Quinazolines. VII. Synthesis of 1,3-Diamino-5,6-dihydrobenzo[*f*]quinazolines (1a,b)

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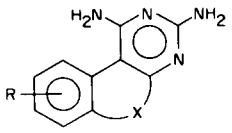
Eighteen new 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (**6**, R = alkyl, Cl, MeO) were synthesized *via* the condensation of appropriate 2-tetralones with cyanoguanidine under fusion conditions. Methods were developed for the preparation of a number of heretofore undescribed 2-tetralones as precursors. The final products can be viewed as conformationally rigid analogs of pyrimethamine (**2**), and are of interest as inhibitors of dihydrofolate reductase and as potential antimalarial and antitumor agents.

Conformationally rigid condensed 2,4-diaminopyrimidine ring systems of general structure **1** may be viewed as analogs of pyrimethamine (**2**) and other small-molecule inhibitors of dihydrofolate reductase (2), and are therefore of potential interest as chemotherapeutic agents for the treatment of malarial infections and experimental animal tumors (3).



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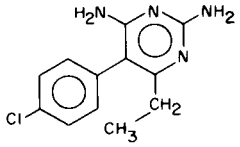
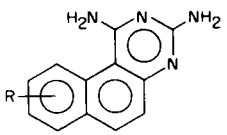


2

Several tricyclic systems of the type expressed by structure **1** have been studied in this laboratory, the earliest examples being 1,3-diaminobenzo[*f*]quinazolines (**3**) (4,5). More recent accounts have dealt with 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines (**4**) (6), 1,3-diamino-5*H*-[1]benzopyrano(and thiopyrano)[3,4-*d*]pyrimidine (**5**, Y = O, S) (7), and 2,4-diamino-10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidines (**5**, Y = CH_2CH_2) (7a). In this paper, we should like to present a detailed report concerning still another group of related compounds, the 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (**6**).



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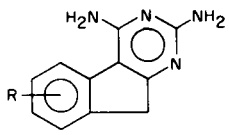

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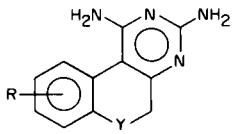
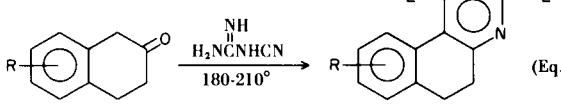


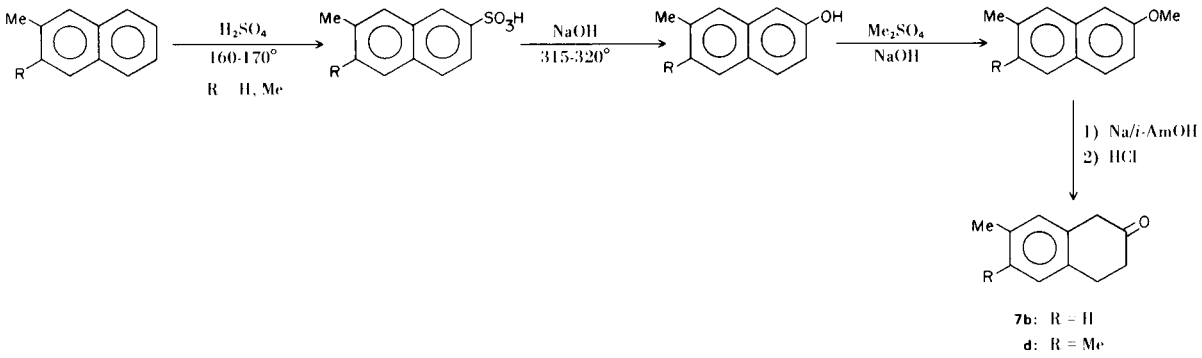
5 (Y = O, S, CH_2CH_2)
6 (Y = CH_2)

The parent member of the 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline series (**6**, R = H) was first described in 1962 as the product of the fusion reaction between 2-tetralone and cyanoguanidine (Equation 1) (8), and its angular rather than linear structure was later established conclusively through an alternate synthesis from guanidine and 1-cyano-3,4-dihydro-2-methoxynaphthalene (9,10). The intermediate cyano enol ether was prepared from 1-(2-cyanoethyl)-2-cyanomethylbenzene *via* Thorpe-Ziegler cyclization, acid hydrolysis, and *O*-alkylation with diazomethane, a strategy employed concurrently to convert 1,2-bis(cyanomethyl)benzenes into 2,4-diamino-9*H*-indeno-[2,1-*d*]pyrimidines (6). In the work described here, a series of alkyl-, chloro-, and methoxy-substituted 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (**6a-6r**) was synthesized *via* the cyanoguanidine fusion method, which was judged to be preparatively more attractive than the guanidine/cyano enol ether approach. The physical constants of a number of heretofore unreported 2-tetralones and naphthalene precursors synthesized in connection with this program are presented in Tables I and II, respectively; those of the final products, **6a-6r**, are shown in Tables III and IV.



(Eq. 1)

FLOW SHEET I



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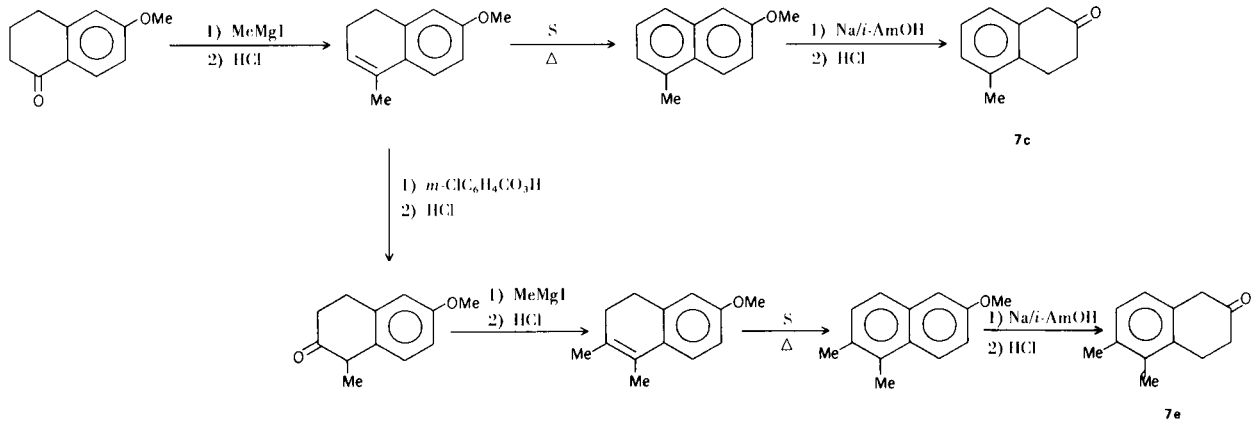

