Quinazolines. VIII. Synthesis of 1,3-Diaminobenzo[*f*]quinazolines (1)

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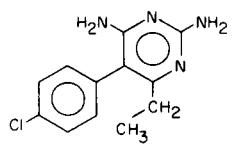
Twenty-one 1,3-diaminobenzo[*f*]quinazolines (**2**, R = H, alkyl, halogen, methoxy) were synthesized as planar tricyclic analogs of the antimalarial agent pyrimethamine (**1**). The synthetic methods included i) condensation of 1-cyano-2-naphthylamines with cyanamide in the presence of pyridine hydrochloride, ii) cyclization of N^1,N^5-bis(2-naphthyl)biguanide hydrochlorides in diphenyl ether at 250°, iii) reaction of 2-naphthylamine hydrochlorides with excess sodium dicyanamide in boiling 1-octanol, and iv) selenium dioxide dehydrogenation of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines. A number of new 2-naphthols and 2-naphthylamines were synthesized as intermediates. Substituent effects on the ultraviolet absorption spectra of 1,3-diaminobenzo[*f*]quinazolines were investigated and found to be additive. These compounds are of interest as inhibitors of dihydrofolate reductase and as potential antimalarial and antitumor agents.

A systematic program of synthesis of dihydrofolate reductase inhibitors of the 2,4-diaminopyrimidine type (2) has been in progress in our laboratory for a number of years. In connection with this program, compounds that could be viewed as conformationally rigid tricyclic analogs of pyrimethamine (**1**) were of particular interest, both as possible experimental antitumor agents and, more recently, as candidate antimalarial agents for use against pyrimethamine-resistant plasmodia. Previously reported examples of such compounds have included 2,4-diamino-9*H*-indeno[2,1-*d*]pyrimidines (3), 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines (4,5), 2,4-diamino-10,11-dihydro-9*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidines (5a), and 1,3-diamino-5*H*-[1]benzopyrano(and thiopyrano)-[3,4-*d*]pyrimidines (6). The present paper deals with the synthesis of still another related series, the 1,3-diaminobenzo[*f*]quinazolines (**2**). Preliminary work on these fully aromatic compounds was first reported in 1966 (7,8).

In all, twenty-one 1,3-diaminobenzo[*f*]quinazolines (**2a-2u**) were synthesized during this program. The physical constants of these compounds are presented in Tables I and II; those of a number of heretofore unreported 2-naphthylamine and N^1,N^5-bis(2-naphthyl)biguanide intermediates are shown in Tables III and IV, respectively.



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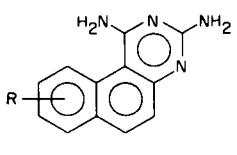
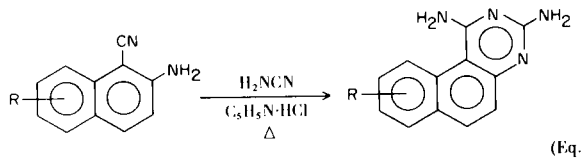


