Defined Dimensional Alterations in Enzyme Substrates. Birch Reduction of *lin*-Benzopurines. A Contribution to Information Concerning the Binding Sites of Adenosine Deaminase and Xanthine Oxidase

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An informative approach toward definition of the active sites of enzymes that require purines as substrates or cofactors lies in the use of *dimensional probes*,[1] compounds that differ from the natural bases, ribonucleosides, or ribonucleotides by defined dimensional changes. These compounds retain both the pyrimidine and imidazole rings present in purines, but the rings are separated by intervening chemical frameworks. When there is formal insertion of a benzene ring (actually four additional carbons) into the middle of the purine ring system, the compounds are referred to as *lin*-benzopurines.[1,2] 4,9-Dihydro-*lin*-benzopurines[3] are constructed to pose the question as to whether the contributing terminal rings must be coplanar for the observation of binding and activity, especially in those enzyme systems where the reactivity of the *lin*-benzopurines has been established. While we have furnished some general synthetic methodology for the bent[4] 4,9-dihydro-*lin*-benzopurines, we sought more direct reduction methods from the corresponding *lin*-benzopurines that would make the dihydro compounds more readily available.

The most obvious method, and one that had been tried unsuccessfully earlier, was the Birch reduction.[5-9] This route should produce 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) from *lin*-benzohypoxanthine (**1a**), 4,9-dihydro-*lin*-benzoxanthine (**2b**) from *lin*-benzoxanthine (**1b**), 4,9-dihydro-*lin*-benzoguanine (**2c**) from *lin*-benzoguanine (**1c**), and 4,9-dihydro-*lin*-benzoadenine (**6**) from *lin*-benzoadenine (**1d**). The selective reduction of the central ring of *lin*-benzoxanthine (**1b**) and *lin*-benzoguanine (**1c**) by means of excess lithium in liquid ammonia containing 1 molar equiv of *tert*-butyl alcohol illustrates the deactivating influence of an electron-donating substituent on the heterocyclic ring and not on the benzene ring. Both new 4,9-dihydro-*lin*-benzopurines (**2b**, **2c**) could be obtained regularly in yields in the 70–90% range. These reactions were *not* successful unless certain precautions were observed, as indicated in the following notes, some of which may actually amplify or confirm information generally available concerning other Birch reductions, but all of which are germane to the experiments described here.

1. Since impurities, especially water, may drastically alter the course of a Birch reduction, ammonia should be dried over sodium amide (about 1 h) and then be distilled into the oven-dried reaction vessel.

2. The duration of the reaction is important. Extension of the reaction time beyond that described for each case in the Experimental Section led to increased formation of side products, presumably polyhydro-*lin*-benzopurines.

3. All operations during separation, isolation, and recrystallization of the dihydro-*lin*-benzopurines should be carried out under nitrogen or argon with deaerated solvents.

4. All the dihydro-*lin*-benzopurines described here are stable in solid form if protected from moisture and oxygen. All are hygroscopic.

5. In contrast to the aromatic *lin*-benzopurines (**1a–d**), which are fluorescent,[1] their 4,9-dihydro analogues are not, but can be detected readily on a TLC plate by the complexes they form with iodine (red spots).

The Birch reduction of *lin*-benzohypoxanthine (**1a**) under the same conditions employed for the successful reduction of **1b** and **1c** gave 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) as the major product, accompanied by *lin*-benzopurine (**3**) and traces of 4,5,6,9-tetrahydro-*lin*-benzohypoxanthine. The reduction of *lin*-benzoadenine (**1d**) with excess lithium in ammonia (heterogeneous) at −78 °C yielded *lin*-benzopurine almost exclusively according to a TLC analysis of the crude reaction product. The reductive cleavage of **1a** and **1d** to **3** presumably proceeds via the intermediacy of a 5,6-dihydro compound which can tautomerize under the alkaline conditions to 5,8- and/or 7,8-dihydo-*lin*-benzohypoxanthine or -adenine. These isomers from both precursors could give rise to *lin*-benzopurine (**3**), which was identified by NMR and mass spectroscopy. It was not produced in the Birch reduction of the *lin*-benzopurines having substituents at the 6-position, e.g., **1b** and **1c**. Attendant products from the reduction of **1a** and **1d** could be detected by TLC on silica gel using acetone–methanol, 5:1, with development by iodine, but attempts to isolate the corresponding products in pure form were not successful, probably because of their instability.[10]

