophiles such as benzophenone and 2-chlorobenzoxazole. In these two cases, due to electronic or steric factors, no productive reaction was observed at −130 °C; i.e., only some 9-(tetrahydropyran-2-yl)purine (**2**) was formed. At higher temperature, ca. −95 °C, the 8-substituted compounds **5** and **6** were formed, with no 6-substituted isomers being observed.

From a consideration of the relative reactivities of the 6-halopurines and the relative acidities of the purine protons, we considered that 6-chloro-9-(tetrahydropyran-2-yl)purine (**7**) would be cleanly and effectively deprotonated with *n*-butyllithium at low temperature. The reaction of the carbanion generated from compound **7** with *n*-butyllithium at −78 °C, followed by various electrophiles, provided, after workup, substituted 6-chloropurines (**8a,b**) in good yield. The protecting group at position 9 is readily removable, or the 6-chloro group can be replaced with amino (**9a,b**), hydroxy, mercapto, etc., followed by removal of the 9-tetrahydropyran-2-yl group. The chloro substituent in **8** can also be removed by hydrogenolysis, leading to compounds of type **4a** and **5**. Our synthetic methodology leads to purines with the possibility of variation in both the 6 and 8 substituents. The utilization of the carbanion derived from compound **7** is of particular interest for the synthesis of various photoproducts derived from 6-substituted purines. The deprotected version of compound **9a** has in fact been observed as the product of the photochemical or γ-ray-induced reaction of adenine with 2-propanol.[25] It is anticipated that the group atta-

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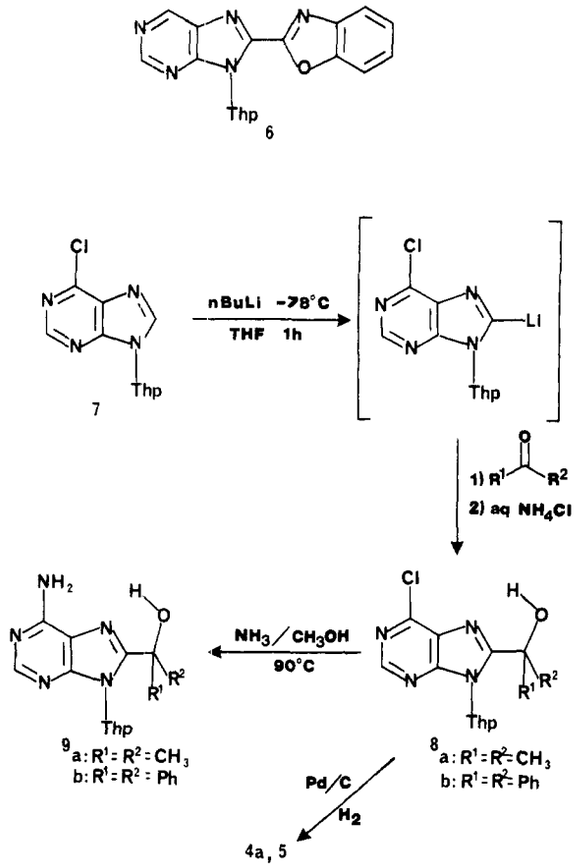

ched at position 9 may also be protected ribosyl or deoxyribosyl for the synthesis of 6- and 8-substituted ribosyl- or deoxyribosylpurines as a variant of the alkylation method.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian EM-390, HA-100, or 220 spectrometer using tetramethylsilane as an internal standard. Mass spectra were run on a Varian-MAT CH-5 spectrometer (10 and 70 eV) coupled with a 620i computer and a STATOS recorder. Microanalyses were performed by Mr. Josef Nemeth and his staff and by Midwest Microlab, Ltd., Indianapolis, IN. Thin-layer chromatograms were run on EM silica gel F-254 plates (thickness 0.25 mm). Except where noted, column chromatography utilized Brinkmann silica gel (0.05–0.2-mm grade). Low-temperature reactions were maintained by an FTS Systems MC-4-130-TCH ultralow multicool system.