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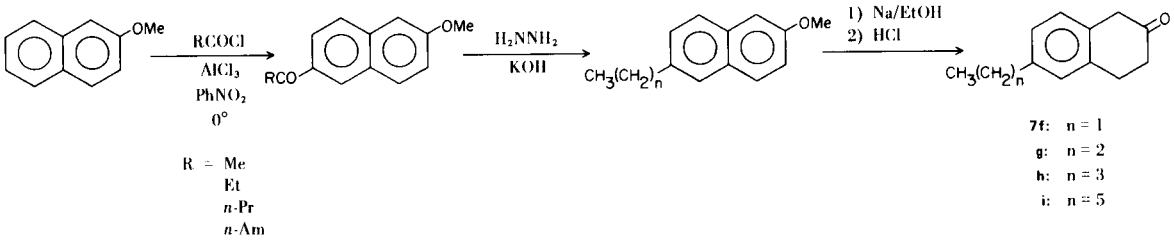

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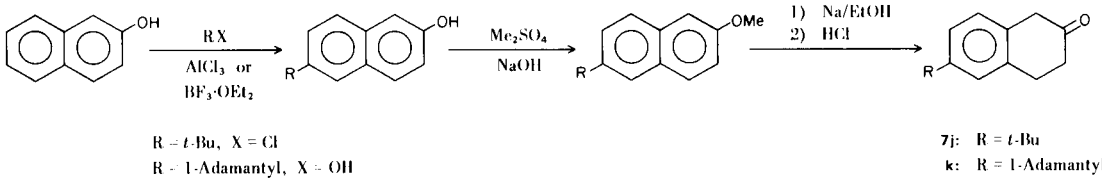
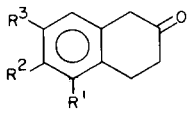


TABLE I



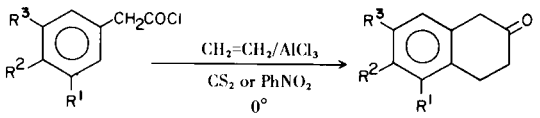
Compound	Substitution R^1	R^2	R^3	B.p., °C/mm	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
7b	H	H	Me	77/0.01	$C_{11}H_{12}O$	82.46	7.55	82.25	7.91
7d	H	Me	Me	93-94/0.05	$C_{12}H_{14}O$ (a)				
7e	Me	Me	H	100-110/0.1	$C_{12}H_{14}O$ (a)				
7f	H	Et	H	92-96/0.01	$C_{12}H_{14}O$	82.72	8.10	82.76	8.16
7g	H	*n*-Pr	H	84-85/0.05	$C_{13}H_{16}O$	82.94	8.56	82.65	8.50
7h	H	*n*-Bu	H	48-50/0.005	$C_{14}H_{18}O$	83.12	8.96	83.11	9.05
7j	H	*t*-Bu	H	89-104/0.005 (b)	$C_{14}H_{18}O$	83.12	8.96	82.95	8.93
7k	H	1-Adamantyl	H	(c)	$C_{20}H_{24}O$	85.66	8.62	85.56	8.70

(a) Correct analyses could not be obtained because of compound instability. (b) m.p. 65.5-69.5°. (c) m.p. 111-113° (petroleum ether, b.p. 40-60°).

TABLE II

Compound	B.p., °C/mm	M.p., °C	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
6-Methoxy-1,2-dimethyl-3,4-dihydronaphthalene	75-76/0.005		$C_{13}H_{16}O$	82.93	8.57	82.83	8.09
2-Methoxy-5,6-dimethylnaphthalene	118-119/0.005	68-70	$C_{13}H_{14}O$	83.83	7.58	83.60	7.58
6,7-Dimethyl-2-naphthol		158-160	$C_{12}H_{12}O$	83.68	7.02	84.04	6.92
2-Methoxy-6,7-dimethylnaphthalene		103-105	$C_{13}H_{14}O$	83.83	7.58	84.23	7.56
2-*t*-Butyl-6-methoxynaphthalene		75-76	$C_{15}H_{18}O$	84.08	8.46	84.09	8.36
6-(1-Adamantyl)-2-naphthol		192-195	$C_{20}H_{22}O$	86.28	7.96	86.04	8.17
2-(1-Adamantyl)-6-methoxynaphthalene		143-145	$C_{21}H_{24}O$	86.25	8.27	86.14	8.28

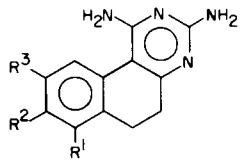
A potentially useful route to 2-tetralones, which was employed recently for the synthesis of several monochloro- and dichloro-substituted derivatives (11), involves condensation of phenylacetyl chlorides with ethylene at 0° in the presence of aluminum chloride (12). In the present work, this reaction was extended to *m*- and *p*-tolylacetyl chloride and 3,4-xylylacetyl chloride. Cyclization with the symmetrical *p*-tolyl compound led, expectedly, to 6-methyl-2-tetralone (**7a**) (13) as the sole product. With the unsymmetrical *m*-tolyl and 3,4-xylyl derivatives, on the other hand, cyclization proceeded nonselectively, as in the previously reported reaction of *m*-chlorophenylacetyl chloride (11). Glpc analysis indicated that cyclization with *m*-tolylacetyl chloride led to a 3:1 mixture of 7-methyl-2-tetralone (**7b**) and 5-methyl-2-tetralone (**7c**). Similar reaction of 3,4-xylylacetyl chloride gave a 4:1 mixture of 6,7-dimethyl-2-tetralone (**7d**) and 5,6-dimethyl-2-tetralone (**7e**). The apparent increase in selectivity of the latter ring closure can perhaps be ascribed to a buttressing phenomenon. However, an attempt to increase cyclization selectivity by carrying out the reaction in nitrobenzene instead of carbon disulfide (14) failed to eradicate the minor component in the product mixture. Thus, the low degree of directional specificity in the cyclization with unsymmetrical phenylacetyl chlorides must be recognized as a significant limitation of this approach (15).