An attempt to prepare 4,9-dihydro-*lin*-benzoadenine (**6**) by P_2S_5 conversion of 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) to 4,9-dihydro-8-mercaptoimidazo[4,5-*g*]quinazoline (**4**), methylation to 4,9-dihydro-8-(methylthio)imidazo-[4,5-*g*]quinazoline (**5**), and displacement of the 8-SCH_3 group with ammonia failed in the final step. However, it was possible to obtain 4,9-dihydro-*lin*-benzoadenine (**6**) by reduction of *lin*-benzoadenine (**1d**) with lithium in methylamine and hexamethylphosphorous triamide (HMPT) at −6.5 °C during a 30-min reaction time. *lin*-Benzopurine (**3**) was also isolated and some *lin*-benzoadenine (**1d**) was recovered under these reduction conditions.

Identification and structure proof of the 4,9-dihydro-*lin*-benzopurines **2a–c** and **4–6** described herein were provided by means of their distinctive ^1H NMR and mass spectra. The behavior of **2a** and **2b** with the enzyme

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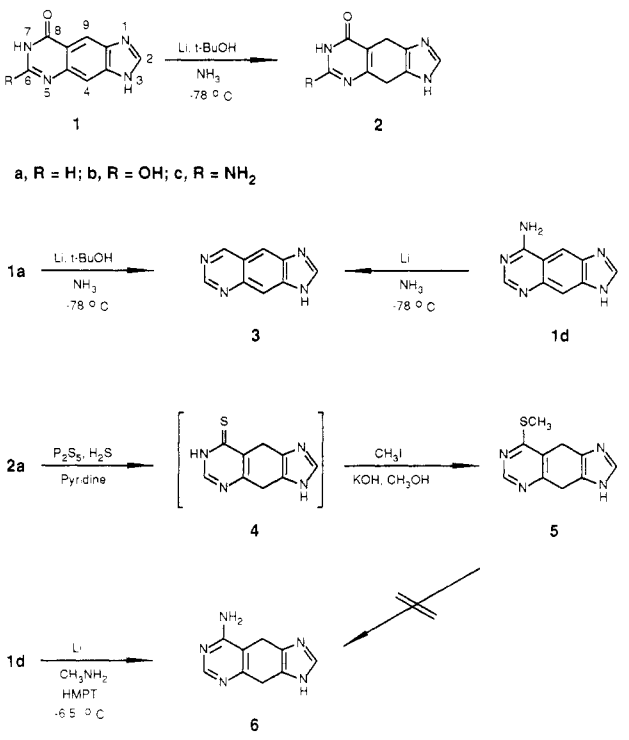

xanthine oxidase and that of **6** with adenosine deaminase were examined.

Although adenosine deaminase (calf intestinal mucosa)[11] does not deaminate adenine to hypoxanthine, we found earlier[1,12] that it does convert the "stretched-out" free base *lin*-benzoadenine (**1d**) to *lin*-benzohypoxanthine (**1a**). By contrast, we have now found that the enzyme does not recognize 4,9-dihydro-*lin*-benzoadenine (**6**) as a substrate since there was no appreciable change in the UV spectrum of **6** when it was subjected to the identical deaminase conditions that were satisfactory with **1d**. This shows that the altered bonding of **6** and/or the dearomatization of the central ring of **1d** changes the enzyme-binding characteristics sufficiently to preclude reaction. 4,9-Dihydro-*lin*-benzoadenine (**6**) was also not an inhibitor of the deamination of *lin*-benzoadenine (**1d**) with adenosine deaminase. These findings, combined with our earlier results concerning substrate reaction or nonreaction with adenosine deaminase, help establish the spatial and dimensional limitations for binding to this enzyme. Thus, adenosine, the laterally extended (by 2.4 Å) *lin*-benzoadenosine,[12] and *lin*-benzoadenine[12] were active as substrates, while adenine, the angular *prox*- and *dist*-benzoadenines,[12-14] the bent 4,9-dihydro-*lin*-benzoadenine (**6**), and the laterally extended (by 4.8 Å) *lin*-naphthoadenosine[15] and *lin*-naphthoadenine[15] were inactive.

In the case of xanthine oxidase (buttermilk),[16] both hypoxanthine and *lin*-benzohypoxanthine (**1a**) are substrates for oxidation in the pyrimidine and imidazole rings.[1,12,13] We have now found that the bent 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) is oxidized by air in the presence of xanthine oxidase at approximately two-thirds the rate of the transformation of *lin*-benzohypoxanthine (**1a**) to *lin*-benzoxanthine (**1b**). The product of the xanthine oxidase promoted reaction of **2a** was identified by spectral comparison with 4,9-dihydro-*lin*-benzoxanthine (**2b**). That this was the final product of the reaction, i.e., that oxidation had occurred in the pyrimidine ring alone, was shown by the fact that authentic **2b** was unaltered under the same conditions that effected the conversion of **2a** to **2b**.