6-(2-Hydroxy-2-propyl)-9-(tetrahydropyran-2-yl)purine (3a). A solution of 6-iodo-9-(tetrahydropyran-2-yl)purine (**1**;[18] 100 mg, 0.3 mmol) in freshly distilled THF (20 mL) was cooled to <–95 °C under positive argon atmosphere and treated with *n*-butyllithium (2.1 M in hexane, 0.15 mL, 0.33 mmol). After 30 s, acetone (175 mg, 3 mmol) in hexane (3 mL) was added. The stirring was continued for an additional 1 h with the temperature gradually rising to –70 °C before the reaction mixture was inversely quenched with saturated aqueous NH_4Cl (35 mL) and Et_2O (35 mL). The aqueous layer was extracted with additional Et_2O (35 mL), and the organic layers were combined, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (6 g) by using a gradient of 0–3% absolute EtOH/$CHCl_3$ (450 mL each). The fractions corresponding to three different zones (by TLC; 9:1 $CHCl_3$/absolute EtOH) were collected: **3a** (R_f 0.49, 30 mg, 38% yield), **2** (R_f 0.35, 13 mg, 21% yield), **4a** (R_f 0.29, 11 mg, 14% yield).

When the reaction was repeated at –130 °C with THF/Et_2O/petroleum ether (4:1:1) as the solvent and was worked up in the same manner, the products obtained were **3a** (44 mg, 55% yield) and **2** (14 mg, 21% yield). No **4a** was observed. This temperature is preferred for obtaining **3a**. The spectral data for **3a**, mp 98–99 °C, were as follows: NMR ($CDCl_3$) δ 1.55–2.3 (m, 6, CH_2's), 1.75 (s, 6, CH_3), 3.6–3.92 (m, 1, OCH_2), 4.04–4.3 (m, 1, OCH_2), 5.77 (d of d, J = 4 and 8 Hz, 1, N–CH–O), 8.25 (s, 1, 8-CH), 8.89 (s, 1,2-CH); MS *m/e* 262 (M^+), 247 ($M^+ - CH_3$), 163 (B, $M^+ - CH_3$ – Dhp; Dhp = dihydropyran (C_5H_8O)).

Anal. Calcd for $C_{13}H_{18}N_4O_2$: C, 59.52; H, 6.92; N, 21.26. Found: C, 59.53; H, 7.01; N, 21.26.

6-(2-Hydroxy-2-propyl)purine. To a solution of **3a** (57 mg, 0.22 mmol) in ethanol (4 mL) was added H_2O (1 mL) and glacial acetic acid (0.5 mL). After the solution was stirred at room temperature for 36 h, the solvents were removed in vacuo by azeotroping with benzene to yield a white fluffy solid (34 mg, 89% yield): mp 177–178 °C; NMR ($(CD_3)_2SO$) δ 1.60 (s, 6, CH_3), 5.74 (br, 1, NH or OH), 8.49 (s, 1, purine CH), 8.83 (s, 1, purine CH); MS *m/e* 178 (M^+), 163 ($M^+ - CH_3$), 120 ($M^+ - C_3H_6O$).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.56; H, 5.70; N, 31.40.

8-(2-Hydroxy-2-propyl)-9-(tetrahydropyran-2-yl)purine (4a). Method A. A solution of **1** (100 mg, 0.3 mmol) in THF (20 mL) was cooled to <–95 °C under a positive argon atmosphere, and *n*-butyllithium (2.2 M in hexane, 0.15 mL, 0.33 mmol) was added. Stirring was continued for 1 h as the internal temperature was raised to –78 °C, at which time acetone (175 mg, 3 mmol) in hexane (3 mL) was added. After being stirred an additional 45 min, the reaction was quenched and worked up in the usual fashion. Chromatography was carried out as described above and gave **4a** (58 mg, 73% yield) along with some **3a** (2 mg, 2% yield) and **2** (7 mg, 12% yield).