7a: $R^1 = R^3 = H$, $R^2 = Me$
b: $R^1 = R^2 = H$, $R^3 = Me$
c: $R^2 = R^3 = H$, $R^1 = Me$
d: $R^1 = H$, $R^2 = R^3 = Me$
e: $R^3 = H$, $R^1 = R^2 = Me$

Inasmuch as single products were not obtainable *via* the aforementioned reactions of *m*-tolylacetyl and 3,4-xylylacetyl chloride, alternate methods of synthesis of

TABLE III



Compound	Substitution R1	R2	R3	M.p., dec., °C	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
6a	Me	H	H	272-273.5	$C_{13}H_{14}N_4$	69.00	6.24	24.76		68.97	6.29	24.75	
6b	H	Me	H	281-282	$C_{13}H_{14}N_4$	69.00	6.24	24.76		68.91	6.15	25.02	
6c	H	H	Me	239-241	$C_{13}H_{14}N_4$	69.00	6.24	24.76		69.17	6.25	24.74	
6d	Me	Me	H	300-302	$C_{14}H_{16}N_4$	69.98	6.71	23.31		69.96	6.45	23.48	
6e	H	Me	Me	265-267	$C_{14}H_{16}N_4$	69.98	6.71	23.31		69.89	6.82	23.49	
6f	H	Et	H	240	$C_{14}H_{16}N_4$	69.98	6.71	23.31		69.86	6.75	23.35	
6g	H	*n*-Pr	H	233.5-236	$C_{15}H_{18}N_4$	70.83	7.13	22.02		70.77	7.08	22.36	
6h	H	*n*-Bu	H	217-218	$C_{16}H_{20}N_4$	71.61	7.51	20.87		71.40	7.58	20.77	
6i	H	*t*-Bu	H	226-227	$C_{16}H_{20}N_4$	71.61	7.51	20.87		71.49	7.59	20.78	
6j	H	*n*-Hexyl	H	204-207	$C_{18}H_{24}N_4$	72.93	8.16	18.90		72.85	8.15	18.86	
6k	H	1-Adamantyl	H	312-314	$C_{22}H_{26}N_4$	76.26	7.56	16.17		76.04	7.33	16.10	
6l	H (Cl)	H	Cl (H)	298-299.5	$C_{12}H_{11}ClN_4$	58.42	4.50	22.71	14.37	58.16	4.41	22.49	14.66
6m	H	Cl	H	292-294	$C_{12}H_{11}ClN_4$	58.42	4.50	22.71	14.37	58.60	4.68	22.49	14.59
6n	Cl	H	Cl	278-280	$C_{12}H_{10}Cl_2N_4$	51.26	3.59	19.93	25.22	51.24	3.43	19.74	25.43
6o	H	Cl	Cl	266-268	$C_{12}H_{10}Cl_2N_4$	51.26	3.59	19.93	25.22	51.62	3.60	20.01	25.33
6p	MeO	H	H	256-259	$C_{13}H_{14}N_4O$	64.45	5.82	23.12		64.59	5.72	23.31	
6q	H	MeO	H	234.5-235	$C_{13}H_{14}N_4O$	64.45	5.82	23.12		64.59	5.79	23.20	
6r	H	H	MeO	237-238	$C_{13}H_{14}N_4O$	64.45	5.82	23.12		64.22	5.83	23.23	

TABLE IV

Ultraviolet and Infrared Spectral Data

Compound	R	Ultraviolet: λ_{max}^{EtOH}, mμ (ε x 10^{-3})				Ultraviolet: $\lambda_{max}^{pH\ 1\text{-}EtOH}$, mμ (ε x 10^{-3})				Infrared (a): ν_{max}^{KCl}, cm^{-1}
6a	7-Me	278	(17.3),	295 (b)	(15.1)	273	(17.2),	295 (b)	(9.5)	3400, 3280, 3170, 2940, 1630, 1565, 1470, 1460, 1430, 1410
6c	9-Me	278	(17.4),	299	(17.9)	273	(17.9),	293	(11.4)	3400, 3230, 2990, 1650, 1630, 1575, 1480, 1430
6d	7,8-Me_2	278	(19.5),	295 (b)	(15.9)	275	(19.5),	295 (b)	(11.2)	3390, 3230, 2990, 1640, 1625, 1575, 1470, 1430, 1410
6e	8,9-Me_2	278	(18.4),	301	(16.6)	274	(18.4),	291 (b)	(12.0)	3390, 3220, 2940, 1645, 1625, 1575, 1480, 1440
6f	8-Et	277	(18.6),	295	(16.6)	273	(18.6),	295 (b)	(12.1)	3440, 3350, 3230, 3030, 1650, 1625, 1575, 1550, 1430
6g	8-*n*-Pr	277	(18.3),	297	(16.4)	273	(20.0),	295 (b)	(13.0)	3450, 3390, 3220, 2990, 2900, 1640, 1580, 1560, 1490, 1440, 1400
6j	8-*n*-Hex	277	(15.6),	297	(14.1)	273	(16.3),	295	(10.6)	3450, 3390, 3230, 2940, 2860, 1640, 1575, 1550, 1480, 1430
6m	8-Cl	282	(18.1),	303	(18.7)	275	(20.1),	291	(15.1)	3430, 3390, 3220, 2940, 1640, 1565, 1470, 1430, 1410
6n	7,9-Cl_2	285	(14.3),	311	(19.0)	276	(17.2),	295 (b)	(11.3)	3400, 3340, 3220, 2990, 1640, 1575, 1480, 1420, 1410
6o	8,9-Cl_2	283	(16.9),	312	(20.9)	276	(19.9),	296	(13.8)	3450, 3280, 1655, 1645, 1575, 1535, 1480, 1440, 1420
6p	7-MeO	280	(17.8),	306	(13.4)	272	(17.3)			3390, 3230, 2990, 2850, 1640, 1620, 1580, 1480, 1460, 1425, 1400
6q	8-MeO	280	(21.1),	297 (b)	(17.2)	277	(19.9)			3400, 3230, 2970, 2860, 1640, 1625, 1565, 1480, 1445, 1430, 1400
6r	9-MeO	278	(14.8),	309	(17.1)	262 (b)	(15.2),	273	(15.4)	3390, 3230, 2980, 2860, 1650, 1635, 1575, 1490, 1425, 1410

(a) Significant peaks appearing between 3500 cm^{-1} and 1400 cm^{-1}. (b) Inflection.

