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Linear Benzoadenine. A Stretched-Out Analog of Adenine

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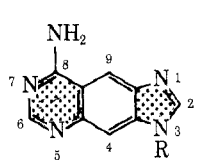
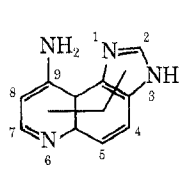
The synthesis of 8-aminoimidazo[4,5-*g*]quinazoline (**1**), an extended or "stretched-out" version of adenine which is given the descriptive name *lin*-benzoadenine, is reported. The synthesis involves the elaboration of 7-chloro-4-quinazolone (**6**) to imidazo[4,5-*g*]quinazolin-8-one (**11**) in four steps, followed by thiation to 8-mercaptoimidazo[4,5-*g*]quinazoline (**12**) and subsequent replacement of the thiol function by ammonia to yield the *lin*-benzoadenine isomer **1**. The aralkyl derivatives of **1**, *e.g.*, 8-amino-1- and 3-benzylimidazo[4,5-*g*]quinazoline (**17** and **16**), which are necessary to serve as uv models in assigning the structure of nucleoside and nucleotide targets and to direct further substitution, were obtained indirectly *via* benzylation of 8-methylthioimidazo[4,5-*g*]quinazoline (**13**). The structure assignment of the 3-benzyl isomer was checked by an unambiguous synthesis, and its value as a uv model was confirmed by spectral comparison with 8-amino-3-cyclohexylaminoimidazo[4,5-*g*]quinazoline (**30**). A general comparison of the uv spectra of various 8-methylthio- and 8-aminoimidazo[4,5-*g*]quinazoline derivatives in neutral, acidic, and basic solution indicates that first protonation occurs mainly on the imidazole ring of the methylthio compounds and on the quinazoline ring of the amino compounds.

There has been considerable interest in the synthesis of analogs of the naturally occurring nucleic acid bases and their corresponding nucleosides, nucleotides, and coenzymes.[1] In the course of our continuing study of the role of purines and pyrimidines in nature, we questioned what properties might be associated with compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or "stretched-out" purine model. Compounds such as **1** and **1a** would be expected to have 1,N^6 binding sites similar to those in adenine and adenosine, stronger π-bonding characteristics, and larger spatial requirements. The physical and biological properties of compounds **1** and **1a** and their congeners hold considerable interest since they are previously unknown and since differences in their behavior in relation to the corresponding naturally occurring adenine compounds might be relatable to defined geometrical changes.

In this paper we describe the synthesis, structure proof, and properties of the linear benzolog of adenine, 8-aminoimidazo[4,5-*g*]quinazoline (**1**), for which we suggest the descriptive name *lin*-benzoadenine.[2] This name is capable of easy adaptation to derivatives related to adenosine, adenylic acid, adenosine 5′-diphosphate, and the like. In the following paper we discuss the preparation of the structural isomers of **1**, 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), which are the proximal and distal isomers of benzoadenine, respectively.[2] We feel justified in using the term "benzo" in the trivial names of these three compounds because *only when the additional ring is central* does it contain no nitrogens and is accordingly "benzo."



1, R = H
1a, R = β-D-ribofuranosyl



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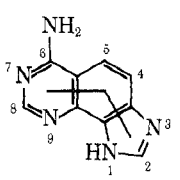
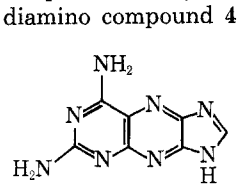


3

A review of the literature reveals only several cases where tricyclic heterocyclic systems related to **1** have been described. For none of the compounds was their preparation based on the criterion that they might be biologically active as purine surrogates. Taylor and Sherman synthesized diamino compound **4** during the course of work on



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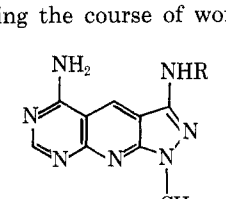
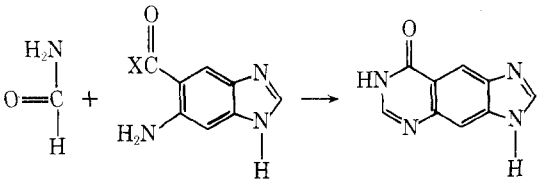


5, R = H, CHO, $COCH_3$

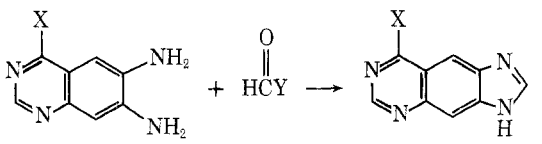
pteridine compounds.[3] Derivatives of **5** were synthesized and discussed on the basis of their relationship to tetrasubstituted pyridines.[4]

We approached the synthesis of the *lin*-benzoadenine **1** with the view that its preparation should be relatively simple and amenable to large batch scale-up. At first inspection, three possible routes to this ring system seem viable: the fusion of a pyrimidine ring onto an appropriately substituted benzimidazole (Scheme I); the construction of an imidazole moiety onto a disubstituted quinazoline (Scheme II); or the annelation of a tetrasubstituted benzene ring to form both heterocyclic rings simultaneously (Scheme III).

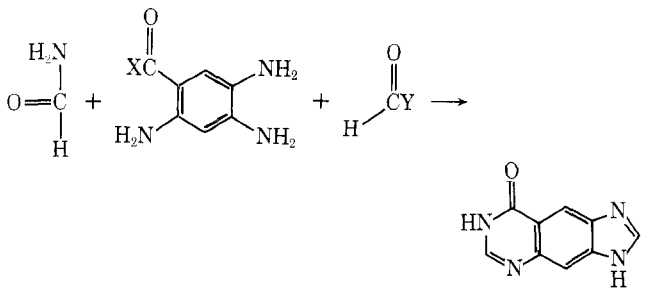
Scheme I



Scheme II



Scheme III



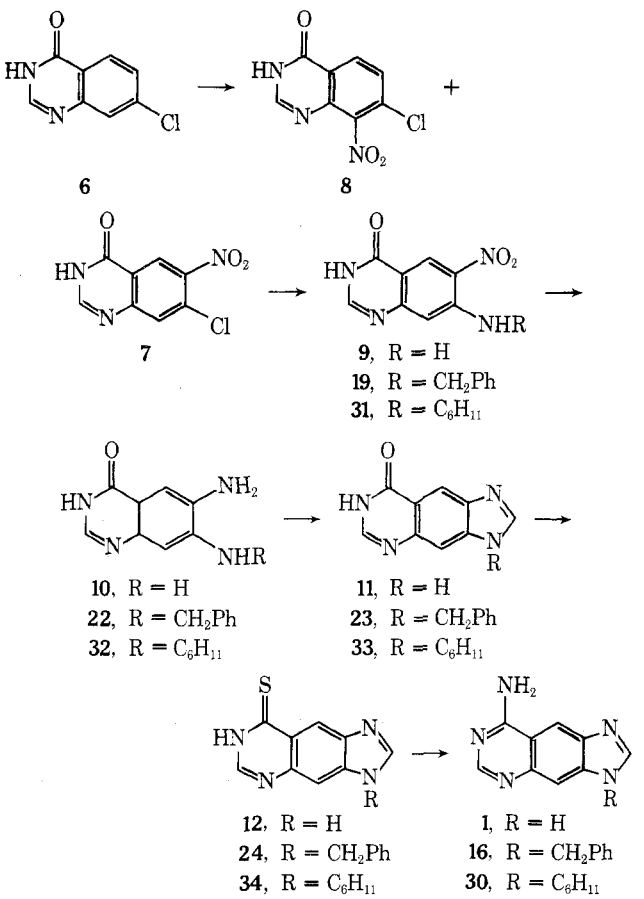
The first and third schemes were limited by the necessity for adjacent placement of aldehyde or ester and nitro or amino functions, which offered some synthetic difficulties. The polyfunctional substitution pattern required by Scheme III is probably synthetically accessible, although further elaboration of such a highly substituted benzene system might be limited because of the high reactivity inherent in such a system. The second scheme seemed most practical since the construction of monosubstituted quinazolones is well represented in the literature.[5] Further elaboration to a 6,7-disubstituted quinazoline as required by Scheme II appeared quite feasible and this, therefore, was the approach that we used.

