4 reaction in Scheme I. Excess ethylene sulfide was used in our reaction to shift the equilibrium to **1a**; however, distillation of the product (**1a**) did not give **3** as an impurity as was observed with the ref 4 reaction in Scheme I. This may result from an impurity such as bromine or a bromo compound in the product from the ref 4 reaction in Scheme I acting as a catalyst for the reaction of **1a**.

These results clearly demonstrate the validity of the potential equilibrium given in eq 1.

Experimental Section

All reagents were used as obtained from Aldrich without further purification. ^1H and ^{13}C nuclear magnetic resonance (NMR) data were obtained on a JEOL FX90Q Fourier transform nuclear magnetic resonance (FTNMR) spectrometer and were referenced vs. tetramethylsilane. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN.

Bromoethyl Benzyl Sulfide (1a). To 75 g of ethylene sulfide was added 171 g of benzyl bromide. The neat mixture was heated to 50 °C and monitored by ^1H NMR for the disappearance of the benzyl bromide methylene proton signal. This occurred after 24 h, at which time the solution was flushed with dry nitrogen gas to remove excess ethylene sulfide. The crude reaction mixture afforded a quantitative yield of the bromoethyl benzyl sulfide (**1a**), and the ^1H NMR spectrum was comparable to that from the product obtained by Schneider's procedure.[4] An aliquot of our product was distilled to give **1a**: bp 120–123 °C (0.55 torr), [lit.[4] bp 111 °C (0.2 torr)]; ^1H NMR ($CDCl_3$) δ 2.78 (t, 2, CH_2S), 3.31 (t, 2, $BrCH_2$), 3.68 (s, 2, SCH_2Ph), 7.25 (s, 5, Ph).

Chloroethyl Trityl Sulfide (1c). To a flask was added 5.58 g (0.02 mol) of trityl chloride and 2.4 g (0.04 mol) of ethylene sulfide in 25 mL of dichloromethane and stirred for 48 h at room temperature. The solvent was evaporated, and the residue was recrystallized once from benzene/petroleum ether (50:50) to afford **1c** in an 81% yield.

The ^1H NMR spectra of this solid and the analytical sample were identical: ^1H NMR ($CDCl_3$) δ 2.63 (t, 2, CH_2S), 3.08 (t, 2, $ClCH_2$), 7.15–7.52 (m, 15, Ph_3C). A sample was twice recrystallized as above to give **1c**, mp 119.5–121 °C.

Anal. Calcd for $C_{21}H_{19}ClS$: C, 74.43; H, 5.65; Cl, 10.46; S, 9.46. Found: C, 74.36; H, 5.85; Cl, 10.41; S, 9.71.

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Registry No. **1a**, 60671-59-2; **1c**, 108418-96-8; **3**, 100-39-0; **4**, 420-12-2; trityl chloride, 76-83-5.

A Convenient Synthesis of *lin*-Benzopurines through a Common Intermediate

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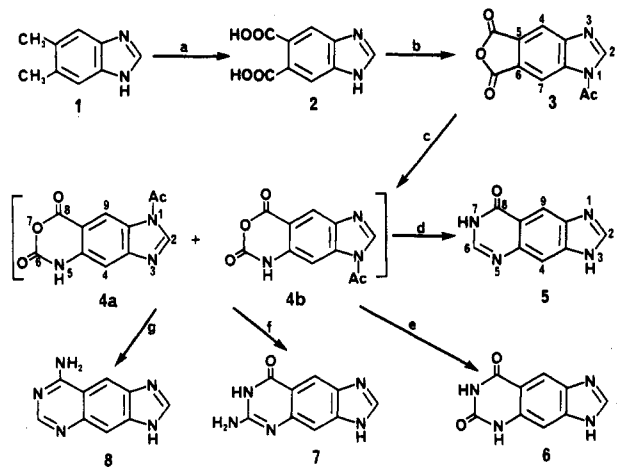
Continuing interest in *lin*-benzopurine derivatives as dimensional probes of binding and activity[1] has prompted us to seek improvement in the synthesis of the tricyclic heteroaromatic nuclei so as to make the entire series more readily available. For example, the initial synthesis of *lin*-benzoadenine required the separation of isomeric

Scheme I[a]



[a] (a) $KMnO_4$, H_2O/*tert*-butyl alcohol; (b) $(CH_3CO)_2O$; (c) Me_3SiN_3; (d) $HC(=NH)NH_2{\cdot}CH_3COOH$; (e) H_2NCONH_2; (f) NH_2CN, $(CH_3)_3COK$; (g) NH_3/DMF, $POCl_3$, NH_4OH.