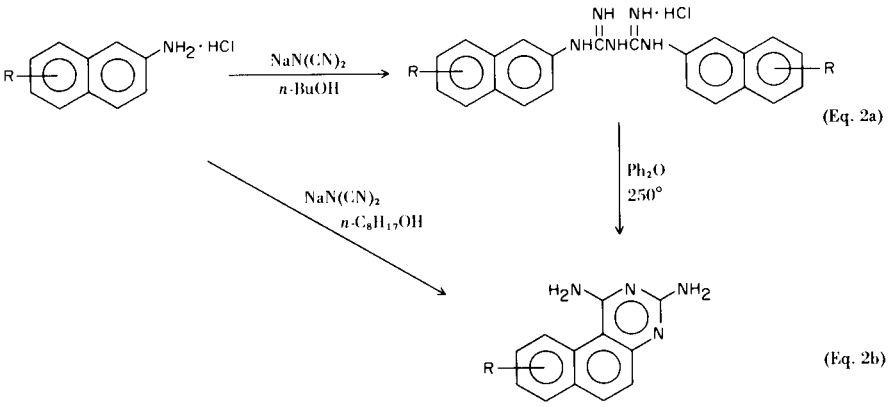
2

Several routes to 1,3-diaminobenzo[*f*]quinazolines were given consideration from the standpoint of preparative convenience. Originally, the parent compound, **2a**, had been synthesized from 1-cyano-2-naphthylamine, cyanamide, and pyridine hydrochloride under fusion conditions, and also from 1,3-dichlorobenzo[*f*]quinazoline by high-temperature amination in a sealed glass vessel under scrupulously anhydrous conditions (7). The general inconvenience of the latter reaction led to its early abandonment. On the other hand, the cyanamide reaction (Equation 1) proved to be acceptable when the starting material was not too difficult to prepare. An example illustrating this approach is the synthesis of 1,3-diamino-8-bromobenzo-[*f*]quinazoline (**2r**) described in the Experimental section. 1,6-Dibromination of 2-acetamidonaphthalene (9), selective replacement of the 1-bromo substituent with cuprous cyanide in refluxing *N*,*N*-dimethylformamide, and alkaline hydrolysis of the *N*-acetyl blocking group afforded a good overall yield of the heretofore unknown 6-bromo-1-cyano-2-naphthylamine. Ring closure to **2r** with cyanamide and pyridine hydrochloride proceeded in about the same yield as in the synthesis of **2a** (7) despite the presence of the potentially deactivating halogen substituent.



(Eq. 1)

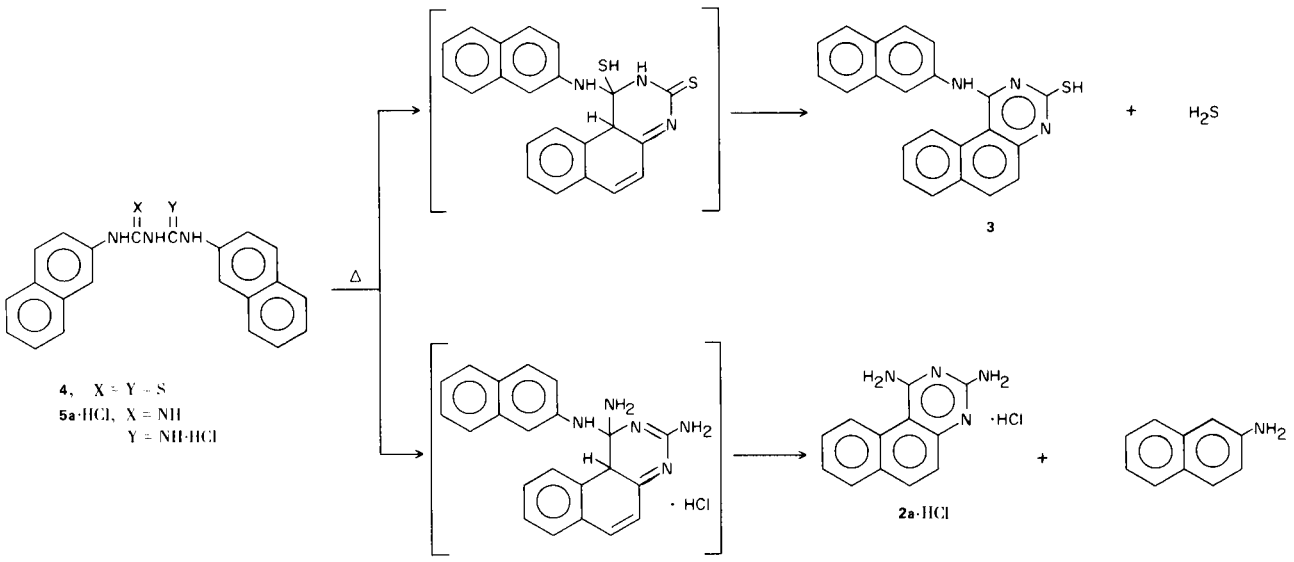
While the aforementioned synthesis of **2r** was in progress, efforts were being made to develop an alternative route to 1,3-diaminobenzo[*f*]quinazolines which would not require separate introduction of a 1-cyano group into the naphthalene nucleus prior to ring closure of the pyrimidine ring. Of particular interest in this connection was a paper by Dziewoński and coworkers (10) describing the thermal cyclization of 2-naphthylthiourea to 1-(2-naphthylamino)-3-mercaptobenzo[*f*]quinazoline (**3**). The same product was also obtained directly from 2-naphthylamine and thiourea, and N^1,N^5-bis(2-naphthyl)dithiobiuret (**4**) was proposed as a hypothetical reaction intermediate. Consideration of the probable mechanism of ring closure (Chart I) suggested that selective expulsion of hydrogen sulfide instead of 2-naphthylamine was favored in the final aromatization step because of the difference in polarizability between carbon-sulfur and carbon-nitrogen bonds. It occurred to us that replacement of the thiono functions in **4** by imino groups might promote the formation of a 1-amino rather than a 1-(2-naphthylamino) derivative. In this instance, the last step could involve only carbon-nitrogen bond cleavage, and departure of the bulky 2-naphthylamine molecule should provide greater relief of steric strain than loss of ammonia. Accordingly, N^1,N^5-bis(2-naphthyl)biguanide hydrochloride (**5a**·hydrochloride), prepared from 2-naphthylamine hydrochloride and sodium dicyanamide *via* the general procedure of Curd and Rose (11), was heated in diphenyl ether (Equation 2a). After only two minutes at 250°, **5a**·hydrochloride was transformed into **2a**·hydrochloride