7b-7e were devised (Flow Sheets I and II). Selective sulfonation of 2-methyl- and 2,3-dimethylnaphthalene at the 7-position at 160-170° and alkaline fusion of the resulting acids yielded 7-methyl-2-naphthol (16) and 6,7-dimethyl-2-naphthol, respectively. Alkylation with dimethyl sulfate, followed by reduction with sodium in isoamyl alcohol and acid hydrolysis, led to **7b** and **7d**. The reaction sequence developed by Bhattacharyya (17) for the preparation of **7c** was modified as follows for the synthesis of **7e**. Condensation of 6-methoxy-1-tetralone with methyl magnesium iodide, followed by oxidation with *m*-chloroperbenzoic acid and acid-catalyzed isomerization of the epoxide, gave 6-methoxy-1-methyl-2-tetralone (18). Further condensation with methyl magnesium iodide, dehydrogenation with sulfur, and reduction of the resultant 2-methoxy-5,6-dimethylnaphthalene with sodium in isoamyl alcohol furnished **7e**.

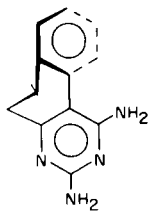
Although condensation of *p*-tolylacetyl chloride with ethylene provided a very convenient synthesis of **7a**, a more general route to 6-alkyl-2-tetralones (Flow Sheets III and IV) involved the use of 6-alkyl-2-methoxynaphthalenes as intermediates. Aluminum chloride-catalyzed Friedel-Crafts reactions of 2-methoxynaphthalene with acetyl chloride (19), propionyl chloride (19a,20), *n*-butyroyl chloride (19a,20a) and *n*-hexanoyl chloride (19a,21) in nitrobenzene at 0° afforded the known 6-acyl derivatives, which were reduced to 6-alkyl-2-methoxynaphthalenes *via* the Wolff-Kishner method (20a,22). Reduction with sodium in ethanol (23) then gave 6-ethyl-, 6-*n*-propyl-, 6-*n*-butyl-, and 6-*n*-hexyl-2-tetralone (**7f-7i**). Of these four compounds, **7i** had been synthesized earlier by Bannister and Elsner (21), but **7f-7h** were new. In two instances, branched-alkyl derivatives were also prepared. Zinc chloride-catalyzed alkylation of 2-naphthol with *t*-butyl chloride in ligroin afforded 6-*t*-butyl-2-naphthol as reported by Buu-Hoi and coworkers (24a) and at variance with Contractor and coworkers (24b), who considered that alkylation had taken place in position 3. Similar alkylation with 1-adamantanol and boron trifluoride gave 6-(1-adamantyl)-2-naphthol. Treatment with dimethyl sulfate, reduction with sodium in alcohol, and acid hydrolysis converted these naphthols into 6-*t*-butyl-2-tetralone (**7j**) and 6-(1-adamantyl)-2-tetralone (**7k**), respectively.

All the 2-tetralones prepared in this work were identified by means of their characteristic blue color reaction with alcoholic sodium hydroxide and air (23,25), their infrared absorption in the 1720 cm^{-1} region, and their nmr spectra. The latter exhibit, typically, a singlet at τ 6.5 for the 1-CH_2 group, a broad triplet at τ 7.0 for the 4-CH_2 group, and a well-resolved multiplet at τ 7.5 for the 3-CH_2 group. Broadening of the signal ascribed to the 4-CH_2 protons may be due to second-order interaction with the adjacent aromatic proton. Multiplicity of the 3-CH_2 signal presumably results from simultaneous spin-spin coupling with 4-CH_2 and 1-CH_2 groups. Because of their pronounced tendency to decompose on storage, the 2-tetralones were converted as soon as possible into 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines, or else were kept in the form of fairly stable, crystalline bisulfite adducts (23). In two instances, with **7d** and **7e**, extreme air sensitivity prevented us from obtaining acceptable microanalytical values. Nonetheless, infrared and nmr spectral properties left no doubt as to the correct structure of these compounds, and glpc analysis confirmed their purity.

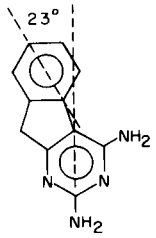
Fusion reactions of 2-tetralones with cyanoguanidine were carried out in an open flask at temperatures ranging from 180° to 210° for periods of 20-45 minutes, as reported earlier (8). The molten reaction mixtures underwent varying degrees of darkening, but this did not interfere much with the subsequent work-up. Steam evolution was evident during the reaction, and partial to complete solidification usually occurred near the end. After trituration with acetone and ether to dissolve tars, the crude solid was subjected to one of several purification schemes (see Experimental) in order to remove unreacted cyanoguanidine and byproducts such as melamine. In one procedure, the solid was digested with hot *N,N*-dimethylformamide, and the digest was diluted with water until the product precipitated out; in another, digestion was performed with ethanolic ammonia instead of *N,N*-dimethylformamide. A third approach involved digestion with boiling hydrochloric acid and reprecipitation of the product with base. In several instances, the products appeared to be complexed with cyanoguanidine. The complexes had higher melting points than the pure products, and could be identified by the presence of weak nitrile absorption in the infrared (26). Disruption of the complexes was usually accomplished *via* any of the aforementioned purification routes. After one or more crystallizations from alcohol, the 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines were isolated as colorless, well-formed needles showing no tendency to darken on standing. In this respect, these compounds differ sharply from the 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines (**4**), which crystallize poorly and are very difficult to maintain in colorless form.