Method B. To a solution of 6-chloro-8-(2-hydroxy-2-propyl)-9-(tetrahydropyran-2-yl)purine (**8a**, see below; 60 mg, 0.2 mmol) in ethanol (6 mL) and H_2O (4 mL) were added Et_3N (0.05 mL) and 10% palladium on charcoal (30 mg). This reaction mixture was hydrogenated at 3 atm of H_2 during 20 min and was then filtered and treated with 2.5% aqueous Na_2CO_3 (5 mL). The solution volume was reduced to 10 mL, and the concentrate was extracted with Et_2O (4 × 40 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was evaporated in vacuo to give **4a** (51 mg, 97% yield).

The spectral data for **4a**, mp 128.5–130 °C, were as follows: NMR ($CDCl_3$) δ 1.55–2.33 (m, 6, CH_2's), 1.76 (s, 3, CH_3), 1.80 (s, 3, CH_3), 3.55–4.4 (m, 2, OCH_2), 6.25 (d of d, J = 2 and 11 Hz, 1, N–CH–O), 8.89 (s, 1, purine CH), 8.99 (s, 1, purine CH); MS *m/e* 262 (M^+), 179 ($M^+ - C_5H_7O$), 163 (M^+ – Dhp – CH_3), 161 (M^+ – Dhp – OH).

Anal. Calcd for $C_{13}H_{18}N_4O_2$: C, 59.52; H, 6.91; N, 21.36. Found: C, 59.68; H, 7.05; N, 21.17.

8-(2-Hydroxy-2-propyl)purine. A solution of **4a** (48 mg, 0.18 mmol) in ethanol (5 mL) was treated as described above with glacial acetic acid and H_2O. A similar workup gave colorless product (25 mg, 76% yield): mp 194.5–195.5 °C dec; NMR ($(CD_3)_2SO$) δ 1.60 (s, 6, CH_3), 5.73 (s, 1, NH or OH), 8.80 (s, 1, purine CH), 8.91 (s, 1, purine CH); MS *m/e* 178 (M^+), 163 (B, $M^+ - CH_3$), 135 ($M^+ - C_2H_3O$), 121 ($M^+ - C_3H_5O$).

Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.63; H, 5.61; N, 31.30.

6-(α-Hydroxybenzyl)-9-(tetrahydropyran-2-yl)purine (3b) and 8-(α-Hydroxybenzyl)-9-(tetrahydropyran-2-yl)purine (4b). The lithiopurine derivative was generated as described above from **1** (100 mg, 0.3 mmol) and *n*-butyllithium (2.2 M in hexane, 0.15 mL, 0.33 mmol) in THF (20 mL). After the reaction solution was stirred for 30 s at <–95 °C, benzaldehyde (160 mg, 1.5 mmol) in THF (3 mL) was added. The solution was stirred for an additional 45 min before quenching and workup in the usual manner. The residue was washed with petroleum ether (10 mL) to remove excess benzaldehyde and then applied to a silica gel column. Chromatography was carried out as for **3a**, and the fractions corresponding to the product zones (by TLC; 9:1 $CHCl_3$/absolute EtOH) were collected: **3b** (R_f 0.44, 35 mg, 38% yield), **2** (R_f 0.34, 4 mg, 7% yield), **4b** (R_f 0.32, 14 mg, 15% yield).

When the reaction was repeated at –130 °C with THF/Et_2O/petroleum ether (4:1:1) as the solvent and was worked up in the

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usual manner, **3b** (52 mg, 56% yield) was obtained along with some **2**. This is the temperature to use in order to obtain **3b** free from **4b**. Compound **3b** was characterized as follows: NMR ($CDCl_3$) δ 1.55–2.3 (m, 6, CH_2's), 3.6–3.95 (m, 1, OCH_2), 4.05–4.3 (m, 1, OCH_2), 5.22 (d, J = 8 Hz, 1, N–CH–O), 6.39 (d, J = 7.5 Hz, 1, CHOH), 7.06 (m, 3, ArH), 7.27 (m, 2, ArH), 8.28 (s, 1, 8-CH), 8.96 (s, 1, 2-CH); MS m/e 310 (M^+), 226 (B, M^+ – Dhp).