(Eq. 2a)

(Eq. 2b)

CHART I



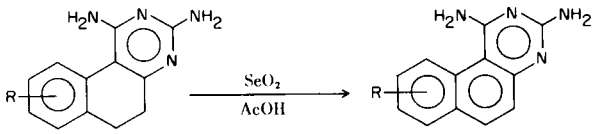
in approximately 30% yield. Work-up of the mother liquor confirmed the presence of 2-naphthylamine as required by the postulated mechanism of cyclization. In similar fashion, substituted N^1,N^5-bis(2-naphthyl)biguanide derivatives **5b**·hydrochloride-**5f**·hydrochloride (Table IV) were synthesized from 2-naphthylamines and converted into 1,3-diaminobenzo[*f*]quinazolines **2m**, **2n**, **2r**, **2t**, and **2u**. Yields obtained *via* this so-called "two-step bisarylbiguanide cyclization" (Table I, Method B) were generally in the 30-50% range; varying amounts of starting material could be recovered if desired.

A procedure was also developed wherein isolation of the N^1,N^5-bis(2-naphthyl)biguanide salt prior to ring closure was obviated. This involved treatment of a 2-naphthylamine hydrochloride derivative with two moles of sodium dicyanamide per mole of amine (a four-fold excess over the stoichiometric amount) in refluxing 1-octanol for 18 hours (Equation 2b). Yields of 1,3-diaminobenzo-[*f*]quinazolines obtained directly *via* this so-called "one-step bisarylbiguanide cyclization" (Table I, Method C) ranged from 11% for **2o** to 47% for **2u**, the average value for thirteen compounds being about 25%. No starting material could be recovered, since sodium dicyanamide was present in excess. It is of interest that when the reaction was performed with the stoichiometric amount of sodium dicyanamide (0.5 mole per mole of 2-naphthylamine hydrochloride), the product proved to be a 1,3-dihydroxy rather than a 1,3-diaminobenzo[*f*]quinazoline. Apparently, excess sodium dicyanamide must be present as a hydrochloric acid scavenger protecting the diamine from hydrolysis during prolonged reflux.

Although it led to lower yields in those instances where a direct comparison could be made, Method C was judged to have certain practical advantages over Method B as a general procedure. In Method B, temperature and length of heating of the bisarylbiguanide salt are of critical importance (8) and may vary from one compound to another. Thus, with the biguanide salt derived from 5-chloro-2-naphthylamine hydrochloride, for example, it was found that heating to the usual 250° caused extensive decomposition and charring. Acceptable yields of **2l** could be obtained only when the temperature was reduced to 210°. Furthermore, we observed that N^1,N^5-bis(2-naphthyl)biguanide salts vary considerably in ease of handling and purification, as exemplified by our consistent lack of success in the preparation of analytically pure, crystalline products from 5-chloro-, 5,6-dichloro-, or 5,7-dichloro-2-naphthylamine. In contrast to all other biguanides investigated in this work (Table IV), these three 5-chloronaphthyl compounds invariably gave gelatinous, discolored precipitates upon attempted crystallization from a variety of solvents.

A further complication in the use of Method B is that, while cyclization of N^1,N^5-bis(2-naphthyl)biguanide hydrochloride at 250° is rapid, the formation of high-melting by-products sometimes also occurs to a significant extent. These by-products, which can be separated readily from 1,3-diaminobenzo[*f*]quinazolines by virtue of their low solubility, appear to be naphthyl-substituted melamines or isomelamines on the basis of their physical properties and microanalytical data. They probably arise *via* thermal breakdown of the bisarylbiguanides to arylcyanamides, which are known to trimerize readily at elevated temperature (12). When the cyclization of N^1,N^5-bis(2-naphthyl)-biguanide salts is effected more slowly and at lower temperatures, as in Method C, the production of high-melting by-products is suppressed.