substituted quinazolones at an intermediate stage.[2] Now, by recourse to symmetrical substitution on benzimidazole, it is possible to avoid isomeric diversion away from precursors that lead to the linear tricyclic ring system. 5,6-Dimethylbenzimidazole (**1**), which is readily available, was oxidized by potassium permanganate to benzimidazole-5,6-dicarboxylic acid (**2**) in 48% yield. Conversion to 1-acetylbenzimidazole-5,6-dicarboxylic anhydride (**3**) in 93% yield was effected by heating **2** with acetic anhydride. The five-membered cyclic anhydride was enlarged to a six-membered oxazinedione ring by treatment with azidotrimethylsilane, Me_3SiN_3 (Scheme I).[3-5]

The mixture of 1- and 3-acetylimidazo[4,5-*g*]-7,5-benzoxazine-6,8(5*H*)-dione (**4a, 4b**) was then used directly in the crude form as the pivotal intermediate for the synthesis of *lin*-benzohypoxanthine (**5**),[2] *lin*-benzoxanthine (**6**),[6] *lin*-benzoguanine (**7**),[7,8] and *lin*-benzoadenine (**8**).[2] In short, the intermediate **4a,b** serves as the common branch point for all the stretched-out purines related to the naturally occurring purines. Some of our observations that led to the development of more efficient synthetic methodology for the tricyclic series are worthy of comment. It is important to use freshly distilled azidotrimethylsilane in anhydrous acetonitrile with the rigorous exclusion of moisture to effect an efficient conversion of anhydride **3** to the complex isatoic anhydride intermediate **4a,b**. Extension of the reaction time beyond that described in the Experimental Section led to increased formation of an unwanted side product.[9] Formamidine acetate[4,5] in DMF or Cellosolve was used to convert **4a,b** to *lin*-benzohypoxanthine, imidazo[4,5-*g*]quinazolin-8(7*H*)-one (**5**),[2] in 86% overall yield from **3**. Fusion with urea[5] produced *lin*-benzoxanthine, imidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione (**6**),[6] in an overall yield of 55% or greater. The NMR

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spectrum of **6** in $(CD_3)_2SO$ gave evidence of 1*H* and 3*H* tautomers.[10]

For the conversion of **3** through **4a,b** to *lin*-benzoguanine, 6-aminoimidazo[4,5-*g*]quinazolin-8(7*H*)-one (**7**),[7,8] we tested new reaction conditions with isatoic anhydride as a model. Upon treatment of the latter with cyanamide and potassium *tert*-butoxide in DMF, 2-aminoquinazolin-4(3*H*)-one was produced in 55% yield. Under the same conditions, *lin*-benzoguanine (**7**) was obtained in 59% overall yield from **3** via **4a,b**. Direct conversion of the same precursor to *lin*-benzoadenine, 8-aminoimidazo[4,5-*g*]quinazoline (**8**),[2] in 56% overall yield was accomplished by using the general sequential treatment described by Foster and Elam:[11] (a) anhydrous ammonia in anhydrous DMF; (b) $POCl_3$; (c) concentrated NH_4OH. In the course of each of the four conversions described above (**3** → **4a,b** → **5–8**), the N-acetyl group is removed, with the result that the structures of the final products are as indicated except for possible ambiguity concerning the tautomeric forms in different environments.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a General Electric QE-300 spectrometer. The electron-impact mass spectra were run on a Varian MAT CH-5 low-resolution spectrometer and on a 731 high-resolution spectrometer. Acetonitrile and *N,N*-dimethylformamide were distilled from calcium hydride.