Infrared and ultraviolet absorption spectral data for a representative number of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines are presented in Table IV. The infrared spectra of these compounds, taken in potassium chloride disks, generally showed one or two peaks in the 3350-3450 cm^{-1} region, a single peak in the 3220-3280 cm^{-1} region, and one or two peaks in the 2850-3000 cm^{-1} region. In addition, a complex series of peaks was ob-

served in the 1400-1650 cm^{-1} region, corresponding to the various possible ring stretching modes of the system. Ultraviolet absorption spectra in ethanol solution showed maxima at 277-285 mμ and 295-311 mμ, the longer wavelength band being reduced to a shoulder in certain compounds. Chloro and methoxy substitution in the phenyl ring caused bathochromic displacement of both bands, indicating that they are probably due to $\pi \rightarrow \pi^*$ transitions. In general, 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines appear to absorb at longer wavelengths than non-bridged 2,4-diamino-5-phenyl-6-alkylpyrimidines (27). This is in accord with the view that the phenyl and pyrimidine rings are more nearly coplanar in the bridged compounds than in the freely rotating open-chain analogs. It is also noteworthy, however, that 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines absorb at a slightly *longer* wavelength than 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines with similar phenyl substitution (6). Consideration of Dreiding molecular models (28) suggests a possible explanation for this finding. Whereas the phenyl and pyrimidine rings exist in a coaxial but non-coplanar arrangement in **6**, they are coplanar but not coaxial in **4**. Resonance interaction between the π-electron systems of these bridged compounds may thus depend not only upon the dihedral angle between the planes of the two aromatic rings (7a), but also, to a significant extent, upon the ability of the rings to assume a coaxial alignment as shown below.



6: coaxial, non-coplanar



4: coplanar, non-coaxial

EXPERIMENTAL (29)

Synthesis of 2-Tetralones.

6-Methyl-2-tetralone (**7a**).

A solution of *p*-tolylacetyl chloride (30) (20 g., 0.12 mole) in dry carbon disulfide (400 ml.) was added to a well-stirred suspension of anhydrous aluminum chloride (32 g., 0.24 mole) in carbon disulfide (600 ml.) at 0-5° (internal), and ethylene gas was bubbled through the cooled mixture for 4 hours. The reaction mixture was then poured into ice (500 g.) and concentrated hydrochloric acid (50 ml.). The aqueous layer was extracted with dichloromethane (750 ml.), and the combined organic layers were washed with saturated sodium chloride, dried, and evaporated. Distillation of the dark residue afforded 10.5 g. (55% yield) of **7a** as a yellow liquid, b.p. 90-94° (0.05-0.075 mm) (13); nmr τ (deuteriochloroform) 7.69 (singlet, aromatic methyl), 7.53 (well-resolved multiplet, 3-CH_2), 7.01 (broad triplet, 4-CH_2), 6.50 (singlet, 1-CH_2), ~3.0 (aromatic proton pattern).

7(and 5)-Methyl-2-tetralone (**7b** and **7c**).

A. In Carbon Disulfide.

m-Tolylacetyl chloride (31) (10 g., 0.059 mole) and aluminum chloride (16 g., 0.12 mole) were suspended in dry carbon disulfide (510 ml.),ethylene gas was bubbled through the stirred suspension at 0-5° for 4 hours, and the mixture was worked up as in the preceding experiment. Conversion of the crude product into a crystalline bisulfite adduct and treatment of the latter with sodium carbonate yielded a mixture of **7b** and **7c**. Glpc analysis of this mixture on a 6 ft. 10% SE-30 silicone gum column at 145° showed the 7- and 5-isomers to be present in a ratio of approximately 3:1.

B. In Nitrobenzene.

m-Tolylacetyl chloride (10 g., 0.059 mole) and aluminum chloride (16 g., 0.12 mole) in nitrobenzene (510 ml.) were treated with ethylene gas at 4-8° for 4 hours, the mixture was poured into ice and concentrated hydrochloric acid (25 ml.), and an aliquot of the organic layer was analyzed as described above. In this instance, the ratio of 7- and 5-isomers was found to be about 2:1.

6,7(and 5,6)-Dimethyl-2-tetralone (**7d** and **7e**).

Ethylene gas was bubbled for 5 hours through a mixture of 3,4-xylylacetyl chloride (32) (10 g., 0.055 mole) and aluminum chloride (15 g., 0.11 mole) in carbon disulfide (500 ml.) at 0-5°. Work-up of the reaction as described above gave a mixture of **7d** and **7e**. Glpc analysis on a 6 ft. 10% SE-30 silicone gum column at 210° showed the ratio of 6,7- and 5,6-isomers to be approximately 4:1.

5-Methyl-2-tetralone (**7c**).

A solution of 6-methoxy-1-tetralone (100 g., 0.57 mole) in dry benzene (400 ml.) was added dropwise to a stirred solution of methyl magnesium iodide prepared from methyl iodide (114 g.) and magnesium metal (15.5 g.) in ether (600 ml.). After 2 hours of refluxing, the mixture was treated with saturated ammonium chloride (300 ml.) at 0°. Extraction with ether (300 ml.) and vacuum distillation gave 82 g. (82% yield) of 6-methoxy-1-methyl-3,4-dihydronaphthalene (18) as a colorless liquid, b.p. 70-71° (0.05 mm). Dehydrogenation of this compound (60 g., 0.34 mole) with powdered sulfur (12 g.) at 305° (internal) for 2 hours afforded 50 g. (68% yield) of 2-methoxy-5-methylnaphthalene (17), b.p. 85° (0.005 mm), m.p. 52-54° (solid formed in the receiver). Sodium metal (125 g.) cut into small pieces was added to a solution of this compound (57 g., 0.33 mole) in isoamyl alcohol (1250 ml.) at a rate sufficient to maintain gentle reflux. After another 5 hours under reflux, enough ice water was added to the cooled mixture to give two layers. The aqueous layer was extracted with dichloromethane (1000 ml.), and the combined alcohol and dichloromethane layers were dried and evaporated. The crude enol ether thereby obtained was dissolved in ethanol (300 ml.), concentrated hydrochloric acid (50 ml.) was added, and the mixture was refluxed for 30 minutes and evaporated under reduced pressure. Distillation of the residue afforded 38 g. of light yellow oil, b.p. 100-160° (0.01 mm), which gave 14 g. of crystalline bisulfite adduct upon treatment with sodium bisulfite (23). Pure **7c** (17) (7.2 g., 14% yield) was regenerated from the bisulfite adduct with sodium carbonate (23).