Results and Discussion

Nitration of 7-chloro-4-quinazolone (**6**)[6] gave a 4:1 mixture (nmr) of the isomeric chloronitroquinazolones **7** and **8**, respectively. These isomers were separated by fractional crystallization, and the 6,7-disubstituted isomer **7** was obtained in 58% yield. The structure assigned to **7** was supported by the nmr spectrum which showed three singlet aromatic proton resonances at δ 7.97, 8.28, and 8.53. The nmr spectrum of the 7,8-disubstituted derivative **8** showed a singlet at δ 8.22 (H-2) and an AB quartet at δ 7.75 and 8.25 (H-5 and H-6). Treatment of compound **7** with butanolic ammonia in a sealed tube at 175° afforded 7-amino-6-nitro-4-quinazolone (**9**) in 98% yield. Reduction to diaminoquinazolone **10** could be effected by either catalytic hydrogenation or treatment with Raney nickel and hydrazine hydrate.[7] Ring closure proceeded readily in formic acid to give imidazoquinazolone **11**. Treatment of **11** with phosphorus pentasulfide in pyridine afforded the corresponding thio compound **12**. Compound **12** was converted to *lin*-benzoadenine **1** (8-aminoimidazo[4,5-*g*]quinazoline) upon heating in ammonia–saturated butanol in a sealed tube at 200°.

This compound (**1**) proved to be extremely insoluble in water and nonacidic organic solvents such as chloroform, acetonitrile, dimethylformamide, and dimethyl sulfoxide. This insolubility imposed experimental problems in assessing the reactivity of the compound. In particular, compound **1** did not react with alkylating reagents such as benzyl bromide or methyl iodide under normal reaction conditions. This was especially inconvenient since it was necessary to determine the preferred sites of alkylation and to prepare alkyl derivatives of **1** which would serve as uv models to aid in the structure assignment of the nucleoside and nucleotide target compounds. Consequently, an indirect approach was undertaken. The alkylation of the very soluble methylthio analog (**13**) of **1** was investigated. Compound **13**, easily prepared by the S-methylation of **12**, was readily convertible to the linear benzoadenine upon treatment with butanolic ammonia. It was anticipated that the derivatives obtained from the alkylation of **13** could also be easily converted to their respective benzoadenine derivatives (Scheme IV).

Scheme IV



The reaction of the methylthio compound **13** with benzyl bromide and potassium carbonate in dimethylformamide at room temperature resulted in nearly equal amounts of two isomeric benzyl derivatives, **14** and **15**. Both isomers **14**

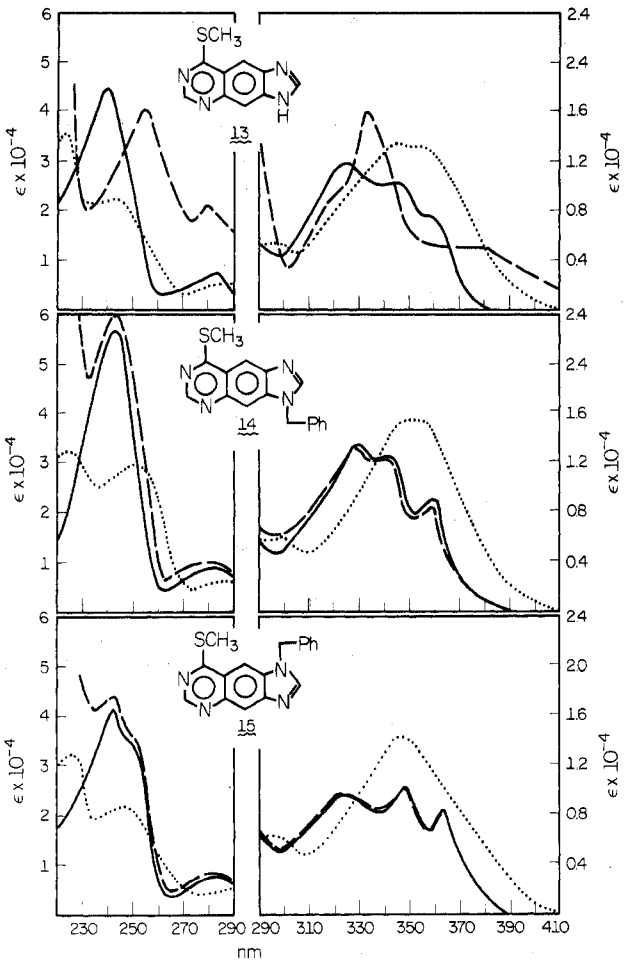


Figure 1. The uv spectra of 8-methylthioimidazo[4,5-*g*]quinazoline and its derivatives in 95% ethanol (——), 0.1 *N* HCl in 95% ethanol (· · · ·), and 0.1 *N* NaOH in 95% ethanol (- - - -).

and **15** could be converted to their respective amino analogs **16** and **17**, derivatives of *lin*-benzoadenine **1**. That the two pairs of benzyl derivatives (**14**, **15** and **16**, **17**) had similar spectral properties (as shown by a comparison of uv spectra in Figures 1 and 2) indicated that substitution had probably occurred at the anticipated positions, N-3 and N-1, of the methylthiobenzopurine **13**. In order to assign the structures of the benzylmethylthio derivatives as those indicated in **14** and **15**, 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**14**) was prepared by an unambiguous synthesis.

Direct treatment of chloronitroquinazolone **7** with neat benzylamine interestingly afforded *N*-benzyl-2-amino-4-benzylamino-5-nitrobenzamide (**18**) as the sole isolable product. However, when the reaction was controlled using **7** with an excess of benzylamine in butanol as the solvent, the desired 7-benzylamino-6-nitro-4-quinazolone (**19**) was isolated. The ring opening of 4-quinazolones resulting from nucleophilic attack of neat primary amines to afford either anthranilamides or N-3 substituted quinazolones was reported some years ago from this laboratory.[8] In order to obtain further confirmation of the structures assigned to intermediates **18** and **19**, both compounds were converted to a dibenzylquinazolone **20** identical from both sources, from **18** by heating with formic acid and from **19** by reaction with potassium hydroxide and benzyl bromide in methanol. 3-Benzyl-7-benzylamino-6-nitro-4-quinazolone (**20**) was also prepared independently from **7** *via* benzylation to 3-benzyl-7-chloro-6-nitro-4-quinazolone (**21**) followed by benzylamine displacement in hot butanol. The quinazolone