Compound **4b** was characterized as follows: mp 67–68 °C; NMR ($CDCl_3$) δ 1.45–2.05 (m, 6, CH_2's), 3.3–3.7 (m, 1, OCH_2), 3.9–4.25 (m, 1, OCH_2), 5.80 (d of d, J = 2 and 10.5 Hz, 1, N–CH–O), 6.21 (d, J = 3 Hz, 1, CHOH), 7.32 (s, 5, ArH), 8.87 (s, 1, purine CH), 8.96 (s, 1, purine CH); MS m/e 310 (M^+), 227 ($M^+ - C_5H_7O$), 226 (M^+ – Dhp).

Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.84; N, 18.05. Found: C, 65.82; H, 6.05; N, 17.99.

6-(α-Hydroxybenzyl)purine. A solution of **3b** (124 mg, 0.4 mmol) in ethanol (5 mL) was treated as described above with glacial acetic acid and H_2O. A similar workup afforded colorless product (66 mg, 73% yield): mp 194 °C dec; NMR ($(CD_3)_2SO$) δ 6.07 (s, 1, CHOH), 6.45 (br, 1, NH or OH), 7.27 (m, 3, ArH), 7.55 (m, 2, ArH), 8.57 (s, 1, purine CH), 8.82 (s, 1, purine CH); MS m/e 226 (B, M^+), 209 (M^+ – OH), 149 ($M^+ - C_6H_5$).

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.68; H, 4.23; N, 24.82.

6-(1-Hydroxy-2-phenylethyl)-9-(tetrahydropyran-2-yl)purine (3c). The lithiopurine derivative was generated as before from **1** (100 mg, 0.3 mmol) and n-butyllithium (2.2 M in hexane, 0.15 mL, 0.33 mmol) in THF (20 mL). After the reaction solution was stirred for 30 s (<–95 °C), phenylacetaldehyde (179 mg, 1.5 mmol) in THF (0.5 mL) and hexane (2.5 mL) was added. The resultant solution was stirred for an additional 1 h before quenching and workup in the usual manner. The residue was chromatographed as before, and the fractions corresponding to the product zones (by TLC; 9:1 $CHCl_3$/absolute EtOH) were collected: **2** (R_f 0.31, 31 mg, 50% yield), **3c** (R_f 0.5, 34 mg, 35% yield).

The proportion of **3c** was not increased when the reaction was run at –130 °C; abstraction of hydrogen appears to be preferred when this electrophile is used. Compound **3c** was characterized as follows: mp 88–89 °C; NMR ($CDCl_3$) δ 1.55–2.3 (m, 6, Thp CH_2's), 3.13 (d of d, J = 4 and 13.5 Hz, 1, CH_2), 3.44 (d of d, J = 7.5 and 13.5 Hz, 1, CH_2), 3.6–3.95 (m, 1, OCH_2), 4.05–4.5 (m, 2, OCH_2 and OH), 5.41–5.63 (m, 1, CHOH), 5.78 (d of d, J = 4 and 8 Hz, 1, N–CH–O), 7.19 (s, 5, ArH), 8.25 (s, 1, 8-CH), 8.87 (s, 1, 2-CH); MS m/e 324 (M^+), 233 ($M^+ - C_7H_7$), 149 ($M^+ - C_7H_7$ – Dhp).

Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.79; H, 6.06; N, 17.17.

6-(1-Hydroxy-2-phenylethyl)purine. A solution of **3c** was hydrolyzed as described above to remove the 9-protecting group (50% yield): mp 195 °C dec; NMR ($(CD_3)_2SO$) δ 3.20 (m, 2, CH_2), 5.20 (m, 1, CHOH), 5.79 (br, 1, OH or NH), 7.17 (s, 5, ArH), 8.48 (s, 1, purine CH), 8.83 (s, 1, purine CH); MS m/e 240 (M^+), 223 (M^+ – OH), 149 (B, $M^+ - C_7H_7$).

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.04; N, 23.32. Found: C, 64.84; H, 4.85; N, 23.17.