The fourth route to 1,3-diaminobenzo[*f*]quinazolines employed in this work was aromatization of the corresponding 5,6-dihydro derivatives (5) by treatment with selenium dioxide in refluxing glacial acetic acid (Equation 3). This technique, which had been used previously for the synthesis of 1,3-diaminobenzo[*f*]quinazoline (**2a**) (4), was carried out with a total of eight compounds; yields ranged from 12% for **2s** to 49% for **2t**, the average being about 25% (Table I, Method D). In some instances, incomplete aromatization resulted in considerable loss of material during product purification. However, since no attempt was made to define optimum dehydrogenation conditions for each compound, the yields reported probably do not represent maximum attainable values.



(Eq. 3)

A number of the substituted 2-naphthylamine derivatives reported here are new. They were prepared, in all instances, from the corresponding 2-naphthols *via* the Bücherer reaction. The 2-naphthols were on hand in our laboratory in the form of methyl ethers, which were intermediates in the synthesis of 2-tetralones (5,13). A typical procedure is presented in the Experimental Section, and the structures and physical constants of the products are summarized in Table III. For conversion into N^1,N^5-bis(2-naphthyl)biguanide salts, 2-naphthylamine hydrochlorides were stirred under reflux with the stoichiometric amount of sodium dicyanamide in 1-butanol for 10-30 minutes or in 2-methoxyethanol for 5 minutes. The products (Table IV) were readily identified by means of their reaction with copper ammonium sulfate reagent (14), which produced solid copper complexes possessing a characteristic deep purple color.

Infrared spectra (potassium chloride) of the 1,3-diaminobenzo[*f*]quinazolines (Table II) exhibited associated

TABLE I

Compound	R	Method (a)	Yield, %	M.p., °C	Formula	Analysis (b) C	H	N	Cl
2b	7-Me	C	16	245.5-247	$C_{13}H_{12}N_4$	69.62	5.39	24.98	
						69.41	5.58	24.79	
2c	8-Me	D	33	263-264	$C_{13}H_{12}N_4$	69.62	5.39	24.98	
						69.64	5.49	24.94	
2d	9-Me	C	33	216-218	$C_{13}H_{12}N_4$	69.62	5.39	24.98	
						69.63	5.39	24.99	
2e	7,8-Me_2	C	27	257-258.5	$C_{14}H_{14}N_4$	70.57	5.92	23.51	
						70.43	5.88	23.50	
2f	8-Et	D	17	196-197	$C_{14}H_{14}N_4$	70.57	5.92	23.51	
						70.34	6.01	23.35	
2g	8-*n*-Pr	C	26	200.5-201.5	$C_{15}H_{16}N_4$	71.40	6.39	22.21	
						71.40	6.41	22.29	
2h	8-*n*-Bu	C	38	194-195.5	$C_{16}H_{18}N_4$	72.15	6.81	21.03	
						72.19	6.68	20.95	
2i	8-*t*-Bu	C	37	270-272	$C_{16}H_{18}N_4$	72.15	6.81	21.03	
						72.28	6.90	21.07	
2j	8-*n*-Hex	C	11	187.5-188	$C_{18}H_{22}N_4$	73.43	7.53	19.03	
						73.56	7.59	19.00	
2k	8-(1-Ad)	C	33	308-310	$C_{22}H_{24}N_4$	76.71	7.02	16.27	
						76.51	7.18	16.40	
2l	7-Cl	B (c)	30	256-257	$C_{12}H_9ClN_4$	58.90	3.71	22.90	14.49
						58.86	3.74	22.90	14.58
2m	8-Cl	B	37	250-253	$C_{12}H_9ClN_4$	58.90	3.71	22.90	14.49
		C	18			58.64	3.76	22.77	14.82
		D	19						
2n	9-Cl	B	47	251-252	$C_{12}H_9ClN_4$	58.90	3.71	22.90	14.49
		C	21			58.68	3.71	22.97	14.69
2o	7,8-Cl_2	C	11	278-280	$C_{12}H_8Cl_2N_4$	51.63	2.89	20.07	
						51.90	2.88	19.60	
2p	7,9-Cl_2	D	23	296-298	$C_{12}H_8Cl_2N_4$	51.63	2.89	20.07	25.40
						51.57	3.08	20.05	25.29
2q	8,9-Cl_2	D	32	265-268	$C_{12}H_8Cl_2N_4$	51.63	2.89	20.07	25.40
						51.68	2.84	20.18	25.27
2r	8-Br	A	33	266-267	$C_{12}H_9BrN_4$	49.84	3.14	19.38	
		B	38			49.64	3.17	19.14	
2s	7-MeO	D	12	258-261	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	
						65.03	4.91	23.31	
2t	8-MeO	B	53	264-265	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	
		C	25			64.78	5.20	23.36	
		D	49						
2u	9-MeO	B	42	274-275	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	
		C	47			64.95	4.99	23.51	
		D	22						

(a) Method A: cyanamide/pyridine hydrochloride fusion; Method B: two-step bisarylbiguanide cyclization; Method C: one-step bisarylbiguanide cyclization; Method D: selenium dioxide dehydrogenation. (b) Calculated values (%) in upper row; found values (%) in lower row. (c) Cyclization performed at 210°, without purification of the intermediate biguanide.