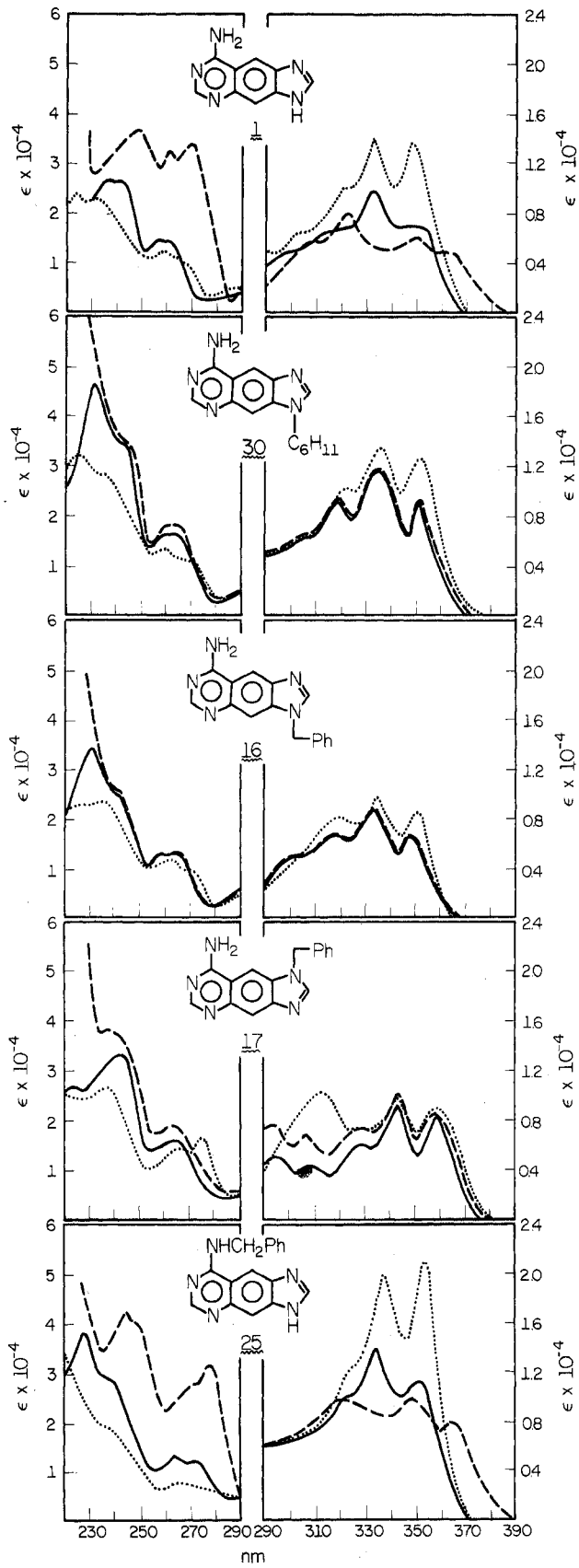
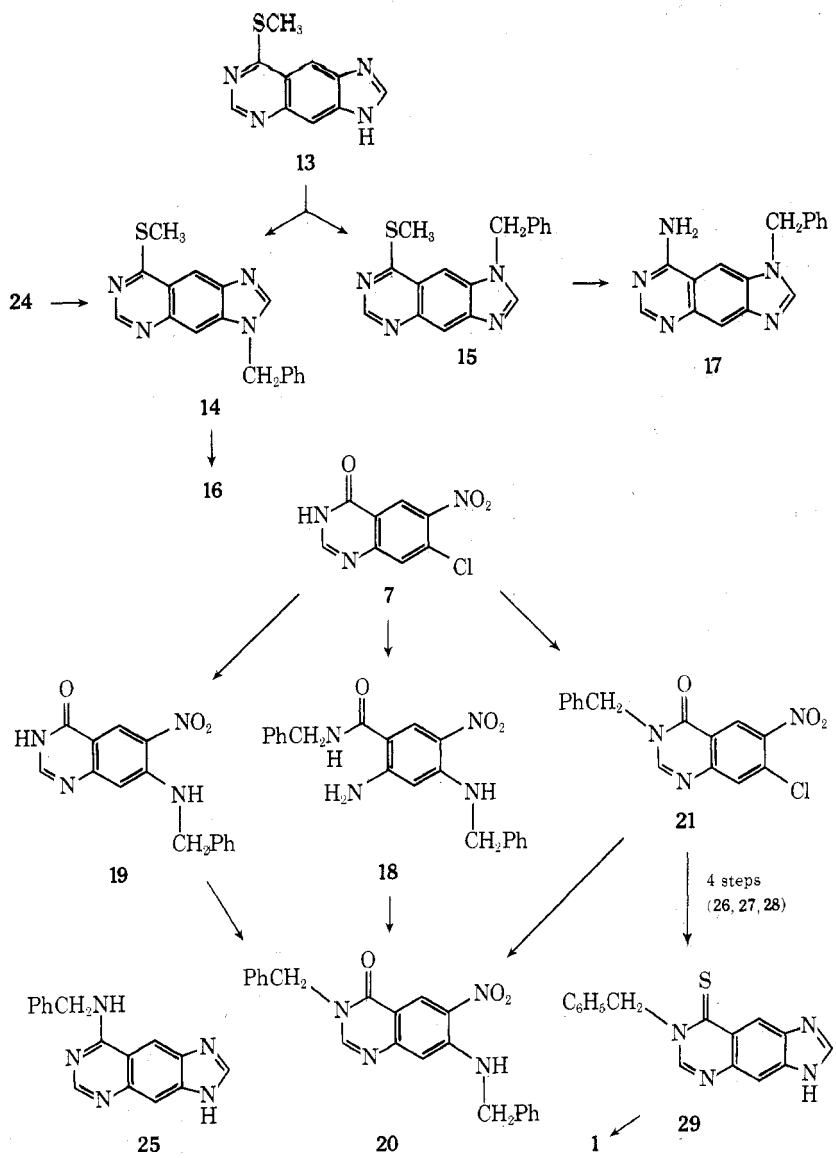


Figure 2. The uv spectra of *lin*-benzoadenine and its derivatives in 95% ethanol (——), 0.1 *N* HCl in 95% ethanol (· · · ·) (0.01 *N* HCl in 95% ethanol for **17**), and 0.1 *N* NaOH in 95% ethanol (- - - -).

19 was hydrogenated catalytically to the corresponding amino compound **22**. Cyclization in formic acid yielded 3-benzylimidazo[4,5-*g*]quinazolin-8-one (**23**), which was then

Scheme V



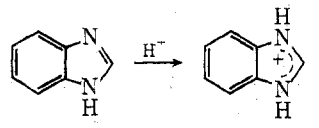
converted to the corresponding thio compound **24** with phosphorus pentasulfide and pyridine. Alkylation of the potassium salt of **24** completed the unambiguous route to compound **14**, identical in all its properties with one of the alkylation products of methylthioimidazoquinazoline **13**. Both compounds **14** and **24** were converted to 8-amino-3-benzylimidazo[4,5-*g*]quinazoline (**16**) upon heating in a sealed tube with alcoholic ammonia. This compound (**16**) was debenzylated with sodium in liquid ammonia to afford the unsubstituted compound **1** described above (Scheme V).

The preparation of other possible isomers of **16** and **17** was also investigated. Thus, 8-benzylaminoimidazo[4,5-*g*]quinazoline (**25**) was obtained from the reaction of the mercaptoquinazoline type **12** with benzylamine in ethanol. The preparation and isolation of isomers containing the benzyl substituent on either of the quinazoline nitrogens proved elusive, probably indicating the decreased stability of such compounds. Thus, when 3-benzyl-7-chloro-6-nitro-4-quinazolone (**21**) was treated with alcoholic ammonia, the corresponding nitroamine **26** was isolated, which was reduced to 3-benzyl-6,7-diamino-4-quinazolone (**27**), and this was condensed with formic acid to yield 7-benzylimidazo[4,5-*g*]quinazolin-8-one (**28**). Subsequent thiation afforded mercapto derivative **29**. Surprisingly, the reaction of **29** with alcoholic ammonia proceeded with the apparent loss of benzylamine to afford the unsubstituted *lin*-benzoadenine **1** directly.