The latter oxidation was not due alone to the presence of the pyrimidine moiety in **2a** since it has been known for many years[17] that uracil and thymine are not substrates for buttermilk xanthine oxidase. The degree of substrate specificity helps to define the dimensional adaptivity of the hydrophobic pocket of this enzyme. Thus, the following related substrates are oxidized: hypoxanthine, *lin*-benzohypoxanthine, and *lin*-benzoinosine (both extended by 2.4 Å),[12] the angular *dist*- and *prox*-benzohypoxanthines (the latter very slowly),[12] the bent 4,9-dihydro-*lin*-benzohypoxanthine (**2a**), and the extended (by 4.8 Å) *lin*-naphthohypoxanthine.[18] All are accommodated and all are oxidized (at least) in the pyrimidine ring.

Experimental Section

^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer. Fast atom bombardment mass spectra (FABMS) and high-resolution mass spectra (HRFABMS) were obtained on a VG ZAB-1F instrument equipped with a high-field magnet and a VG 11/250 data system. Microanalyses were performed by Josef Nemeth and his staff. Ultraviolet spectra were recorded on a Hewlett-Packard HP 8451A diode array spectrophotometer.

General Procedure for the Birch Reduction of *lin*-Benzoxanthine and *lin*-Benzoguanine. 4,9-Dihydro-*lin*-benzoxanthine (2b). A mixture of *lin*-benzoxanthine (**1b**) (202 mg, 1 mmol) and *tert*-butyl alcohol (74 mg, 1 mmol) was cooled to −78 °C. Liquid ammonia (30 mL), predried over sodium amide and then distilled, was added to the mixture with the exclusion of moisture. Lithium (34 mg, 5 mmol) was added to the stirred solution in small pieces within 5 min. The reaction mixture was stirred vigorously for an additional 30 min at −78 °C. After addition of ammonium chloride (265 mg, 5 mmol), ammonia was evaporated under a stream of nitrogen. The crude reaction mixture was dried overnight at 0.1 mmHg, powdered, and then treated with methanol (10–15 mL) that had been deaerated with nitrogen. The heterogeneous mixture was stirred briefly under nitrogen and the solid material that deposited was collected by filtration and washed with water (2 mL) and then methanol (2–3 mL). After drying in vacuo, compound **2b** was obtained as a colorless powder that was hygroscopic (yield, 189 mg, 93%). An analytical sample was obtained by recrystallization from boiling methanol that had been deaerated with dry nitrogen: mp >350 °C dec; UV λ_{max} 216 and 266 nm (50 mM KPi, pH 7.42); ^{1}H NMR ($(CD_3)_2SO$) δ 3.32 (s, 2), 3.58 (s, 2), 7.56 (s, 1), 12.00 (br s, 1), 12.50 (br s, 1); FABMS, m/z 205 $(M + 1)^+$; HRFABMS, m/z 205.0726 (calcd for $C_9H_9N_4O_2$ $(M + 1)^+$, 205.0725). Anal. Calcd for $C_9H_8N_4O_2 \cdot H_2O$: C, 48.64; H, 4.50; N, 25.22. Found: C, 48.59; H, 4.22; N, 25.31.

4,9-Dihydro-*lin*-benzoguanine (2c), prepared in 71% yield from *lin*-benzoguanine on a 1-mmol scale as described above, was recrystallized from boiling methanol: mp >320 °C dec; ^{1}H NMR ($(CD_3)_2SO$) δ 3.36 (s, 2), 3.51 (s, 2), 6.46 (s, 2, NH_2), 7.53 (s, 1); FABMS, m/z 204 $(M + 1)^+$; HRFABMS, m/z 204.0885 (calcd for $C_9H_{10}N_5O$ $(M + 1)^+$, 204.0885). The hygroscopic nature of the compound led to variability in the microanalytical data.