Synthesis of 9-(Tetrahydropyran-2-yl)purine and Subsequent Metalation. A solution of **1** (700 mg, 2.1 mmol) in THF (50 mL) was cooled to –78 °C under a positive argon atmosphere, and n-butyllithium (2.5 M in hexane, 1.0 mL, 2.5 mmol) was added. The solution was stirred for 25 min and then inversely quenched and worked up in the usual manner. The residue was chromatographed as before and pure **2** was obtained as an oil through combination of the appropriate fractions (320 mg, 75% yield): NMR ($CDCl_3$) δ 1.5–2.3 (m, 6, CH_2's), 3.6–3.92 (m, 1, OCH_2), 4.05–4.28 (m, 1, OCH_2), 5.77 (d of d, J = 4 and 8 Hz, 1, N–CH–O), 8.27 (s, 1, purine CH), 8.96 (s, 1, purine CH), 9.12 (s, 1, purine CH); MS m/e 204 (M^+).

In a manner similar to that described earlier, **2** (258 mg, 1.27 mmol) was dissolved in THF (30 mL), the temperature was lowered to –78 °C, and n-butyllithium (2.6 M in hexane, 0.6 mL, 1.6 mmol) was added. After 30 min, acetone (350 mg, 6 mmol) was added. The stirring was continued for an additional 30 min prior to inverse quenching and workup in the usual manner. Chromatographic separation of the residue resulted in the isolation of **2** (74 mg, 29% yield) and **4a** (125 mg, 38% yield) as characterized by comparison with authentic samples by TLC and NMR. No **3a** was observed.

8-(Hydroxydiphenylmethyl)-9-(tetrahydropyran-2-yl)purine (5). Method A. The lithiopurine was generated as before from **1** (100 mg, 0.3 mmol) and n-butyllithium (2.2 M in hexane, 0.15 mL, 0.33 mmol) in THF (20 mL). After the reaction solution was stirred at <–95 °C for 30 s, benzophenone (182 mg, 1 mmol) in THF (3 mL) was added. The resultant solution was stirred for 1.5 h before quenching and workup in the usual fashion. The solid residue was washed with petroleum ether (70 mL) to remove excess benzophenone before application to a silica gel column. The fractions corresponding to the product zone (by TLC; 9:1 $CHCl_3$/absolute EtOH) were combined; **5** (R_f 0.49, 47 mg, 40% yield).

Method B. To a solution of 6-chloro-8-(hydroxydiphenylmethyl)-9-(tetrahydropyran-2-yl)purine (**8b**, see below; 80 mg, 0.19 mmol) in ethanol (20 mL) and H_2O (10 mL) was added Et_3N (0.05 mL) and 10% palladium on charcoal (40 mg). This reaction mixture was hydrogenated at 3 atm of H_2 during 20 min and then worked up as for the hydrogenolysis of **8a** (62 mg, 85% yield). The spectral data for **5**, mp 173–173.5 °C, were as follows: NMR ($(CD_3)_2SO$) δ 1.1–2.0 (m, 6, CH_2's), 2.65–3.05 (m, 1, OCH_2), 3.55–3.9 (m, 1, OCH_2), 5.65 (br d, J = 11 Hz, 1, N–CH–O), 7.30 (s, 10, ArH), 7.47 (s, 1, OH), 8.88 (s, 1, purine CH), 9.05 (s, 1, purine CH); MS m/e 386 (M^+), 302 (B, M^+ – Dhp), 225 (M^+ – Dhp – C_6H_5).

Anal. Calcd for $C_{23}H_{22}N_4O_2 \cdot {}^1/_4H_2O$: C, 70.68; H, 5.80; N, 14.33. Found: C, 70.32; H, 5.87; N, 14.25.

8-(Hydroxydiphenylmethyl)purine. A solution of **5** was hydrolyzed as described before to remove the 9-protecting group (75% yield): mp 267.5–268 °C dec; NMR ($(CD_3)_2SO$) δ 7.2–7.55 (m, 10, ArH), 8.85 (s, 1, purine CH), 8.97 (s, 1, purine CH); MS m/e 302 (B, M^+), 284 ($M^+ - H_2O$), 225 ($M^+ - C_6H_5$), 197 ($M^+ - C_7H_5O$).