TABLE II

Ultraviolet and Infrared Spectral Data

Compound	R	Ultraviolet λ_{max}^{EtOH}, mμ (ε x 10^{-3})				$\lambda_{max}^{pH\ 1\text{-}EtOH}$, mμ (ε x 10^{-3})				Infrared (a) λ_{max}^{KCl}, cm^{-1}
2a (b)	H	214	(23.6)	280	(15.4) (c)	217	(34.0)	341	(3.5)	3420, 3220, 1640, 1565,
		218	(23.7)	292	(11.0)	237	(24.2)	356	(3.2)	1515, 1490, 1470, 1440,
		250	(22.6) (c)	352	(3.0)	260	(27.7)			1420, 1405
		266	(44.0)	365	(2.9)	308	(6.1)			
2b	7-Me	216	(19.5)	297	(6.2) (c)	222	(26.0)	346	(3.7)	3490, 3390, 3230, 1640,
		237	(13.3)	310	(3.3) (c)	238	(20.5)	360	(3.4)	1560, 1505, 1495, 1470,
		252	(15.2)	357	(2.2)	264	(21.6)			1440, 1420
		270	(32.3)	370	(2.1)	317	(5.7)			
2c	8-Me (d)	239	(20.5) (c)	292	(13.6)	239	(14.8)	347	(2.2)	3570, 3450, 3230, 1650,
		250	(26.9) (c)	357	(3.7)	260	(19.3)	362	(2.2)	1610, 1560, 1545, 1515,
		266	(53.1)	372	(3.5)	310	(3.9)			1495, 1465, 1450, 1410
		282	(17.9) (c)							
2d	9-Me	267	(50.4)			217	(39.2)	341	(4.9)	3430, 3330, 3170, 1625,
		295	(11.8) (c)			238	(29.0)	355	(4.3)	1600, 1550, 1505, 1480,
		353	(3.4)			262	(34.0)			1450, 1430, 1400
		368	(3.4)			313	(8.1)			
2e	7,8-Me_2	234	(20.8)	310	(5.6)	217	(38.1)	352	(4.8)	3480, 3390, 3230, 1645,
		242	(24.2)	358	(3.6)	239	(33.1)	366	(4.6)	1620, 1560, 1510, 1460,
		250	(10.2)	373	(3.5)	263	(33.4)			1450, 1420
		270	(45.5)			317	(7.8)			
2l	7-Cl	225	(25.8)	358	(3.0)	240	(28.1)	345	(3.8)	3450, 3270, 1650, 1625,
		273	(41.7)	370	(2.8)	264	(27.7)	360	(3.8)	1560, 1495, 1470, 1430,
		299	(11.6)			314	(6.6)			1420
2m	8-Cl	223	(26.1)	304	(7.6) (c)	221	(38.5)	332	(2.0)	3640, 3505, 3390, 3170,
		267	(55.3)	360	(3.3)	241	(29.5)	348	(3.6)	1625, 1565, 1500, 1490,
		293	(16.4)	373	(3.2)	260	(41.3)	362	(3.7)	1470, 1440, 1410
						305	(6.3)			
2n	9-Cl	220	(29.4)	298	(13.3)	220	(41.8)	314	(8.1)	3710, 3510, 3390, 3190,
		269	(54.8)	354	(3.4)	242	(28.8)	339	(3.9)	1660, 1625, 1550, 1470,
		286	(17.4) (c)	367	(3.4)	263	(32.7)	354	(3.8)	1430
2o	7,8-Cl_2	225	(23.5)	298	(15.3)	226	(32.7)	311	(6.6)	3450, 3220, 1620, 1590,
		240	(21.4)	363	(2.6)	243	(33.3)	348	(3.1)	1550, 1490, 1445, 1425,
		273	(42.0)	378	(2.5)	263	(34.8)	365	(3.2)	1400
2p	7,9-Cl_2	222	(25.3) (c)	304	(14.3)	227	(38.4)	320	(8.3)	3450, 3225, 1650, 1620,
		230	(28.1)	360	(3.0)	245	(28.6)	343	(4.0)	1550, 1495, 1460, 1420,
		276	(51.6)	373	(3.1)	268	(31.9)	358	(3.8)	1400
2q	8,9-Cl_2	227	(29.6)	360	(3.5)	223	(41.3)	312	(7.1)	3700, 3510, 3450, 3220,
		270	(60.4)	374	(3.5)	245	(31.8)	346	(3.4)	1670, 1625, 1585, 1550,
		299	(16.9)			264	(41.4)	361	(3.6)	1485, 1460, 1440, 1410
2s	7-MeO	235	(24.3)	323	(6.7)	222	(30.8)	280	(18.9) (c)	3390, 3170, 1650, 1610,
		253	(21.6)	353	(3.5)	238	(35.1)	328	(5.8)	1560, 1515, 1500, 1455,
		275	(39.7)	366	(3.3)	270	(24.3)	358	(5.8)	1430, 1420
		285	(25.3) (c)							
2t	8-MeO	264	(51.3)			237	(25.3)	357	(3.9) (c)	3570, 3450, 3390, 3220,
		292	(14.3) (c)			259	(42.4)	368	(3.8)	1640, 1610, 1560, 1515,
		366	(4.0)			280	(14.6) (c)			1490, 1460, 1440
		380	(4.0)			305	(6.5) (c)			
2u	9-MeO	244	(20.8)	319	(5.5)	236	(30.0)	335	(9.0)	3510, 3390, 3180, 1655,
		272	(41.0)	347	(4.8)	267	(25.0)	348	(8.2)	1625, 1550, 1470, 1425,
		289	(16.4)	362	(4.1)					1400