4,9-Dihydro-*lin*-benzohypoxanthine (2a) and *lin*-Benzopurine (3). Via the procedure described above, *lin*-benzohypoxanthine (744 mg, 4 mmol) was reduced with *tert*-butyl alcohol (296 mg, 4 mmol) and lithium (110 mg, 16 mmol) in dry liquid ammonia (100 mL) at −78 °C during 30 min. After addition

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of ammonium chloride (848 mg, 16 mmol), the ammonia was evaporated under a stream of nitrogen. The light yellow residue was dried overnight at 0.1 mmHg and then dissolved in warm methanol previously deaerated with nitrogen. The mixture was filtered rapidly by suction, and the filtrate was cooled at 5 °C for 1 h. The white solid that precipitated, together with additional solid that resulted from concentration of the mother liquor under vacuum, was collected and washed with water and methanol (yield of **2a**: 305 mg, 40%). An analytical sample was obtained by recrystallization from boiling methanol saturated with nitrogen: mp >350 °C dec; UV λ_{max} 226 nm (50 mM KPi, pH 7.42); ^{1}H NMR ($(CD_3)_2SO$) δ 3.52 (m, 2), 3.74 (m, 2), 7.58 (s, 1), 8.09 (s, 1), 12.00 (br s, 1), 12.50 (br s, 1); FABMS, m/z 189 $(M + 1)^+$; HRFABMS, m/z 189.0782 (calcd for $C_9H_9N_4O$ $(M + 1)^+$, 189.0776). Anal. Calcd for $C_9H_8N_4O \cdot 0.5H_2O$: C, 54.82; H, 4.56; N, 28.42. Found: C, 54.47; H, 4.39; N, 28.15.

***lin*-Benzopurine (imidazo[4,5-*g*]quinazoline) (3)** was obtained by removal of solvent in vacuo from the mother liquor as a dark yellow oil. Flash chromatography (silica gel, acetone) gave **3** as a hygroscopic yellow solid: 136 mg (20%); mp 299–300 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 8.15 (s, 1), 8.42 (s, 1), 8.69 (s, 1), 9.15 (s, 1), 9.68 (s, 1); EI mass spectrum (relative intensity) (10 eV), m/z 170 (M^+, 100); HRFABMS, m/z 171.0668 (calcd for $C_9H_7N_4$ $(M + 1)^+$, 171.0671). Anal. Calcd for $C_9H_6N_4 \cdot 0.5H_2O$: C, 60.33; H, 3.91. Found: C, 60.20; H, 3.61.

***lin*-Benzopurine (3)** was also obtained when *lin*-benzoadenine (**1d**) was subjected to the general Birch reduction conditions described above. Via the treatment with ammonium chloride and evaporation of the ammonia, the resulting yellow solid was extracted three times with boiling methanol. Removal of the solvent in vacuo followed by column chromatography (silica gel, acetone) gave **3** in isolated yield of 52%, identical in all respects to the byproduct of the reduction of *lin*-benzohypoxanthine.

4,9-Dihydro-8-(methylthio)imidazo[4,5-*g*]quinazoline (5). A mixture of 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) (94 mg, 0.5 mmol), purified P_2S_5 (222 mg, 1 mmol), and dry pyridine (5 mL) was heated at reflux for 15 h. During this time, dry H_2S was bubbled slowly through the solution. The reaction mixture was allowed to stand at 5 °C overnight. The precipitated solid was collected by filtration and then treated with warm water (5 mL). The grey crystals that were deposited were washed with water and dried in vacuo to give **4,9-dihydro-8-mercaptoimidazo[4,5-*g*]quinazoline (4)** (57 mg, 56%), slightly contaminated with 8-mercaptoimidazo[4,5-*g*]quinazoline according to TLC (silica gel, acetone–methanol, 5:1); ^{1}H NMR ($(CD_3)_2SO$) δ 3.74 (s, 2), 3.86 (s, 2), 7.78 (s, 1), 8.29 (s, 1), 13.00 (br s, 2).

The crude mixture was used directly for conversion to **5**. Methyl iodide (42 mg, 0.3 mmol) was added to a stirred suspension of the mercapto compound (50 mg, 0.25 mmol) and potassium hydroxide (17 mg, 0.3 mmol) in 50% aqueous methanol (3 mL). Stirring was continued under nitrogen for 1 h. The solid that precipitated was collected by filtration, washed with water (1–2 mL), and dried at 0.1 mmHg for 24 h to give **5** (yield, 44 mg, 82%). Further purification was effected by radial preparative-layer chromatography[19] under nitrogen (silica gel, acetone–methanol, 5:1): mp 305 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 2.51 (s, 3, SCH_3), 3.70 (s, 2), 3.97 (s, 2), 7.66 (s, 1), 8.83 (s, 1), 12.00 (br s, 1); FABMS, m/z 219 $(M + 1)^+$; HRFABMS, m/z 219.0702 (calcd for $C_{10}H_{11}N_4S$ $(M + 1)^+$, 219.0704). This compound was not readily convertible into 4,9-dihydro-*lin*-benzoadenine (**6**) by treatment with ammonia in ethanol in a steel bomb at 110–120 °C, nor could **6** be obtained by fusion of **2a** with phenyl phosphorodiamidate (PPDA).