Anal. Calcd for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.49; H, 4.61; N, 18.70.

8-(Benzoxazol-2-yl)-9-(tetrahydropyran-2-yl)purine (6). With the use of identical reagent amounts, the lithiopurine was generated as for **5**. After the reaction solution was stirred for 30 s at <–95 °C, a solution of 2-chlorobenzoxazole (154 mg, 1 mmol) in THF (3 mL) was added. The resultant solution was stirred for 1 h before quenching and workup in the usual fashion. The residue was chromatographed as before, and the product zones (by TLC; 9:1 $CHCl_3$/absolute EtOH) were combined; **2** (R_f 0.35, 11 mg, 18% yield) and **6** (R_f 0.57, 43 mg, 44% yield): mp >330 °C; NMR ($CDCl_3$) δ 1.55–2.2 (m, 6, CH_2's), 3.84–3.94 (m, 1, OCH_2), 4.20–4.27 (m, 1, OCH_2), 7.12 (d of d, J = 1.6 and 11 Hz, 1, N–CH–O), 7.51 (m, 2, ArH), 7.74 (d, 1, ArH), 7.92 (d, 1, ArH), 9.12 (s, 1, purine CH), 9.29 (s, 1, purine CH); MS m/e 321 (M^+), 238 ($M^+ - C_5H_7O$), 237 (M^+ – Dhp).

Anal. Calcd for $C_{17}H_{15}N_5O_2$: C, 63.54; H, 4.70; N, 21.80. Found: C, 63.61; H, 4.66; N, 22.00.

8-(Benzoxazole-2-yl)purine. A solution of **6** was hydrolyzed as described above to remove the 9-protecting group: mp >300 °C; NMR ($(CD_3)_2SO$) δ 7.45–7.60 (m, 2, ArH), 7.81–7.98 (m, 2, ArH), 8.95 (s, 1, purine CH), 9.20 (s, 1, purine CH); MS m/e 237 (B, M^+).

Anal. Calcd for $C_{12}H_7N_5O$: C, 60.75; H, 2.97; N, 29.53. Found: C, 61.01; H, 3.19; N, 29.44.

6-Chloro-8-(2-hydroxy-2-propyl)-9-(tetrahydropyran-2-yl)purine (8a). A solution of 6-chloro-9-(tetrahydropyran-2-yl)purine (**7**)[18] (100 mg, 0.42 mmol) in THF (25 mL) was cooled to –78 °C under a positive argon atmosphere, n-butyllithium (2.1 M in hexane, 0.21 mL, 0.44 mmol) was added, and the solution was stirred for 1 h. Acetone (175 mg, 3 mmol) was added, and the solution was stirred an additional 30 min and was then quenched and worked up in the usual manner. The residue was chromatographed on silica gel (7.5 g) by using $CHCl_3$ as an eluent. The combination of the appropriate fractions gave **7** (9 mg, 9% recovery) and the product **8a** (87 mg, 70% yield): mp 220 °C dec; NMR ($CDCl_3$) δ 1.5–2.2 (m, 6, CH_2's), 1.78 (s, 3, CH_3), 1.82 (s, 3, CH_3), 3.55–3.9 (m, 1, OCH_2), 4.13–4.37 (m, 1, OCH_2), 6.22 (d of d, J = 2 and 11 Hz, 1, N–CH–O), 8.67 (s, 1, 2-CH); MS m/e (rel intensity) 296 (5.5), 298 (1.9, M^+), 213 (33), 215 (10, $M^+ - C_5H_7O$), 85 (B, $C_5H_9O^+$).

Anal. Calcd for $C_{13}H_{11}ClN_4O_2$: C, 52.61; H, 5.78; N, 18.88. Found: C, 52.60; H, 5.83; N, 18.50.