Benzimidazole-5,6-dicarboxylic Acid (2). Into a 5-L, three-necked, round-bottomed flask equipped with condenser, thermometer, mechanical stirrer, thermostated dropping funnel, and heating mantle was poured 700 mL of a 1:1 (v/v) mixture of water and *tert*-butyl alcohol followed by 40.0 g (0.274 mol) of 5,6-dimethylbenzimidazole (Aldrich). Stirring of this heterogeneous mixture at room temperature for 15–30 min gave a homogeneous, slightly brown solution, to which was added dropwise during 4 h a solution of 432.4 g (2.74 mol) of $KMnO_4$ dissolved in 3.0 L of H_2O from a dropping funnel thermostated at 60 ± 2 °C. This was best accomplished by adding a homogeneous solution of $KMnO_4$, prepared separately at 68–70 °C, to the funnel in 500-mL portions. The temperature of the reaction mixture increased slowly to 70 ± 2 °C, and the rate of addition of the $KMnO_4$ solution and heating were regulated so as to keep the temperature at this level. The heat was turned off, and stirring was continued for 15 min. Anhydrous Na_2SO_3 (150 g, 1.19 mol) was added in five portions to decompose the excess unreacted $KMnO_4$ while the temperature of the reaction mixture rose to 78–80 °C. The hot mixture was stirred 30 min and filtered, and the MnO_2 cake was washed with 500 mL of boiling water. The combined filtrates were concentrated to approximately 1.5 L at 40–45 °C under vacuum and then diluted to 3.0 L with distilled water. To the solution cooled at 0–2 °C was added 600 mL of cold aqueous acetic acid (2:1, v/v). The white solid that precipitated, together with additional solid that resulted from concentration of the mother liquor, was recrystallized from boiling water. After drying in vacuo at 70 °C, compound **2** was obtained as a colorless powder that was hygroscopic: yield, 26.9 g (48%).[12] From the analytical sample water was removed by azeotropic distillation with benzene using a Dean–Stark apparatus. This sample dried at 110 °C and 0.01 mmHg for 48 h still contained approximately 15% of benzene according to ^1H NMR and analytical data: mp 294–296 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 7.37 (s, 0.6 H, benzene), 7.88 (s, 2, 4-H and 7-H), 8.46 (s, 1, 2-H), 12.92 (br s, 3, 2 × COOH and NH).

Anal. Calcd for $C_9H_6N_2O_4 \cdot 0.15C_6H_6$: C, 54.57; H, 3.16; N, 12.86. Found: C, 54.36; H, 3.19; N, 12.41.

1-Acetylbenzimidazole-5,6-dicarboxylic Anhydride (3). A suspension of 20.7 g (0.10 mol) of benzimidazole-5,6-dicarboxylic acid (**2**) in 200 mL of acetic anhydride was stirred for 3 h at 145–150 °C (oil bath) with exclusion of moisture. After cooling to 5 °C, the white precipitate was collected by filtration, washed with 150 mL of anhydrous ether, and dried overnight at 80 °C and 15 mmHg to provide 21.3 g (93%) of compound **3**. An analytical sample was obtained by recrystallization from ethyl acetate: mp 272–274 °C dec; ^1H NMR ($(CD_3)_2SO$) δ 2.84 (s, 3, CH_3), 8.47 (s, 1, 4-H), 8.61 (s, 1, 7-H), 9.32 (s, 1, 2-H); mass spectrum (EI) (10 eV), *m/z* (relative intensity) 230 (M^+, 24), 188 ($M^+ - 42$, 27), 186 ($M^+ - 44$, 15); IR (KBr) 1850, 1790, 1750 cm^{-1}.

Anal. Calcd for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.63; N, 12.17. Found: C, 57.38; H, 2.61; N, 12.08.

Mixture of 1- and 3-Acetylimidazo[4,5-*g*]-7,5-benzoxazine-6,8(5*H*)-dione (4a,b). To a suspension of 5.0 g (21.7 mmol) of **3** in 300 mL of anhydrous acetonitrile was added 12 mL (90 mmol) of freshly distilled azidotrimethylsilane at room temperature with the exclusion of moisture. The mixture was stirred vigorously while the temperature of the oil bath was raised gradually to 90–95 °C. After an additional 3 h of stirring, the solution was cooled to 5 °C and 1.5 mL of water was added dropwise. Removal of the solvent at reduced pressure provided a mixture of **4a** and **4b** in approximately equal proportions, as indicated by the proton NMR spectrum in $(CD_3)_2SO$: δ 2.75 (s, 3, CH_3), 7.37 (s, 0.5 H), 7.98 (s, 0.5 H), 8.23 (s, 0.5 H), 8.62 (s, 0.5 H), 8.99 (s, 0.5 H), 9.13 (s, 0.5 H), 11.60 (s, 0.5 H), 11.78 (s, 0.5 H); mass spectrum (10 eV), *m/z* (relative intensity) 245 (M^+, 16), 201 (63). The crude mixture was used directly in conversions to 5–8 without purification.

***lin*-Benzohypoxanthine (Imidazo[4,5-*g*]quinazolin-8(7*H*)-one, 5).** The crude mixture of **4a,b** obtained as described above from 5.0 g (21.7 mmol) of **3** was dissolved in 60 mL of anhydrous DMF, 7.5 g (72 mmol) of formamidine acetate[4,5] was added, and the reaction mixture was heated for 3 h in an oil bath at 155 °C. The reaction mixture was cooled to 50 °C, and the precipitated solid was collected by filtration and washed with 100 mL of water. Drying at 100 °C under 15 mmHg provided 3.45 g (86% overall yield) of compound **5** as a white powder: mp >320 °C (lit.[2] mp >320 °C); ^1H NMR ($(CD_3)_2SO$) δ 7.87 (s, 1), 8.01 (s, 1), 8.35 (s, 1), 8.53 (s, 1), 12.02 (br s, 1), 12.86 (br s, 1); mass spectrum (10 eV), *m/z* (relative intensity) 186 (M^+, 100), 159 (20); high resolution mass spectrum, *m/z* 186.0543 (calcd for $C_9H_6N_4O$, 186.0541).