(a) Significant peaks appearing between 3700 cm^{-1} and 1400 cm^{-1}. (b) Reference (7). (c) Inflection. (d) Other 8-alkyl derivatives (compounds **2f-2s** Table I) showed essentially the same ultraviolet absorption maxima as **2c**.

TABLE III

Compound	M.p., °C	Formula	Calcd., % C	H	N	Found, % C	H	N
5-Methyl-2-naphthylamine	(a)	$C_{11}H_{11}N$	84.03	7.06	8.91	84.12	6.91	8.82
5,6-Dimethyl-2-naphthylamine	(b)	$C_{12}H_{13}N$	84.17	7.65	8.18	84.27	7.65	8.20
6-*n*-Propyl-2-naphthylamine	70-72	$C_{13}H_{15}N \cdot \frac{1}{4}H_2O$	82.27	8.23	7.38	82.24	8.46	7.36
6-*n*-Butyl-2-naphthylamine	70-72	$C_{14}H_{17}N$	84.37	8.59	7.02	84.34	8.74	7.14
6-*t*-Butyl-2-naphthylamine	72-74	$C_{14}H_{17}N$	84.37	8.59	7.02	84.25	8.65	7.00
6-*n*-Hexyl-2-naphthylamine	82-84	$C_{16}H_{21}N$	84.52	9.31	6.16	84.31	9.30	6.09
6-(1-Adamantyl)-2-naphthylamine	146-148	$C_{20}H_{23}N$	86.60	8.36	5.05	86.46	8.75	4.57
6-Bromo-1-cyano-2-naphthylamine	171-172	$C_{11}H_7BrN_2$ (c)	53.46	2.86	11.34	53.35	2.78	11.50

(a) B.p. 160-170° (0.005 mm). (b) B.p. 118-119° (0.05 mm). (c) Br: Calcd. 32.34; Found, 32.17.

TABLE IV

Compound	R	M.p., °C	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
5a·HCl	H	256-257	$C_{22}H_{19}N_5 \cdot HCl$	67.77	5.17	17.96	9.10	67.95	5.18	17.89	8.97
5a	H	173 (a)	$C_{22}H_{19}N_5$	74.76	5.42	19.82		74.59	5.63	19.81	
5b·HCl	6-Cl	264-265	$C_{22}H_{17}Cl_2N_5 \cdot HCl$	57.69	3.95	15.27		57.73	3.95	15.00	
5c·HCl	7-Cl	273.5-274	$C_{22}H_{17}Cl_2N_5 \cdot HCl$	57.59	3.95	15.27		57.68	3.93	15.40	
5d·HCl	6-Br	269-271	$C_{22}H_{17}Br_2N_5 \cdot HCl$	48.24	3.31	12.79		47.88	3.28	12.59	
5d	6-Br	195-197	$C_{22}H_{17}Br_2N_5$	51.68	3.35	13.70		52.13	3.19	13.77	
5e·HCl	6-MeO	274-275.5	$C_{24}H_{23}N_5O_2 \cdot HCl$	64.09	5.33	15.57	7.89	64.25	5.44	15.33	7.89
5f·HCl	7-MeO	252-253	$C_{24}H_{23}N_5O_2 \cdot HCl$	64.09	5.33	15.57	7.89	64.34	5.76	15.35	8.02

(a) Lit. (19), m.p. 175-177°.