6-Chloro-8-(2-hydroxy-2-propyl)purine. A solution of **8a** was hydrolyzed as described above to remove the 9-protecting group (95% yield): mp 201–203 °C dec; NMR ($(CD_3)_2CO$) δ 1.73 (s, 6, CH_3), 8.59 (s, 1, 2-CH); MS *m/e* (rel intensity) 212 (60), 214 (17, M^+), 197 (100), 199 (42, $M^+ - CH_3$), 169 (18), 171 (7, $M^+ - C_2H_3O$), 155 (57), 157 (22, $M^+ - C_3H_5O$).

Anal. Calcd for $C_8H_9ClN_4O$: C, 45.18; H, 4.27; N, 26.35. Found: C, 45.29; H, 4.45; N, 26.05.

6-Chloro-8-(hydroxydiphenylmethyl)-9-(tetrahydropyran-2-yl)purine (8b). A solution of **7** (240 mg, 1 mmol) in THF (40 mL) was treated with *n*-butyllithium (2.6 M in hexane, 0.5 mL, 1.3 mmol) as before. After an analogous workup and chromatography, the product was obtained as a colorless solid (260 mg, 62% yield): mp 224 °C dec; NMR ($CDCl_3$) δ 1.5–2.0 (m, 6, CH_2's), 3.14 (m, 1, OCH_2), 3.98 (m, 1, OCH_2), 5.17 (s, 1, OH), 5.29 (d of d, J = 2 and 11 Hz, 1, N–CH–O), 7.30 (s, 5, ArH), 7.36 (s, 5, ArH), 8.67 (s, 1, purine CH); MS *m/e* (rel intensity) 420 (2), 422 (0.9, M^+), 336 (100), 338 (34, M^+ – Dhp).

Anal. Calcd for $C_{23}H_{21}ClN_4O_2$: C, 65.63; H, 5.03; N, 13.31. Found: C, 65.39; H, 4.95; N, 13.52.

6-Chloro-8-(hydroxydiphenylmethyl)purine. A solution of **8b** was hydrolyzed to remove the 9-protecting group (88% yield): mp 233–236 °C dec; NMR ($(CD_3)_2CO$) δ 7.30 (m, 6, ArH), 7.54 (m, 4, ArH), 8.61 (s, 1, purine CH); MS *m/e* (rel intensity) 336 (100), 338 (34, M^+), 318 (15), 320 (6, $M^+ - H_2O$), 259 (28), 261 (10, $M^+ - C_5H_5$).

Anal. Calcd for $C_{18}H_{13}ClN_4O$: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.40; H, 3.69; N, 16.69.

6-Amino-8-(2-hydroxy-2-propyl)-9-(tetrahydropyran-2-yl)purine (9a). A solution of **8a** (50 mg, 0.16 mmol) in methanol (5.5 mL) was saturated with NH_3 at 0 °C in a sealable tube. The reaction tube was sealed and heated for 12 h at 90 °C. The tube was cooled and opened, the solvent was removed in vacuo, and the residue was extracted with hot acetone. The acetone was removed in vacuo, and the compound was applied to a column of neutral alumina (activity grade I, ICN Pharmaceuticals) and eluted with a gradient of $CHCl_3$ (300 mL) to 8% EtOH/$CHCl_3$ (300 mL). The combination of the appropriate fractions provided **9a** (35 mg, 75% yield): mp 162–164 °C; NMR ($(CD_3)_2SO$) δ 1.35–2.05 (m, 6, CH_2's), 1.52 (s, 3, CH_3), 1.62 (s, 3, CH_3), 2.85–3.1 (m, 1, OCH_2), 3.75–4.15 (m, 1, OCH_2), 5.68 (br, NH or OH), 6.25 (br d, J = 11 Hz, 1, N–CH–O), 6.88 (br, NH or OH), 8.02 (s, 1, purine CH); MS *m/e* 277 (M^+), 193 (B, M^+ – Dhp), 178 (M^+ – Dhp – CH_3), 175 (M^+ – Dhp – H_2O).

Anal. Calcd for $C_{13}H_{19}N_5O_2 \cdot {}^1/_3H_2O$: C, 55.11; H, 7.00; N, 24.70. Found: C, 55.12; H, 6.82; N, 24.30.