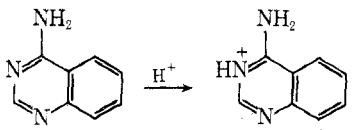
The preparation of the stable benzyl derivatives of **1** was important both in determining the mode of alkylation and in providing uv models which would be necessary for assigning the structures of nucleoside derivatives of **1**. In this latter respect, there was concern that the chromophore inherent in the benzyl substituents might either mask or perturb the uv absorption characteristic for the tricyclic ring systems of the substituted benzoadenines. In order to verify the usefulness of the benzyl-*lin*-benzoadenines as applicable uv models, a corresponding aliphatic derivative, 8-amino-3-cyclohexylimidazo[4,5-*g*]quinazoline (**30**), was also made by a route modeled after the syntheses described above, namely, from the chloronitro compound **7**, by displacement with cyclohexylamine (→**31**), reduction (→**32**), condensation (→**33**), thiation (→**34**), and finally treatment with alcoholic ammonia. A comparison of the uv spectra of the 3-cyclohexyl derivative **30** and the 3-benzyl derivative **16** shows that the absorption maxima due to the three highest wavelength transitions coincide exactly (Figure 2). This supports the usefulness of the two benzyl derivatives

16 and 17 as applicable uv models and indicates further that, for N-substituted *lin*-benzoadenines, the spectra will be more susceptible to the position of substitution than to the type of substitution (*e.g.*, alkyl, aryl, ribosyl) on the particular nitrogen.

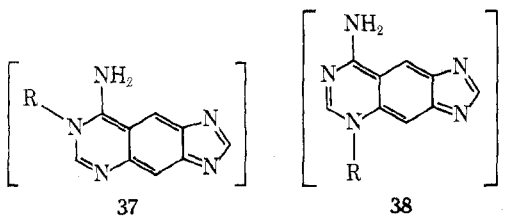
The uv spectra of the methylthio- and amino-substituted imidazo[4,5-*g*]quinazolines as presented in Figures 1 and 2 illuminate some interesting electronic features of these compounds. It is apparent that the low-energy transitions of the *lin*-benzoadenines (**1, 16, 17,** and **30**) show only negligible shifts in adsorption maxima in neutral or acidic solution. The unsubstituted compound **1** shows a bathochromic shift in the long wavelength band in basic solution due to deprotonation of the imidazole ring. In contrast, the three low-energy transitions of the methylthio derivatives **13–15,** which are similar in neutral and basic solution, collapse to a broad peak in acidic solution, with a hypsochromic shift of the lowest energy absorption maxima observed in neutral solution. It is interesting to note that the uv spectrum of benzimidazole (**35**) is essentially unchanged in neutral or basic solution. In acidic solution, however, a marked hypsochromic shift of the low-energy band is observed, which is attributable to protonation on the imidazole ring (**35a**).[9] In contrast, 4-aminoquinazoline (**36**) exhibits nearly identical spectra in acidic, basic, and neutral solution.[10] This has been interpreted to represent protonation of the quinazoline ring, preferably at the N-3 position (**36a**).[10b] The uv



35 **35a**



36 **36a**



37 **38**

evidence suggests that like 4-aminoquinazoline, the major site of first protonation of the *lin*-benzoadenines is on the pyrimidine ring. The methylthio derivatives, however, behave similarly to benzimidazole, with the major site of first protonation on the imidazole ring at positions N-1 and N-3.

The favored sites of protonation for the methylthio compound **13** coincide with the favored sites of alkylation (N-1 and N-3) in the presence of potassium carbonate. For *lin*-benzoadenine **1,** however, the favored sites of protonation and alkylation under these conditions do not necessarily coincide. The effect of alkylation at the preferred site of protonation (N-7 or N-5) would require the formulation of imino tautomers or partially quinonoid structures as shown in **37** and **38.** Such structures, in which the electronic system would be highly polarized, would be of relatively high energy, and their formation would require large activation energies. Alkylation at N-1, N-3, or N^8 would not disturb the aromatic system. By analogy to adenine, however, one would expect the N-1 and N-3 positions to be more reactive in the presence of alkali carbonate toward alkylating reageants than the N^8 position.[11] The convenient syntheses of *lin*-benzoadenine **1** by several converging routes, together with the means of establishing the N position of attachment of substituent groups, provide a reliable basis for making a series of linear benzoadenine compounds corresponding to the adenine-containing nucleosides, nucleotides, and, hopefully, polynucleotides and coenzymes.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting apparatus and are corrected. The nmr spectra were recorded on Varian Associates A-60 or A-56/60 spectrometers by Mr. Robert Thrift and his associates using tetramethylsilane (TMS) as an internal standard. The ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer.[12] Microanalyses were performed by Mr. Joseph Nemeth and his associates, who also weighed samples for the quantitative electronic absorption spectra, and by Midwest Microlab, Ltd., Indianapolis, Ind. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and Statos recorder by Mr. J. Carter Cook and associates. Infrared spectra were determined on a Perkin-Elmer 337 spectrophotometer. Thin-layer chromatograms were run on Eastman chromagram sheet 6060 (silica gel with fluorescent indicator).

7-Chloro-6-nitro-4-quinazolone (7) and 7-Chloro-8-nitro-4-quinazolone (8). 7-Chloro-4-quinazolone[6] (200 g, 1.11 mol) was added slowly to a cooled solution of concentrated sulfuric acid (400 ml) and fuming nitric acid (400 ml). The resulting solution was heated on a steam bath for 2 hr; then the clear solution was poured into 6 l. of ice water. The resulting pale yellow precipitate was filtered and washed with 4 l. of water. The material was dissolved in hot acetic acid (4.5 l.). Compound **7** crystallized on cooling as bright, yellow prisms (14.4 g, 58%): mp 300–303°; nmr [$(CD_3)_2SO$] δ 3.30 (br, 1, NH), 7.97 (s, 1), 8.28 (s, 1), 8.53 (s, 1); mass spectrum *m/e* (rel intensity) 225 (100) and 227 (36).

Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.59; H, 1.79; N, 18.63; Cl, 15.72. Found: C, 42.76; H, 1.79; N, 18.85; Cl, 15.68.

The mother liquors were concentrated to 1 l. Upon cooling, a 5:3 mixture (nmr) of **7:8** was recovered (45 g). The material was dissolved in 1 l. of boiling acetic acid. Upon partial cooling to *ca.* 40° colorless crystals of compound **8** were obtained (25 g, 10%): mp >320°; nmr [$(CD_3)_2SO$] δ 7.75 and 8.25 (AB quartet, 2, J = 9 Hz), 8.22 (s, 1); mass spectrum *m/e* (rel intensity) 225 (100) and 227 (36).

Anal. Calcd for $C_8H_4ClN_3O_3$: C, 42.59; H, 1.79; N, 18.63; Cl, 15.72. Found: C, 42.81; H, 1.82; N, 18.50; Cl, 15.72.

7-Amino-6-nitro-4-quinazolone (9). Two sealed tubes, each containing 7-chloro-6-nitro-4-quinazolone (**7,** 12.5 g, 0.056 mol) in ammonis–saturated butanol (80 ml), were heated for 24 hr at 175°. Upon cooling, compound **9** crystallized as yellow-orange needles (total 22.4 g, 98%). Recrystallization from ethanol afforded an analytically pure sample: mp >320°; nmr [$(CD_3)_2SO$] δ 7.20 (s, 1), 7.78 (s, 1), 8.67 (s, 1); mass spectrum *m/e* 206 (M^+).

Anal. Calcd for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.46; H, 2.97; N, 27.08.

6,7-Diamino-4-quinazolone (10). A mixture of 10 g (0.05 mol) of 7-amino-6-nitro-4-quinazolone (**9**) and 1 g of 10% palladium on carbon was stirred in ethanol (150 ml) under nitrogen. A solution of 10 ml of 99% hydrazine hydrate in ethanol (10 ml) was added dropwise over 1 hr longer and then heated ar reflux for another hour. Enough dimethylformamide was added (*ca.* 100 ml) to dissolve the suspended product. The catalyst was removed by filtration and the solvent was removed *in vacuo.* Upon trituration of the residue with water, 7.8 g (91%) of tan-colored product was obtained. An analytical sample was obtained by recrystallization from ethanol: mp >320°; nmr [$(CD_3)_2SO$] δ 6.75 (s, 1), 7.19 (s, 1), 7.72 (s, 1); mass spectrum *m/e* 176 (M^+).