TABLE V

Substituent Effects on Ultraviolet Absorption Spectra of 1,3-Diaminobenzo[*f*]quinazolines

Compound	Substituent	$\Delta\lambda_{max}^{EtOH}$, 266 mμ	$\Delta\lambda_{max}^{EtOH}$, 266 mμ	$\Delta\lambda_{max}^{EtOH}$, 266 mμ
2b	7-Me	+4	+5	+5
2c	8-Me	0	+5	+7
2d	9-Me	+1	+1	+3
2l	7-Cl	+7	+6	+5
2m	8-Cl	0	+8	+8
2n	9-Cl	+3	+2	+2
2s	7-MeO	+9	+1	+1
2t	8-MeO	-2	+14	+15
2u	9-MeO	+6	-5	-3

N-H bands in the 3170-3230 cm^{-1} and 3390-3450 cm^{-1} regions (symmetric and asymmetric stretching modes, respectively), and in some instances weaker bands at 3500-3700 cm^{-1} (nonassociated N-H). Characteristic multiple peaks were present in the 1400-1660 cm^{-1} region, of which the most prominent were generally at 1640-1660 cm^{-1} and 1550-1575 cm^{-1}.

Ultraviolet spectral data for a representative number of 1,3-diaminobenzo[*f*]quinazolines are given in Table II. In 95% ethanol solution, the principal absorption maxi-

mum for all the compounds studied occurred at 266-276 mμ, with one or two peaks or shoulders of medium intensity in the 285-325 mμ region and two weaker peaks in the 350-380 mμ region. In some instances, up to three additional maxima were also observed in the low wavelength region. Spectra taken at *p*H 1 in ethanol showed the hypsochromic displacements expected for compounds possessing a 2,4-diaminopyrimidine structure. The principal absorption band at 266-276 mμ underwent a hypsochromic shift of 5-10 mμ, whereas the low intensity peaks in the 350-380 mμ region were displaced to lower wavelengths by 10-15 mμ. In nearly every instance, the intensity of the principal peak was attenuated at *p*H 1, whereas that of the long-wavelength maxima was increased.

Detailed inspection of the ultraviolet spectral data revealed interesting substituent effects which have been summarized in Table V. Shown in this tabulation are methyl, chloro, and methoxy substituent shifts, relative to the parent compound, **2a**, at three selected wavelengths. The data given are only for spectra taken in ethanol solution, but very similar effects were noted at *p*H 1 as well. In general, substitution at the 7- and 9-position produced a bathochromic shift in the 266 mμ peak of **2a**, whereas substitution at the 8-position caused no effect or a slight hypsochromic shift. The magnitude of the substituent effect for this peak tended to vary in the order MeO > Cl > Me. Displacements of the 352 and 365 mμ peaks of **2a**, on the other hand, followed a different and less regular pattern. In this instance, substitution at the 8-position, especially by a methoxy group, led to maximum bathochromic displacement, whereas methyl and chloro substitution caused a moderate bathochromic shift at the 7-position and no effect at the 9-position. Methoxy substitution at the 7- and 9-position produced no effect or a small hypsochromic shift.

Analysis of the data in Table V showed substituent effects in this series to be additive. For example, on the basis of shifts observed with compounds **2l** and **2m**, it was calculated that **2o** should exhibit maxima at 274, 366, and 378 mμ in ethanol solution. The actual peaks at 273, 363, and 378 mμ (Table IV) were in close agreement with the calculated values. By the same process, maxima were predicted at 276, 360, and 372 mμ for **2p** (observed: 276, 360, and 373 mμ) and at 269, 362, and 375 mμ for **2q** (observed: 270, 360, and 374 mμ). Equally good correlations were found in the *p*H 1 spectra of these compounds, and also in the 95% ethanol and *p*H 1-ethanol spectra of the monomethyl and dimethyl derivatives, **2b**, **2c**, and **2e**. However, attempts to correlate the spectral data in terms of various Hammett or Taft σ constants as reported recently for 2,4-diaminopyrimidines by Roth and Strelitz (15) gave negative results.