6-Amino-8-(2-hydroxy-2-propyl)purine. A solution of **9a** was hydrolyzed to remove the 9-protecting group: mp 244–245 °C dec (lit.[25] mp 249–251 °C dec); NMR ($(CD_3)_2SO$) δ 1.55 (s, 6, CH_3), 5.55 (br, NH or OH), 6.82 (br, NH or OH), 8.05 (s, 1, purine CH); MS *m/e* 193 (B, M^+), 178 ($M^+ - CH_3$), 175 ($M^+ - H_2O$), 150 ($M^+ - C_2H_3O$), 136 ($M^+ - C_3H_5O$).

Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.56; H, 5.64; N, 36.09.

6-Amino-8-(hydroxydiphenylmethyl)-9-(tetrahydropyran-2-yl)purine (9b). A solution of **8b** (102 mg, 0.24 mmol) in methanol (4.5 mL) was saturated with NH_3 at 0 °C in a sealable tube. The reaction tube was sealed, heated at 90 °C for 12 h, cooled, and opened, and the contents were filtered. The filtrate was evaporated in vacuo, and the residue was extracted with hot $CHCl_3$. The addition of CCl_4 to the chloroform layer effected the precipitation of **9b** (60 mg, 60% yield): mp 253–255 °C dec; NMR ($(CD_3)_2SO$) δ 1.0–2.0 (m, 6, CH_2's), 2.65–3.0 (m, 1, OCH_2), 3.55–3.9 (m, 1, OCH_2), 5.56 (br d, J = 11 Hz, 1, N–CH–O), 6.81 (br, NH or OH), 7.29 (s, 10, ArH), 8.05 (s, 1, purine CH); MS *m/e* 401 (M^+), 317 (M^+ – Dhp), 299 (M^+ – Dhp – H_2O).

Anal. Calcd for $C_{23}H_{23}N_5O_2$: C, 68.81; H, 5.77; N, 17.45. Found: C, 68.47; H, 5.67; N, 17.30.

6-Amino-8-(hydroxydiphenylmethyl)purine. A solution of **9b** was hydrolyzed to remove the 9-protecting group: mp 270–271 °C dec; NMR ($(CD_3)_2SO$) 6.83 (br, NH or OH), 7.10–7.55 (m, 10, ArH), 8.09 (s, 1, purine CH); MS *m/e* 317 (B, M^+), 299 ($M^+ - H_2O$), 240 ($M^+ - C_6H_5$), 212 ($M^+ - C_7H_5O$).

Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.12; H, 4.76; N, 22.07. Found: C, 67.98; H, 4.74; N, 22.00.

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Registry No. 1, 71819-06-2; 2, 16347-32-3; **3a**, 71819-07-3; **3b**, 71819-08-4; **3c**, 71819-09-5; **4a**, 71819-10-8; **4b**, 71819-11-9; **5**, 71819-12-0; **6**, 71819-13-1; **7**, 7306-68-5; **8a**, 71819-14-2; **8b**, 71819-15-3; **9a**, 71819-16-4; **9b**, 71819-17-5; acetone, 67-64-1; 6-(2-hydroxy-2-propyl)purine, 71819-18-6; 8-(2-hydroxy-2-propyl)purine, 71819-19-7; benzaldehyde, 100-52-7; phenylacetaldehyde, 122-78-1; 6-(α-hydroxybenzyl)purine, 71819-20-0; 6-(1-hydroxy-2-phenylethyl)-purine, 71819-21-1; benzophenone, 119-61-9; 8-(hydroxydiphenylmethyl)purine, 71819-22-2; 2-chlorobenzoxazole, 615-18-9; 8-(benzoxazol-2-yl)purine, 71819-23-3; 6-chloro-8-(2-hydroxy-2-propyl)-purine, 71819-24-4; 6-chloro-8-(hydroxydiphenylmethyl)purine, 71819-25-5; 6-amino-8-(2-hydroxy-2-propyl)purine, 23865-41-0; 6-amino-8-(hydroxydiphenylmethyl)purine, 71819-26-6.