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.50; H, 4.40; N, 31.60.

Imidazo[4,5-*g*]quinazolin-8-one (11). From 7-Amino-6-nitro-4-quinazolone (9). A mixture of 5 g (25 mmol) of **9** in formic acid (98%, 200 ml) was hydrogenated at 3 atm over 0.5 g of 10% palladium on carbon for 1–2 hr. The catalyst was removed by filtration and the solution was heated at reflux under nitrogen for 2 hr. Removal of the solvent *in vacuo* and reprecipitation of the residue from water with dilute ammonia afforded 2.5 g (54%) of colorless crystalline **11.** An analytical sample could be obtained by recrystallization several times from water: mp >320°; nmr (TFA) δ 8.82 (s, 1), 9.20 (s, 1), 9.46 (s, 1), 9.66 (s, 1); mass spectrum *m/e* 186 (M^+).

Anal. Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 58.13; H, 3.39; N, 30.04.

B. From 6,7-Diamino-4-quinazolone (10). A solution of **10** (33 g, 0.19 mol) in formic acid (500 ml) was heated at reflux under nitrogen for 2 hr. Removal of the solvent *in vacuo* and reprecipitation of the residue from water with dilute ammonia afforded 33 g (94%) of **11** as colorless crystals identical with material prepared in part A (ir and tlc).

8-Mercaptoimidazo[4,5-*g*]quinazoline (12). A mixture of compound **11** (6.5 g, 35 mmol), purified phosphorus pentasulfide (12 g), and 70 ml of dry pyridine was heated at reflux for 24 hr. The solvent was reduced in volume to *ca.* 20 ml, and the solution was poured into 200 ml of boiling water. On cooling, 5.6 g (79%) of **12** was deposited as yellow crystals. An analytical sample was obtained by recrystallization several times from glacial acetic acid: mp >320°; nmr (TFA) δ 8.54 (s, 1), 9.04 (s, 1), 9.34 (s, 1), 9.49 (s, 1); mass spectrum *m/e* 202 (M^+).

Anal. Calcd for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70; S, 15.85. Found: C, 53.28; H, 3.16; N, 26.26; S, 15.85.

8-Aminoimidazo[4,5-*g*]quinazoline (1). A. From 8-Mercaptoimidazo[4,5-*g*]quinazoline (12). A mixture of 7 g (35 mmol) of mercapto compound **12** and 80 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 48 hr. The crystals were filtered and washed with ethanol to yield 5.4 g (85%) of **1**. The product was dissolved in 150 ml of water by the addition of formic acid and treated with charcoal, and the pH was adjusted to 8 with dilute ammonia. The yield of beige crystals so obtained was 4.5 g (70%). An analytical sample was obtained as the hydrochloride salt (crystallization from water–ethanol–ether): mp >320°; nmr (TFA) δ 8.71 (s, 1), 8.96 (s, 1), 9.26 (s, 1) 9.65 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 237 nm (ϵ 26,500), 242 (26,700), 258 (14,800), 261 (sh), 298 (sh), 318 (6800), 332 (9200), 348 (7000); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 224 nm (ϵ 24,100), 234 (22,800), 258 (12,700), 265 (sh), 289 (sh), 302 (sh), 322 (sh), 333 (14,400), 349 (13,700); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 248 nm (ϵ 36,900), 262 (32,600), 270 (34,100), 310 (sh), 322 (7900), 350 (5900), 365 (sh); mass spectrum *m/e* 185 (M^+ for $C_9H_7N_5$).

Anal. Calcd for $C_9H_8ClN_5$: C, 48.77; H, 3.64; Cl, 15.99; N, 31.60. Found: C, 48.99; H, 3.46; Cl, 16.20; N, 31.79.

B. From 8-Methylthioimidazo[4,5-*g*]quinazoline (13). A mixture of 8.2 g (40 mmol) of methylmercapto compound **13** and 80 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 24 hr. The yield of crude **1** was 5.3 g (75%), identical with the above material (ir and tlc).

C. From 7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of **29** (0.2 g, 0.7 mmol) and 4 ml of ammonia–saturated butanol was heated in a sealed tube at 200° for 24 hr. Upon cooling, **1** was deposited as colorless needles (0.127 g, 9%), identical with the other preparations (ir and tlc).

D. From 8-Amino-3-benzylimidazo[4,5-*g*]quinazoline (16). To a stirred suspension of **16** (0.95 g, 4 mmol) in liquid ammonia (30 ml) was added slowly 1 g of sodium (cut in small pieces). The slurry was stirred under reflux for 45 min. At the end of this period, ammonium chloride was added slowly until the deep blue color of the solution disappeared. The reaction mixture was allowed to stand at 25° until the ammonia evaporated. The residue was suspended in water (100 ml) and ether (50 ml) and then filtered to afford an amorphous solid. Recrystallization from acetic acid–ethanol yielded light tan crystals of **1** (0.55 g, 86%), identical with the other preparations (ir and tlc).

8-Methylthioimidazo[4,5-*g*]quinazoline (13). Methyl iodide (0.17 g, 1.2 mmol) was added to a stirred solution of mercapto compound **12** and potassium hydroxide (0.075 g, 1.0 mmol) in methanol (10 ml) and water (10 ml). After stirring at 25° for 15 min, 1 drop of acetic acid was added and the product crystallized slowly. Recrystallization from water–ethanol afforded **13** as pale yellow needles (0.165 g, 79%): mp 311–314°; nmr (TFA) δ 3.10 (s, 3, SCH_3), 8.83 (s, 1), 9.13 (s, 1), 9.22 (s, 1), 9.70 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 240 nm (ϵ 44,500), 284 (7500), 327 (11,600), 341 (10,500), 358 (7600); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 244 nm (ϵ 21,600), 290 (sh), 299 (5200), 344 (13,400), 355 (sh); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 255 nm (ϵ 40,300), 279 (21,200), 323 (sh), 337 (15,900), 364 (sh); mass spectrum *m/e* 216 (M^+).

Anal. Calcd for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91; S, 14.83. Found: C, 55.29; H, 3.65; N, 25.90; S, 14.60.

Alkylation of 8-Methylthioimidazo[4,5-*g*]quinazoline (13). A mixture of **13** (0.4 g, 2 mmol), anhydrous potassium carbonate (0.28 g, 2 mmol), and benzyl bromide (0.34 g, 2 mmol) was stirred at 25° for 10 hr in dry dimethylformamide (20 ml). The reaction mixture was poured into water (150 ml) and upon standing produced a precipitate. This material was filtered, dried, and applied (in acetic acid) to a silica gel column (80 g) packed in chloroform. Elution with chloroform (500 ml) yielded a solution containing mainly 3-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (14) (tlc). The solution was evaporated *in vacuo* and the residue was recrystallized from aqueous ethanol to afford **14** (0.235 g, 42%): mp 223–225° (identical with authentic material checked by ir and tlc). Further elution with chloroform (500 ml), then 2% ethanol in chloroform (300 ml), provided a solution containing 1-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**15**). Evaporation and recrystallization from aqueous ethanol provided this isomer as colorless needles (0.225 g, 41%): mp 211–212°; nmr (TFA) δ 3.05 (s, 3, SCH_3), 5.90 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.00 (s, 1), 8.83 (s, 1), 9.17 (s, 1), 9.48 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 243 nm (ϵ 40,900), 248 (sh), 284 (7500), 323 (9600), 348 (10,200), 366 (8300); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 248 nm (ϵ 22,200), 298 (5200), 348 (14,100); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 243 nm (ϵ 43,800), 248 (sh), 284 (7400), 327 (9900), 348 (10,100), 366 (7700); mass spectrum *m/e* 306 (M^+).

Anal. Calcd for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29; S, 10.46. Found: C, 66.80; H, 4.82; H, 18.37; S, 10.53.