7-Methyl-2-tetralone (**7b**).

A mixture of 2-methylnaphthalene (300 g., 2.11 mole) and concentrated sulfuric acid (300 ml.) was stirred at 160-170° (internal) for 5 hours, then cooled to room temperature and diluted with water (3 liters). Unreacted starting material was filtered off, the filtrate was washed with benzene to remove traces of neutral products, and 2-methylnaphthalene-7-sulfonic acid was precipitated by addition of concentrated hydrochloric acid (300 ml.) at 10°. After being filtered and washed with cold 10% hydrochloric acid, the grey sulfonic acid was redissolved in water (3 liters) and converted into the insoluble white barium salt by addition of concentrated barium hydroxide; yield 305 g. (50%). The barium salt (100 g., 0.17 mole) was mixed with sodium hydroxide (200 g.) and water (30-50 ml.) in a 1-liter stainless steel beaker fitted with a copper thermometer well. The mixture was heated at 315-320° (internal) for 2 hours, then cooled, triturated with small portions of water (total volume 1 liter), and filtered. Acidification of the cooled dark filtrate with concentrated hydrochloric acid gave 142 g. (42% yield) of 7-methyl-2-naphthol (16), which was used in the next step without further purification. A mixture of the naphthol (20 g., 0.13 mole) and dimethyl sulfate (20 g.) in acetone (600 ml.) was treated dropwise with sodium hydroxide (60 g.) in a minimum of water. After being stirred at room temperature for 1 hour, the mixture was diluted with water (60 ml.), heated on the steam bath for another hour, and poured into ice. Filtration and recrystallization from ethanol gave 10 g. (46% yield) of 2-methoxy-7-methylnaphthalene as colorless crystals. Direct reduction of this material with sodium metal (25 g.) in isoamyl alcohol (250 ml.), followed by a work-up similar to that used in the synthesis of **7c**, afforded 4 g. of crude **7b** from which was obtained 2.5 g. of crystalline bisulfite adduct. **Decomposition** of the adduct with sodium carbonate gave 1 g. (11% yield) of pure **7b** as a colorless liquid; nmr τ (deuteriochloroform) 7.64 (singlet, aromatic methyl), 7.50 (well-resolved multiplet, 3-CH_2), 7.00 (broad triplet, 4-CH_2), 6.45 (singlet, 1-CH_2), ~3.0 (aromatic proton pattern).

5,6-Dimethyl-2-tetralone (**7e**).

A solution of 6-methoxy-1-methyl-3,4-dihydronaphthalene (85 g., 0.49 mole) in dichloromethane (300 ml.) was maintained at 0-5° while a solution of 85% *m*-chloroperbenzoic acid (100 g.) in dichloromethane (1 liter) was added slowly with stirring. After 30 minutes, the mixture was allowed to come to room temperature, and excess peracid was decomposed with 10% sodium sulfite (negative test with starch-iodide paper). The filtered reaction mixture was shaken with 10% hydrochloric acid and allowed to stand for 2 hours. Extraction of the organic layer with 5% sodium bicarbonate and water, evaporation of the solvent, and vacuum distillation of the residue afforded 90 g. (97% yield) of crude 6-methoxy-1-methyl-2-tetralone (18), b.p. ~75° (0.01 mm), which was added dropwise in benzene solution (400 ml.) to a solution of methyl magnesium iodide prepared from methyl iodide (114 g.) and magnesium metal (16 g.) in ether (600 ml.). After 2 hours, the cooled mixture was treated with saturated ammonium chloride (300 ml.). The aqueous layer was extracted with ether (500 ml.), and the combined organic layers were washed with 5% sodium carbonate (300 ml.), rinsed with water, dried, and evaporated. Distillation of the residue gave 68 g. (76% yield) of yellow liquid, b.p. 70-80° (0.005 mm). Dehydrogenation of this material (67 g., 0.36 mole) with powdered sulfur (12 g.) at 300° (internal) for 2 hours gave 28 g. (42% yield) of 2-methoxy-5,6-dimethylnaphthalene, b.p. 118-119° (0.005 mm), solidification occurring in the receiver during distillation. Two crystallizations from acetic acid gave colorless needles. Reduction of this compound (40 g., 0.22 mole) was carried out with sodium metal (85 g.) in isoamyl alcohol (850 ml.) according to the procedure used for the preparation of **7c**. The crude product, b.p. 50-95° (0.05 mm), was converted into a crystalline bisulfite adduct (22 g., 40% yield), and the latter was treated with sodium carbonate to regenerate pure **7e** (7.1 g., 19% yield based on 2-methoxy-5,6-dimethylnaphthalene); nmr τ (deuteriochloroform) 7.76 and 7.72 (singlets, aromatic methyls), 6.47 (singlet, 1-CH_2), ~3.1 (aromatic proton pattern). Glpc analysis indicated the product to be homogeneous but repeated attempts to obtain an acceptable microanalysis were unsuccessful.

6,7-Dimethyl-2-tetralone (**7d**).

A mixture of 2,3-dimethylnaphthalene (500 g., 3.2 moles) and concentrated sulfuric acid (600 ml.) was stirred at 155-160° (internal) for 5 hours, then cooled, diluted with water (1 liter), and filtered. The grey sulfonic acid was redissolved in water and converted into the sodium salt by addition of sodium hydroxide. Fusion of the sodium salt with sodium hydroxide in the manner described for the preparation of 7-methyl-2-naphthol afforded 95 g. (17% yield) of 6,7-dimethyl-2-naphthol. Sublimation at 95° (0.005 mm) gave analytically pure colorless material. Reaction of the naphthol (95 g., 0.55 mole) with dimethyl sulfate according to the procedure used with 7-methyl-2-naphthol gave 81 g. (79% yield) of 2-methoxy-6,7-dimethylnaphthalene. Colorless, analytically pure material was obtained by sublimation at 73-75° (0.005 mm). Reduction of this compound (31 g., 0.17 mole) with sodium metal (75 g.) in boiling isoamyl alcohol (900 ml.) for 7 hours, followed by hydrolysis of the crude enol ether (27 g.) with concentrated hydrochloric acid (40 ml.) and ethanol (200 ml.) under reflux for 10 minutes, afforded 16 g. (55% yield) of colorless liquid. As with **7e**, glpc analysis of the distilled product established its homogeneity, but correct microanalytical values could not be obtained.