4,9-Dihydro-*lin*-benzoadenine (6). In a dry 50-mL, three-necked flask, equipped with a mechanical stirrer, a dry ice condenser with a moisture trap, and a septum, methylamine (25–30 mL) was condensed directly under argon from a cylinder. *lin*-Benzoadenine (**1d**) (185 mg, 1 mmol) was dissolved in 10 mL of hot, freshly distilled HMPT and purged with argon. Lithium (27 mg, 4 mmol) was added to the methylamine, followed by the hot solution of **1d** with stirring. The solution of **1d** was added at such a rate that the blue color of the lithium solution persisted. After the addition was complete (30 min), the reaction mixture turned from blue to light yellow. Ammonium chloride (213 mg, 4 mmol) was added slowly, the dry ice suspension was removed from the condenser, and argon was bubbled through the solution to remove as much methylamine as possible. After 2 h, 15 mL of methanol, purged with argon, was added. During the next 2 h, a cream-colored precipitate separated. The precipitate was filtered, washed with 3 mL of methanol, and dried under vacuum to give **6** (44 mg, 23%). The compound was recrystallized from DMF: mp >360 °C; UV λ_{max} 231 and 265 nm (50 mM KPi, pH 7.42); ^{1}H NMR ($(CD_3)_2SO$) δ 3.50 (m, 2), 3.78 (m, 2), 6.75 (s, 2, NH_2, ex), 7.58 (s, 1), 8.21 (s, 1), 12.00 (br s, 1, NH); FABMS, m/z 188 $(M + 1)^+$; HRFABMS, m/z 188.0934 (calcd for $C_9H_{10}N_5$ $(M + 1)^+$, 188.0936).

Enzyme Studies. For the enzyme studies, adenosine deaminase (type VII, from calf intestinal mucosa) and xanthine oxidase (grade I, from buttermilk) were purchased from Sigma Chemical Co.

Adenosine Deaminase. 4,9-Dihydro-*lin*-benzoadenine (**6**) (2.1 mg) was dissolved in 250 mL of 50 mM KPi buffer (pH 7.42), and a 3-mL aliquot of the solution was transferred into a cuvette. A UV spectrum was taken, and the cuvette was placed in a water bath at 25 °C. When the thermal equilibrium was reached, 4 μL of a water solution of adenosine deaminase (100 units/200 μL) was added, the solution was mixed well, and a UV spectrum was taken. The solution was incubated 24 h at 25 °C. No change in the UV spectrum was observed during this time. In a control experiment under the same conditions, adenosine deaminase converted *lin*-benzoadenine (**1d**) into *lin*-benzohypoxanthine (**1a**), as previously reported.[12]

Xanthine Oxidase. *lin*-Benzohypoxanthine (**1a**) and 4,9-dihydro-*lin*-benzohypoxanthine (**2a**) were dissolved separately in 50 mM KPi buffer (pH 7.42) to make 50 μM solutions. In each experiment 1 mL of the substrate solution was mixed with the enzyme (3.2 μL of 13 units/mL suspension) and the change in absorbance (at 300 nm for **1a** and 264 nm for **2a**) was recorded as a function of time. The final absorbance was recorded after 4 h. From a plot of absorbance versus time, the half reaction times were determined. The comparison of the half reaction times showed that **2a** was transformed to **2b** at approximately $^2/_3$ the rate of transformation of **1a** to **1b**. The product of the xanthine oxidase promoted reaction of **2a** was identified by comparison of the UV spectra. 4,9-Dihydro-*lin*-benzoxanthine (**2b**) was not altered by the enzyme under the same enzyme oxidation conditions as described above, proving that it was the final product of the oxidation of **2a** and that further oxidation had not occurred in the imidazole ring.

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Do Simple Optically Active Phase-Transfer Agents Catalyze Enantioselective Ether Formation?[1]

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Much evidence has been accumulated showing that enantioselective phase-transfer catalysis (PTC) of reactions is successful only if there is a multipoint interaction be-

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