3-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (14). Methyl iodide (0.17 g, 1.2 mmol) was added to a stirred solution of mercapto compound **24** (0.3 g, 1.0 mmol) and potassium hydroxide (0.1 g, 1.5 mmol) in methanol (10 ml) and water (10 ml). After the solution was stirred at 25° for 13 min, the product precipitated. Crystallization from ethanol provided **14** as colorless needles (0.27 g, 86%): mp 224–225°; nmr (TFA) δ 3.08 (s, 3, SCH_3), 5.87 (s, 2, CH_2), 7.50 (s, 5, C_6H_5), 8.53 (s, 1), 9.12 (s, 1), 9.22 (s, 1), 9.50 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 243 nm (ϵ 56,400), 284 (8800), 329 (13,600), 342 (12,700), 359 (8900); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 252 nm (ϵ 29,800), 289 (6200), 298 (6200), 352 (15,300); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 243 nm (ϵ 59,600), 284 (9700), 329 (13,000), 338 (sh), 359 (8200); mass spectrum *m/e* 306 (M^+).

Anal. Calcd for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29; S, 10.46. Found: C, 66.75; H, 4.53; N, 18.07; S. 10.41.

8-Amino-3-benzylimidazo[4,5-*g*]quinazoline (16). A. From 3-Benzyl-8-mercaptoimidazo[4,5-*g*]quinazoline (24). A sealed tube containing the mercapto compound **24** (1.0 g, 3 mmol) and 20 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, light tan needles of **16** were obtained (0.95 g, 90%). Recrystallization from dimethylformamide afforded analytically pure material (0.70 g, 75%): mp >320°; nmr (TFA) δ 5.83 (s, 2, CH_2), 7.50 (s, 5, C_6H_5), 8.43 (s, 1), 8.95 (s, 1), 9.22 (s, 1), 9.43 (s, 1); $\lambda_{max}^{95\%tOH}$ 231 nm (ϵ 34,300), 242 (sh), 260 (13,000), 266 (13,000), 306 (sh), 319 (6700), 333 (8800), 349 (6700); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 228 nm (ϵ 23,200), 236 (24,100), 263 (12,200), 271 (10,000), 321 (8000), 335 (9500), 351 (8500); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 242 nm (ϵ 26,200), 260 (13,500), 265 (13,500), 306 (sh), 318 (6900), 338 (9000), 349 (7000); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.84; H, 4.71; N, 25.63.

B. From 3-Benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (14). A sealed tube containing compound **14** (0.12 g, 0.4 mmol) and 5 ml of ammonia–saturated ethanol was heated at 200° for 24 hr. Upon cooling, light tan needles of **16** were obtained (0.08 g, 75%), identical with the material described above (ir and tlc).

8-Amino-1-benzylimidazo[4,5-*g*]quinazoline (17). A sealed tube containing 100 mg (0.33 mmol) of 1-benzyl-8-methylthioimidazo[4,5-*g*]quinazoline (**15**) and 15 ml of ammonia–saturated butanol was heated at 200° for 48 hr. Upon cooling, 25 mg of colorless crystals was deposited. The filtrate was evaporated to dryness *in vacuo*. The resulting residue was crystallized from ethanol to afford colorless crystals of **17** (45 mg, combined yield 78%): mp 295–296°; nmr (TFA) δ 5.88 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.77 (s, 1), 9.15 (s, 1), 9.23 (s, 1), 9.28 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 223 nm (ϵ 26,800), 242 (33,600), 264 (16,000), 295 (5600), 306 (4400), 327 (6200), 343 (9300), 359 (8100); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 237 nm (ϵ 38,300), 264 (19,000), 294 (7700), 306 (6900), 328 (7500), 343 (10,300), 358 (8500); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 236 nm (ϵ 24,200), 267 (12,700), 275 (10,400), 299 (6500), 317 (7690), 328 (sh), 336 (10,100), 352 (9900), 363 (sh); $\lambda_{max}^{0.01\ N\ HCl}$ (95% EtOH) 237 nm (ϵ 27,000), 267 (14,900), 275 (16,600), 313 (10,300), 326.5 (10,000), 343 (9800), 359 (9160); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.18; H, 4.78; N, 24.98.

***N*-Benzyl-2-amino-4-benzylamino-5-nitrobenzamide (18).** A solution of 7-chloro-6-nitro-4-quinazolone (1.0 g, 4 mmol) in benzylamine (10 ml) containing 2 drops of concentrated hydrochloric acid was heated at 130° under nitrogen for 24 hr. Upon cooling to room temperature, the product crystallized and was filtered and washed with ethanol (1.0 g, 59%). Recrystallization from

dimethylformamide–ethanol afforded **18** as yellow needles (0.9 g, 53%): mp 209–210°; nmr (TFA) δ 4.17 (s, 4, CH_2), 7.04 (s, 1), 7.33 (s, 10, C_6H_5), 8.87 (s, 1); mass spectrum *m/e* 376 (M^+).

Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.35; N, 14.88. Found: C, 67.09; H, 5.44; N, 14.94.

7-Benzylamino-6-nitro-4-quinazolone (19). A stirred suspension of **7** (10.0 g, 33 mmol) in benzylamine (10 g) and butanol (300 ml) was heated at reflux under nitrogen for 24 hr. Upon cooling, compound **19** was deposited as yellow needles (11.0 g, 81%): mp 172–173°; nmr [$(CD_3)_2SO$] δ 4.68 (d, 2, J = 6 Hz, CH_2), 6.76 (s, 1), 7.35–7.45 (m, 5, C_6H_5), 8.02 (s, 1), 8.76 (s, 1), 8.67 (t, 1, J = 6 Hz, NH); mass spectrum *m/e* 296 (M^+).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 61.07; H, 4.15; N, 18.94.

3-Benzyl-7-chloro-6-nitro-4-quinazolone (21). A solution of 7-chloro-6-nitro-4-quinazolone (10 g, 44 mmol), benzyl bromide (7.4 g, 44 mmol), and potassium hydroxide [2.8 g (87%), 44 mmol] in methanol (250 ml) was heated at reflux for 1 hr. Upon cooling, colorless crystals of **21** were collected in two crops (12.4 g, 89%): mp 175–177°. One recrystallization from ethanol afforded analytically pure material: mp 175–177°; nmr (TFA) δ 5.61 (s, 2, CH_2), 7.45 (s, 5, C_6H_5), 8.12 (s, 1), 8.88 (s, 1), 9.28 (s, 1); mass spectrum *m/e* (rel intensity) 315 (100) and 317 (37).

Anal. Calcd for $C_{15}H_{10}CLN_3O_3$: C, 57.07; H, 3.19; Cl, 11.23; N, 13.31. Found: C, 56.79; H, 3.21; Cl, 11.44; N, 13.31.

3-Benzyl-7-benzylamino-6-nitro-4-quinazolone (20). A. From 7-Benzylamino-6-nitro-4-quinazolone (19). Benzyl bromide (0.65 g, 3.8 mmol) was added to a stirred solution of compound **19** (1.1 g, 3.3 mmol) and potassium hydroxide [0.25 g (87%), 3.8 mmol] in methanol (25 ml). The solution was heated under reflux for 1 hr and then cooled to yield **20** as yellow-orange needles (1.2 g, 95%): mp 187–188°; nmr (TFA) δ 4.67 (s, 2, CH_2), 5.37 (s, 2, CH_2), 7.27 (s, 1), 7.33 (s, 5, C_6H_5), 7.42 (s, 5, C_6H_5), 9.18 (s, 1), 9.25 (s, 1); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.69; N, 14.50. Found: C, 68.60; H, 4.79; N, 14.61.

B. From *N*-Benzyl-2-amino-4-benzylamino-5-nitrobenzamide (18). A solution of **18** (0.2 g, 0.5 mmol) in 98% formic acid (15 ml) was heated under reflux for 2 hr. The yellow-orange solution was concentrated *in vacuo* to a small volume and treated with dilute ammonia, affording 0.19 g (93%) of **20**: mp 185–188°, identical with the above material (ir and tlc).