6-Ethyl-2-tetralone (**7f**).

6-Acetyl-2-methoxynaphthalene, m.p. 103-105.5° [lit. (19c), m.p. 106.5°] was prepared from 2-methoxynaphthalene, acetyl chloride and aluminum chloride in nitrobenzene (19), and reduced to 6-ethyl-2-methoxynaphthalene, m.p. 59.5-60° [lit. (22) m.p. 62°], by the Wolff-Kishner method (22). Sodium metal (56 g.) was added in small pieces, at a rate sufficient to maintain gentle reflux, to a stirred solution of the above compound (34 g., 0.18 mole) in ethanol (470 ml.) under a nitrogen atmosphere. When all the sodium had dissolved, the mixture was cooled and water (185 ml.) was added cautiously to form a clear solution. Concentrated hydrochloric acid (370 ml.) was then added, and refluxing was resumed for 30 minutes. Extraction of the product into benzene, evaporation of the organic phase to dryness, and treatment with sodium bisulfite afforded 35 g. (68% yield) of crystalline bisulfite adduct. Decomposition of this adduct with aqueous sodium carbonate, extraction with ether, and distillation gave 21 g. (53% yield) of **7f**. The overall yield, based on 6-ethyl-2-methoxynaphthalene, was 36%.

6-*n*-Propyl-2-tetralone (**7g**).

2-Methoxynaphthalene was condensed with propionyl chloride and aluminum chloride in nitrobenzene (20), and the resultant 2-methoxy-6-propionylnaphthalene, m.p. 109-111° [lit. (20c), m.p. 111.5-113.5°], was reduced to 2-methoxy-6-*n*-propylnaphthalene, m.p. 55-56° [lit. (22) m.p. 56°] *via* the Wolff-Kishner method (22). Treatment of the above compound (25 g., 0.13 mole) with sodium metal (38 g.) in ethanol (315 ml.), followed by a work-up

similar to that employed for the reduction of 6-ethyl-2-methoxynaphthalene, afforded 28 g. (77% yield) of crystalline bisulfite adduct, m.p. 130° dec. Decomposition of this adduct (59 g., 0.2 mole) with aqueous sodium carbonate, extraction with ether, and distillation gave 24 g. (63% yield) of **7g**. The overall yield, based on 2-methoxy-6-*n*-propylnaphthalene, was 48%.

6-*n*-Butyl-2-tetralone (**7h**).

6-*n*-Butyroyl-2-methoxynaphthalene, m.p. 80-85° [lit. (19a), m.p. 90°], was prepared from 2-methoxynaphthalene, *n*-butyroyl chloride and aluminum chloride in nitrobenzene at 0° (19a) and converted into 6-*n*-butyl-2-methoxynaphthalene, m.p. 47-52° [lit. (20a), m.p. 52-53°], *via* Wolff-Kishner reduction (22). Further reduction of this compound (53 g., 0.25 mole) with sodium metal (75 g.) in ethanol (670 ml.), followed by a work-up similar to that used with 6-ethyl-2-methoxynaphthalene, afforded 52 g. (69% yield) of crystalline bisulfite adduct. Treatment of the latter with sodium carbonate liberated 19 g. (54% yield) of crude **7h** as a brown oil. The total yield, based on 6-*n*-butyl-2-methoxynaphthalene, was 37%.

6-*t*-Butyl-2-tetralone (**7j**).

6-*t*-Butyl-2-naphthol, m.p. 118-119° [lit. (24b), m.p. 118-119°], was prepared from 2-naphthol, *t*-butyl chloride, and anhydrous zinc chloride (24). Reaction of this compound (56 g., 0.28 mole) in 15% potassium hydroxide solution (1 liter) with dimethyl sulfate (213 g.) at 30-40° for 2 hours gave 52 g. (87% yield) of 6-*t*-butyl-2-methoxynaphthalene. Treatment of this compound (52 g., 0.24 mole) with sodium metal (70 g.) in ethanol (600 ml.), followed by a work-up similar to that employed for the reduction of 6-ethyl-2-methoxynaphthalene, gave 34 g. (47% yield) of crystalline bisulfite adduct. Decomposition of this adduct with sodium carbonate and extraction with ether afforded 13 g. (55% yield) of orange oil which solidified upon refrigeration. The overall yield, based on 6-*t*-butyl-2-methoxynaphthalene, was 26%.

6-(1-Adamantyl)-2-tetralone (**7k**).

Freshly distilled boron trifluoride etherate (56 ml.) was added over a 15 minute period to a mixture of 2-naphthol (20 g., 0.14 mole) and 1-hydroxyadamantane (23 g., 0.15 mole) in 800 ml. of petroleum ether (b.p. 40-60°) at 0°. After another 15 minutes at 0-5°, the mixture was stirred at room temperature for 45 minutes and poured into ice. Filtration, washing with petroleum ether (b.p. 40-60°) and drying afforded 27 g. (71% yield) of crude 6-(1-adamantyl)-2-naphthol. Analytically pure material, m.p. 192-195°, was obtained after two crystallizations from 60% ethanol. Addition of dimethyl sulfate (20 g., 0.16 mole) to a cooled solution of crude naphthol (10 g., 0.036 mole) in acetone (300 ml.), followed by dropwise addition of sodium hydroxide (60 g.) in water (100 ml.), stirring at room temperature for 2 hours, dilution with water (60 ml.), and heating on the steam bath for 1 hour gave 6-(1-adamantyl)-2-methoxynaphthalene (11 g., 95% yield) as a beige powder. The analytical sample was prepared by recrystallization from 95% ethanol. Treatment of this compound (19 g., 0.066 mole) with sodium metal (31 g.) in isoamyl alcohol (750 ml.) under reflux for 7 hours, addition of water (2 liters), and evaporation of the organic layer yielded the crude enol ether as a light purple solid. Hydrolysis of this material with a mixture of 95% ethanol (220 ml.) and 10% hydrochloric acid (80 ml.) on the steam bath for 30 minutes, extraction of the product into ether (250 ml.), careful solvent evaporation under reduced pressure to remove all traces of isoamyl alcohol, and trituration with petroleum ether (b.p. 40-60°) gave 5.8 g. (32% yield) of **7k** of sufficient purity for the next step. The analytical sample was prepared by recrystallization from petroleum ether (b.p. 40-60°) with the aid of decolorizing carbon.