***lin*-Benzoxanthine (Imidazo[4,5-*g*]quinazoline-6,8(5*H*,7*H*)-dione, 6).** A solution of crude **4a,b** obtained from 5 g (21.7 mmol) of **3** and 3.78 g (63 mmol) of urea in 60 mL of DMF was heated in an oil bath at 155 °C for 5 h. The reaction mixture was cooled to room temperature, and the solid that precipitated was collected by filtration and washed with 100 mL of water to give, after drying at 100 °C and 15 mmHg for 24 h, 2.42 g (55% overall yield) of **6** as a light cream powder: mp >300 °C (lit.[6] mp >300 °C); ^1H NMR ($(CD_3)_2SO$) major signals δ 7.26 (s, 1), 8.14 (s, 1), 8.36 (s, 1), 11.02 (s, 1), 11.17 (s, 1), 12.60 (s, 1); mass spectrum (10 eV), *m/z* (relative intensity) 202 (M^+, 100), 159 (55); high resolution mass spectrum, *m/z* 202.04908 (calcd for $C_9H_6N_4O_2$, 202.04908).

Direct Conversion of Isatoic Anhydride to 2-Aminoquinazolin-4(3*H*)-one. To a stirred solution of 1.84 g (44 mmol) of cyanamide in 5 mL of DMF cooled to 5 °C was added 4.92 g (44 mmol) of potassium *tert*-butoxide in small portions over a period of 10–15 min. After addition was complete, the resulting mixture was diluted with 50 mL of DMF, and 6.52 g (40 mmol) of isatoic anhydride was added with the exclusion of moisture. The reaction mixture was heated with stirring in an oil bath at 155 °C for 3 h. The solution was diluted with 300 mL of water and acidified with acetic acid to pH ~6.5. The reaction mixture was then filtered quickly and cooled at 5 °C for 24 h. The resulting precipitate was collected by filtration, washed with 50 mL of water, and dried at 100 °C and 15 mmHg to give 2-aminoquinazolin-4(3*H*)-one as a white powder: yield 3.52 g (55%), mp 314–315 °C (lit.[13] mp 315–316 °C), readily characterized by its spectroscopic properties.

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***lin*-Benzoguanine (6-Aminoimidazo[4,5-*g*]quinazolin-8-(7*H*)-one, 7).** Similar conditions, but with a twofold excess of cyanamide (1.84 g, 44 mmol) and potassium *tert*-butoxide (4.92 g, 44 mmol) over crude **4a,b** from 5.00 g (21.7 mmol) of **3**, were used to obtain *lin*-benzoguanine (**7**) as a white powder from water: yield 2.62 g (59%); mp >300 °C (lit. mp >300 °C); ^{1}H NMR ($(CD_3)_2SO$) δ 6.46 (s, 2), 7.33 (s, 1), 8.16 (s, 1), 8.34 (s, 1), 11.5–12.5 (br s, 2); mass spectrum (10 eV), *m/e* (relative intensity) 201 (M^+, 100), 184 (11.9); high resolution mass spectrum, *m/z* 201.0651 (calcd for $C_9H_7N_5O$, 201.0652).

***lin*-Benzoadenine (8-Aminoimidazo[4,5-*g*]quinazoline, 8).** The previously described synthesis of *lin*-benzoadenine (**8**) required the conversion of **5** through the corresponding 8-thione.[2] In this sequence, compound **8** was obtained directly from the common precursor **4a,b** for **5**, **6**, and **7**. Anhydrous ammonia was bubbled into a suspension of **4a,b** obtained from 1.15 g (5 mmol) of **3** in 10 mL of anhydrous DMF at 10 °C for 30 min. The clear solution was degassed with dry N_2 to remove ammonia. After dropwise addition of 2 mL of phosphoryl chloride at 5–15 °C during 15 min the mixture was heated at 65–70 °C for 2 h and then cooled to 20 °C. Ice water (5 mL) was added, followed by concentrated NH_4OH to basicity (pH ~10.0). The resulting solution was filtered and then heated at 100 °C for 1 h. The solid that precipitated was collected by filtration and washed with 50 mL of water and then dried at 100 °C and 15 mmHg to afford **8**, as a cream powder: yield 0.52 g (56%); mp >320 °C (lit.[2] mp >320 °C); ^{1}H NMR (CD_3COOD) δ 8.45 (s, 1), 8.77 (s, 1), 8.89 (s, 1), 9.01 (s, 1); high resolution mass spectrum, *m/z* 185.0704 (calcd for $C_9H_7N_5$, 185.0701).