C. From 3-Benzyl-7-chloro-6-nitro-4-quinazolone (21). A solution of **21** (0.5 g, 2 mmol) and benzylamine (0.5 g) in butanol (5 ml) was heated at reflux 18 hr under nitrogen. Upon standing at room temperature, yellow-orange needles of **20** were deposited (0.55 g, 87%): mp 178–187°. Recrystallization from ethanol afforded material identical with the above preparations (ir and tlc): mp 186–188°.

6-Amino-7-benzylamino-4-quinazolone (22). A solution of compound **19** (10 g, 42 mmol) in ethanol (50 ml) and dimethylformamide (150 ml) was hydrogenated at 3 atm over 0.2 g of 5% palladium on carbon for 2 hr at 25°. The solution was filtered and evaporated *in vacuo* to a small volume. Addition of water afforded product **22** as a pink solid (8.5 g, 95%). Two recrystallizations from hot butanol using decolorizing charcoal gave colorless needles; mp 293-295°; nmr (TFA) δ 5.83 (s, 2, CH_2), 7.13 (s, 1), 7.37 (s, 5, C_6H_5), 8.50 (s, 1), 9.15 (s, 1); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{15}H_{14}N_4O$: 67.65; H, 5.30; N, 21.03. Found: C, 67.43; H, 5.30; N, 20.90.

3-Benzylimidazo[4,5-*g*]quinazolin-8-one (23). A solution of compound **22** (10 g, 0.05 mol) in 98% formic acid (200 ml) was heated under reflux for 90 min. The solution was heated with decolorizing charcoal. Water was added (100 ml) and the solution was evaporated *in vacuo* (*ca.* 50 ml) until the onset of crystallization. Pale yellow crystals were recovered. A second crop was obtained from the mother liquors by neutralization with ammonia (total yield 9.6 g, 93%). One recrystallization from aqueous dimethylformamide gave pale yellow prisms (8.9 g, 86%): mp >320°; nmr (TFA) δ 5.88 (s, 2, CH_2), 7.57 (s, 5, C_6H_5), 8.55 (s, 1), 9.18 (s, 1), 9.48 (s, 1); mass spectrum *m/e* 276 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; H, 20.28. Found: C, 69.82; H, 4.42; N, 20.28.

3-Benzyl-8-mercaptoimidazo[4,5-*g*]quinazoline (24). A stirred slurry of compound **23** (5.0 g, 20 mmol) and purified phosphorus pentasulfide (8.0 g) in dry pyridine (150 ml) was heated at reflux for 18 hr under nitrogen. The solution was poured into boiling water (800 ml). Upon cooling, bronze-colored needles of **24** were obtained (4.1 g, 78%) which were recrystallized from aqueous dimethylformamide to afford analytically pure material (2.8 g, 53%): mp >320°; nmr (TFA) δ 5.82 (s, 2, CH_2), 7.52 (s, 5, C_6H_5), 8.28 (s, 1), 9.02 (s, 1), 9.22 (s, 1), 9.33 (s, 1); mass spectrum *m/e* 292 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16; S, 10.97. Found: C, 65.77; H, 4.33; N, 19.24; S, 11.02.

8-Benzylaminoimidazo[4,5-*g*]quinazoline (25). A sealed tube containing the mercapto compound **12** (0.5 g, 2 mmol), benzylamine (0.5 g), and 15 ml of ethanol was heated at 200°. The solution was filtered and evaporated to dryness. The resulting solid was suspended in water and filtered to yield a pale yellow solid (620 mg, 92%). Recrystallization from ethanol using decolorizing charcoal afforded **25** as colorless needles: mp >320°; nmr [$(CD_3)_2SO$] δ 4.83 (s, 2, CH_2), 7.08–7.50 (m, 5, C_6H_5), 7.86 (s, 1), 8.37 (s, 1), 8.48 (s, 1), 8.65 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 227 nm (ε 38,200), 236 (sh), 264 (13,000), 272 (12,200), 322 (sh), 334 (14,000), 351 (11,300); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 217 nm (ε 34,500), 237 (sh), 265 (7800), 324 (sh), 338 (19,800), 354 (20,900); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 244 nm (ε 42,200), 248 (sh), 270 (sh), 277 (31,400), 324 (12,500), 349 (9500), 365 (7900); mass spectrum *m/e* 275 (M^+).

Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.66; H, 4.66; N, 25.33.

7-Amino-3-benzyl-6-nitro-4-quinazolone (26). A sealed tube containing **21** (9.0 g, 30 mmol) and 80 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, yellow-orange needles of **26** were collected (6.2 g). The mother liquors were concentrated to give a second crop (0.8 g, combined yield 83%): mp 225–227°. Recrystallization from ethanol afforded an analytically pure sample: mp 228–229°; nmr (TFA) δ 5.40 (s, 2, CH_2), 7.30 (s, 1), 7.43 (s, 5, C_6H_5), 9.03 (s, 1), 9.23 (s, 1); mass spectrum *m/e* 296 (M^+).

Anal. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.65; H, 4.14; N, 18.95.

3-Benzyl-6,7-diamino-4-quinazolone (27). A solution of **26** (2.0 g, 7 mmol) in ethanol (100 ml) was hydrogenated at 3 atm over 0.05 g of 5% palladium on carbon during 2 hr at 25°. The solution was filtered and concentrated to *ca.* 30 ml. Water was added and the solution was stored at 4° overnight. Light tan needles of **27** were recovered (1.3 g, 72%): mp 185–193°. The product was dissolved in ethanol, treated with decolorizing charcoal, and diluted with water as above, affording colorless needles: mp 192–193° (slightly hygroscopic); nmr (TFA) δ 5.55 (s, 2, CH_2), 7.27 (s, 1), 7.42 (s, 5, C_6H_5), 8.52 (s, 1), 8.98 (s, 1); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.79; H, 5.35; N, 21.04.

7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of 6.6 g (24 mmol) of **28**, 24 g of purified phosphorus pentasulfide, and 60 ml of dry pyridine was heated at reflux for 24 hr. The solu- and then diluted with water to a volume of 50 ml. The solution was evaporated to dryness *in vacuo* and the resulting solid was dissolved in hot water. The solution was adjusted to pH 7 with dilute ammonia. Upon cooling, **28** was deposited as colorless crystals (0.425 g, 75%): mp 246–248°. Recrystallization from ethanol afforded an analytically pure sample: mp 248–249°; nmr (TFA) δ 5.55 (s, 2, CH_2), 7.53 (s, 5, C_6H_5), 8.72 (s, 1), 9.20 (s, 1), 9.28 (s, 1), 9.63 (s, 1); mass spectrum *m/e* 276 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.76; H, 4.33; N, 20.61.

7-Benzylimidazo[4,5-*g*]quinazoline-8-thione (29). A mixture of 6.6 g (24 mmol) of **28**, 24 g of purified phosphorus pentasulfide, and 60 ml of dry pyridine was heated at reflux for 24 hr. The solution was poured into boiling water (200 ml), and the yellow precipitate of **29** was collected (5.5 g, 79%). Recrystallization from aqueous dimethylformamide gave an analytical sample: mp 290–291°; nmr [$(CD_3)_2SO$] δ 5.98 (s, 2, CH_2), 7.34 (s, 5, C_6H_5), 7.98 (s, 1), 8.67 (s, 1) 8.78 (s, 1), 9.30 (s, 1); mass spectrum *m/e* 292 (M^+).

Anal. Calcd for $C_{16}H_{12}N_4S$: C, 65.75; H, 4.11; N, 19.17; S, 10.97. Found: C, 65.44; H, 4.25; N, 19.15; S, 11.24.