Synthesis of 1,3-Diamino-5,6-dihydrobenzo[*f*]quinazolines.

1,3-Diamino-5,6-dihydro-7-methylbenzo[*f*]quinazoline (**6a**). Example 1.

Cyanoguanidine (4.1 g., 0.049 mole) and **7c** (7.1 g., 0.044 mole) were heated at 190-210° (internal) for 30 minutes, and the cooled melt was pulverized in a mortar and triturated with 4:1 ether-acetone (3 x 200 ml.). Recrystallization of the resulting tan powder (7.2 g., 72% crude yield) from 95% ethanol (decolorizing carbon) gave four crops weighing a total of 4 g. (40% yield). A second crystallization from 95% ethanol furnished analytically pure **6a** in the form of colorless fibrous needles.

1,3-Diamino-5,6-dihydro-8-methylbenzo[*f*]quinazoline (**6b**). Example 2.

Cyanoguanidine (6.9 g., 0.082 mole) and **7a** (12 g., 0.075 mole) were heated at 190-210° (internal) for 30 minutes. The cooled amber-colored melt was digested with acetone (150 ml.), and the insoluble portion filtered and treated with boiling *N,N*-dimethylformamide (400 ml.). After removal of a small amount of still undissolved material, treatment with decolorizing carbon, and dilution with water, the *N,N*-dimethylformamide solution yielded three crops of crude **6b** weighing a total of 8.4 g. (50% yield). Recrystallization from 95% ethanol (decolorizing carbon) afforded analytically pure **6b** as colorless fibrous needles.

1,3-Diamino-5,6-dihydro-9-methylbenzo[*f*]quinazoline (**6c**). Example 3.

Cyanoguanidine (7 g., 0.083 mole) and **7b** (12 g., 0.075 mole) were heated at 200-210° (internal) for 45 minutes. The cooled solid was broken up, boiled in water (200 ml.), filtered, washed with dichloromethane, and recrystallized from ethanol-water (decolorizing carbon). The colorless fibrous needles, m.p. 249-251°, weighed 2.1 g. (12% yield), and appeared to contain some cyanoguanidine according to the infrared spectrum (nitrile doublet in the 2200-2100 cm^{-1} region). Analytically pure **6c** was obtainable by vacuum sublimation at 165-170° (0.05 mm).

1,3-Diamino-8-*n*-butyl-5,6-dihydrobenzo[*f*]quinazoline (**6h**). Example 4.

Cyanoguanidine (8.1 g., 0.096 mole) and **7h** (18 g., 0.089 mole) were heated at 190-210° (internal) for 45 minutes, and the cooled melt was triturated with ether and digested with 20% ammonium hydroxide (500 ml.) at 75-80° for 10 minutes. Crystallization of the crude product (8.2 g.) from 95% ethanol (2100 ml.) afforded 4.5 g. (21% yield). The analytical specimen was obtained after two additional crystallizations from 95% ethanol.

1,3-Diamino-8-*t*-butyl-5,6-dihydrobenzo[*f*]quinazoline (**6i**). Example 5.

Cyanoguanidine (5.6 g., 0.067 mole) and **7j** (13 g., 0.062 mole) were heated for 30 minutes at 200-220° (internal). The dark red melt was poured into a mortar and allowed to cool, and the solidified mass was pulverized and triturated with acetone (200 ml.). A small quantity of insoluble material was filtered off, and the filtrate was treated with concentrated hydrochloric acid (4 ml.). Digestion of the yellow precipitate of **6i**·hydrochloride (8.1 g.) with 10% sodium hydroxide (100 ml.) liberated the free base (6.5 g., 39% crude yield). Two crystallizations from aqueous ethanol (decolorizing carbon) afforded 2.8 g. (17% yield) of pure **6i** in the form of colorless fibrous needles.

1,3-Diamino-8-chloro-5,6-dihydrobenzo[*f*]quinazoline (**6m**). Example 6.

Cyanoguanidine (7.9 g., 0.094 mole) and 6-chloro-2-tetralone (11) (16 g., 0.086 mole) were heated at 180-210° (internal) for 30 minutes. The cooled fusion mixture was triturated with acetone (400 ml.), and the resulting solid (11 g.) was digested with hot 1 *N* hydrochloric acid (3 x 500 ml.) and boiling water (500 ml.). Treatment of the combined digests with decolorizing carbon and basification to *p*H 14 with 10% sodium hydroxide afforded 6.9 g.(33% yield) of colorless product. Analytically pure material was obtained after three crystallizations from 95% ethanol.

1,3-Diamino-5,6-dihydro-9-methoxybenzo[*f*]quinazoline (**6r**). Example 7.

Cyanoguanidine (5.6 g., 0.067 mole) and 7-methoxy-2-tetralone (33) (10 g., 0.057 mole) were heated at 190-200° (internal) for 30 minutes, and the cooled melt was triturated with acetone (250 ml.) and digested with 4:1 ethanol-ammonia (3 x 250 ml.). Concentration of the combined ethanolic digests afforded 7 g. (51% yield) of crude **6r**, which was purified for analysis by crystallization from *N*,*N*-dimethylformamide-water.

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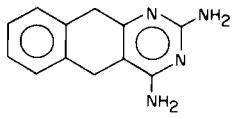
(10) The alternative linear product, 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline (i), has been synthesized in our laboratory by Dr. P. C. Huang *via* another route (to be published).



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