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Regioselective Synthesis of 1-Alkyl-3,6,8-trimethyl-2,7-naphthyridines

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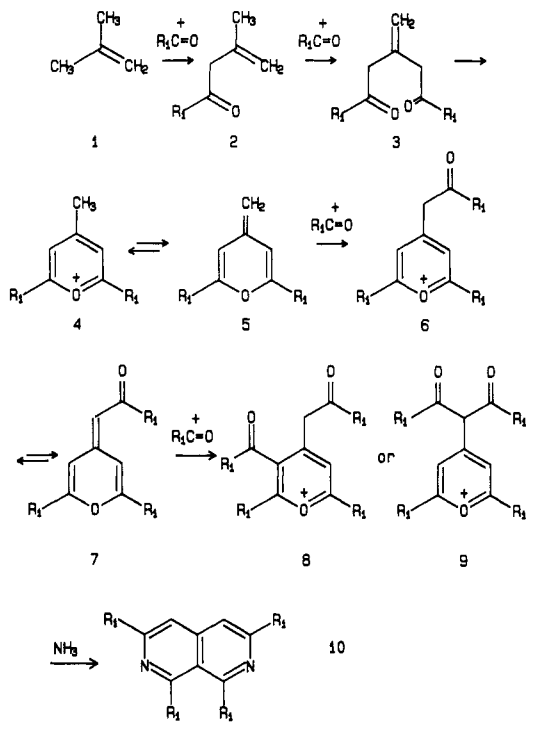
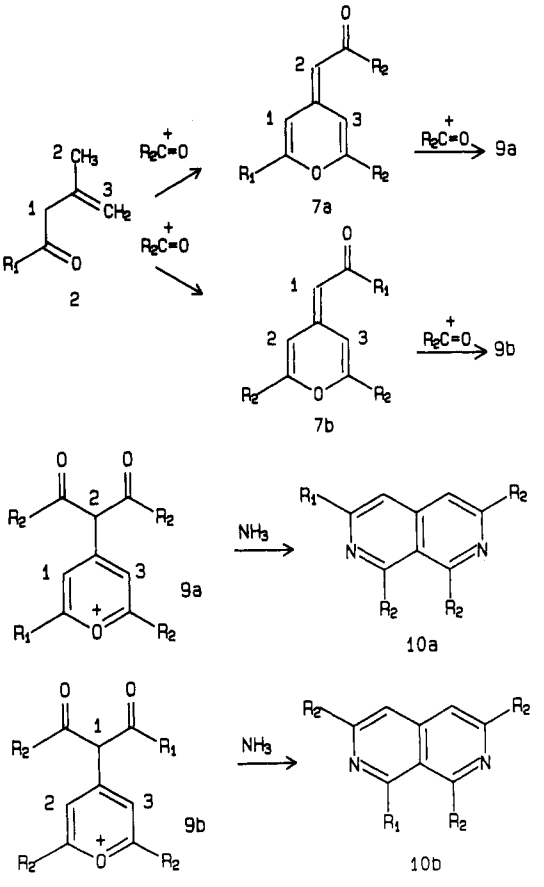
The chemistry of 2,7-naphthyridine derivatives has been little explored, partly due to the difficult and multistep synthesis of these compounds.[1,2] Some of the syntheses reported are not applicable to the preparation of polyalkyl derivatives. We recently reported a short and general synthesis of 1,3,6,8-tetralkyl-2,7-naphthyridines by a one-pot tetraacylation of 2-methyl-1-propene or 2-methyl-1-propene precursors followed by treatment with liquid ammonia (Scheme I).[3,4]

The reaction goes through a monoacylation step, producing the kinetic nonconjugated keto olefin **2**, which is further acylated to give **3**. Ring closure of **3** gives the pyrylium salt **4**. Acylation of **3** followed by ring closure or acylation of **5**, the conjugate base of the pyrylium **4**,

Scheme I



Scheme II



results in the formation of the 4-ketonyl-2,6-dialkylpyrylium salt **6**, which is in equilibrium with its unprotonated form **7**. We have proposed **7** as a possible intermediate for the last acylation, which can occur either in positions 3 or 5 of the methylenepyran framework to give **8** or, preferentially according to calculated electronic charges,[8] on the exocyclic carbon atom leading to **9**. We

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