7-Cyclohexylamino-6-nitro-4-quinazolone (31). A stirred suspension of 7-chloro-6-nitro-4-quinazolone (**7** 5.0 g, 23 mmol) in cyclohexylamine (5.0 g) and butanol (150 ml) was heated at reflux under nitrogen for 16 hr. The resulting solution was poured slowly into 1.5 l. of boiling water. Upon cooling, yellow-orange needles of **31** separated (6.1 g, 90%): mp 263–265°; nmr (TFA) δ 1.4–2.3 (br, 11, C_6H_{11}), 7.27 (s, 1), 9.25 (s, 1), 9.28 (s, 1); mass spectrum *m/e* 288 (M^+).

Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.19; H, 5.75; N, 19.29.

6-Amino-7-cyclohexylamino-4-quinazolone (32). A solution of **31** (2.0 g, 7 mmol) in ethanol (35 ml) and dimethylformamide (35 ml) was hydrogenated at 3 atm over 0.05 g of 5% palladium on

carbon during 1 hr at 25°. The solution was filtered and evaporated to a small volume. Addition of water afforded 1.7 g of a colorless solid (95%). Recrystallization from ethanol yielded **32** as colorless needles (1.5 g, 84%). One further recrystallization afforded an analytically pure sample: mp >320°; nmr (TFA) δ 1.3–2.3 (br, 11, C_6H_{11}), 7.18 (s, 1), 8.42 (s, 1), 9.20 (s, 1); mass spectrum *m/e* 258 (M^+).

Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.92; H, 6.86; N, 21.51.

3-Cyclohexylimidazo[4,5-*g*]quinazolin-8-one (33). A solution of **32** (0.85 g, 3.0 mmol) in 98% formic acid (50 ml) was heated at reflux for 1 hr. The reaction mixture was treated with decolorizing charcoal, diluted with water (50 ml), and concentrated *in vacuo* to a small volume. Dilute ammonia was added to afford **33** as a colorless powder (0.75 g, 85%). Two recrystallizations from ethanol yielded colorless prisms: mp 268–270°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 7.90 (s, 1), 8.01 (s, 1), 8.40 (s, 1), 8.55 (s, 1); mass spectrum *m/e* 268 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.28. Found: C, 67.19; H, 5.95; N, 20.57.

3-Cyclohexyl-8-mercaptoimidazo[4,5-*g*]quinazoline (34). A stirred slurry of **33** (0.75 g, 3 mmol) and purified phosphorus pentasulfide (1.5 g) in dry pyridine (50 ml) was heated 12 hr under reflux. The resulting dark solution was poured into boiling water (600 ml). Upon cooling, **34** separated as a pale yellow precipitate (0.55 g, 69%). Two recrystallizations from acetic acid–ethanol yielded yellow prisms: mp >320°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 8.08 (s, 1), 8.13 (s, 1), 8.80 (s, 1), 8.90 (s, 1); mass spectrum *m/e* 284 (M^+).

Anal. Calcd for $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.27. Found: C, 63.09; H, 5.76; N, 19.57; S, 11.45.

8-Amino-3-cyclohexylimidazo[4,5-*g*]quinazoline (30). A sealed tube containing **34** (0.1 g, 0.4 mmol) and 3 ml of ammonia–saturated ethanol was heated at 150° for 24 hr. Upon cooling, colorless needles of **30** were deposited (0.8 g, 85%). Recrystallization from hot dimethylformamide afforded analytically pure **30**: mp >320°; nmr [$(CD_3)_2SO$] δ 1.2–2.2 (br, 11, C_6H_{11}), 8.62 (s, 1), 9.04 (s, 1), 9.44 (s, 1), 9.56 (s, 1); $\lambda_{max}^{95\%\ EtOH}$ 231 nm (ε 46,700), 242 (sh), 260 (sh), 266 (17,100), 307 (sh), 319 (9100), 334 (11,700), 351 (9100); $\lambda_{max}^{0.1\ N\ HCl}$ (95% EtOH) 225 nm (ε 32,500), 233 (sh), 260 (13,600), 266 (sh), 307 (sh), 322 (10,200), 336 (13,400), 352 (12,600); $\lambda_{max}^{0.1\ N\ NaOH}$ (95% EtOH) 242 nm (sh), 260 (ε 18,000), 266 (sh), 307 (sh), 319 (9500), 334 (12,000), 351 (9500); mass spectrum *m/e* 267 (M^+).

Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.39; H, 6.41; N, 26.20. Found: C, 67.30; H, 6.45; N, 25.96.

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Registry No.—**1**, 53449-12-0; 1 HCl, 53449-13-1; **6**, 31374-18-2; **7**, 53449-14-2; **8**, 53449-15-3; **9**, 53449-16-4; **10**, 53449-17-5; **11**, 53449-18-6; **12**, 53449-19-7; **13**, 53449-20-0; **14**, 53449-21-1; **15**, 53449-22-2; **16**, 53449-23-3; **17**, 53449-24-4; **18**, 53449-25-5; **19**, 53449-26-6; **20**, 53449-27-7; **21**, 53449-28-8; **22**, 53449-29-9; **23**, 53449-30-2; **24**, 53449-31-3; **25**, 53449-32-4; **26**, 53449-33-5; **27**, 53449-34-6; **28**, 53449-35-7; **29**, 53449-36-8; **30**, 53449-37-9; **31**, 53449-38-0; **32**, 53449-39-1; **33**, 53449-40-4; **34**, 53449-41-5; benzyl bromide, 100-39-0; benzylamine, 100-46-9; cyclohexylamine, 108-91-8.

References and Notes

(1) (a) For example, see R. K. Robins, *J. Med. Chem.*, **7**, 186 (1964); (b) R. K. Robins, *Heterocycl. Compounds*, **8**, 162 (1967); (c) J. A. Montgomery, T. P. Johnson, and Y. F. Sheely in "Medicinal Chemistry," Part 1, 3rd ed, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970; (d) D. Cole, University of Illinois Seminar Abstracts, Dec 14, 1972.
(2) The prefix *lin* refers to the linear disposition of the three rings in compound **1**; *prox* for proximal and *dist* for distal refer to the relationship of the amino group in compounds **2** and **3**, respectively, with respect to the imidazole ring. The numbering of the three ring systems is as shown.
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The Angular Benzoadenines. 9-Aminoimidazo[4,5-*f*]quinazoline and 6-Aminoimidazo[4,5-*h*]quinazoline

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The synthesis of 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), angular benzologs of adenine which are given the descriptive names *prox*-benzoadenine and *dist*-benzoadenine, respectively, is reported. The proximal isomer of benzoadenine **2** is synthesized in several steps from 6-acetamido-4-quinazolone (**14**). The distal isomer of benzoadenine **3** is prepared *via* a related route from 7-chloro-8-nitro-4-quinazolone (**4**). The uv spectra of the *lin*-, *prox*-, and *dist*-benzoadenines are discussed in relation to the differing spatial arrangements of the three isomers.

We have undertaken the synthesis of a family of structural analogs of adenine in which a benzene ring has been "inserted" between the imidazole and pyrimidine moieties to form a "stretched-out" purine model. In the preceding paper,[1] we discussed the synthesis and chemical properties of the linearly extended analog, 8-aminoimidazo[4,5-*g*]quinazoline (**1**) for which we proposed the name *lin*-benzoadenine. In this paper we describe the synthesis of the two angular isomers of *lin*-benzoadenine, 9-aminoimidazo[4,5-*f*]quinazoline (**2**) and 6-aminoimidazo[4,5-*h*]quinazoline (**3**), for which we propose the descriptive names, *prox*-benzoadenine (**2**) and *dist*-benzoadenine, respectively.[2]

The similarity of the three isomeric benzoadenines (**1–3**) lies in the fact that they contain binding sites similar to the 1,N^6 binding sites found in adenine and related nucleosides and nucleotides. The differences reside (a) in the spatial re-