Many of the 1,3-diaminobenzo[*f*]quinazolines reported in this and the previous paper (5) have been subjected to biological evaluation in a variety of experimental test systems, including antimetabolite, antimalarial, and antitumor assays (16,17). The results of these investigations are summarized in a recent paper (18).

EXPERIMENTAL (20)

A. Synthesis of 2-Naphthylamines.

1. 6-Bromo-1-cyano-2-naphthylamine.

A mixture of 2-acetamido-1,6-dibromonaphthalene (9) (10 g., 0.029 mole) and cuprous cyanide (2.9 g., 0.032 mole) in *N*,*N*-dimethylformamide (39 ml.) was stirred under reflux for 4 hours and allowed to stand at room temperature for 19 hours. The nearly solid mass was triturated with 10% sodium cyanide solution (200 ml. total) and filtered, and the filter cake was washed with water and dissolved in 95% ethanol (1100 ml.). Treatment with decolorizing carbon and concentration under reduced pressure afforded 6.2 g. (73% yield) of 2-acetamido-6-bromo-1-cyanonaphthalene. Direct hydrolysis of this compound (8.7 g., 0.03 mole) in boiling 1 *N* sodium hydroxide (880 ml.) for 15 minutes and crystallization from 95% ethanol (decolorizing carbon) gave the amine (5.6 g., 75% yield).

2. Bücherer Reactions.

a. Example 1. 5-Methyl-2-naphthylamine.

Fuming hydrobromic acid (100 ml.) was added to a solution of 2-methoxy-5-methylnaphthalene (5) (66 g., 0.38 mole) in glacial acetic acid. After being stirred under reflux for 4 hours, the mixture was poured into ice, and the crude 5-methyl-2-naphthol, m.p. 100-105°, was treated directly with ammonium sulfite (250 g., 2.2 moles) in concentrated ammonium hydroxide (400 ml.) in a stainless steel autoclave at 180-190° for 48 hours. The mixture was filtered and the solid rinsed thoroughly with water, dried, and dissolved in dichloromethane. Saturation of the solution with dry hydrogen chloride gas gave 28 g. (38% yield based on 2-methoxy-5-methylnaphthalene) of amine hydrochloride as a gray solid, m.p. 240-245° dec. Neutralization of the salt with ammonia liberated the free base as an oil. Vacuum distillation afforded analytically pure product in the form of a pale yellow oil which turned red rapidly upon exposure to air and light.

b. Example 2. 6-*n*-Butyl-2-naphthylamine.

6-*n*-Butyl-2-naphthol (5) (116 g., 0.58 mole), anhydrous ammonium sulfite (232 g., 2 moles), and concentrated ammonia (1160 ml.) were heated in a stainless steel autoclave at 180° for 48 hours. The amine hydrochloride (54 g., 39% yield) was a grayish-white solid, m.p. 230-235° dec. Treatment of the salt (2 g.) in water (400 ml.) with 40% sodium hydroxide (5 ml.), followed by crystallization from 95% ethanol (decolorizing carbon), gave the free base in the form of pale pink flakes. The analytical sample was dried at 30° for 48 hours.

B. Synthesis of Bisarylbiguanide Salts.

1. Example 1. N^1,N^5-Bis(2-naphthyl)biguanide Hydrochloride (**5a**·Hydrochloride).

Sodium dicyanamide (21,22) (7.1 g., 0.08 mole) was added to a suspension of 2-naphthylamine hydrochloride (29 g., 0.16 mole) in 2-methoxyethanol (200 ml.). After being stirred under reflux for 5 minutes, the mixture was cooled, diluted with ether (200 ml.), and filtered. The ethanol-washed and ether-rinsed solid (22 g., 71% yield) was purified by repeated crystallization from large

volumes of 0.03 *N* hydrochloric acid (decolorizing carbon). The free base, **5a**, was liberated by treatment of **5a**·hydrochloride with 1 *N* sodium hydroxide and crystallization from 95% ethanol.

2. Example 2. N^1,N^5-Bis(6-bromo-2-naphthyl)biguanide Hydrochloride (**5d**·Hydrochloride).

Sodium dicyanamide (6.9 g., 0.078 mole) was added to a suspension of 6-bromo-2-naphthylamine hydrochloride (23) (41 g., 0.16 mole) in 1-butanol (350 ml.). After being refluxed for 10 minutes, the mixture was cooled, diluted with ether (250 ml.), and filtered. The ethanol-washed and ether-rinsed product (32 g., 73% yield) was purified for analysis by repeated crystallization from aqueous *N*,*N*-dimethylformamide (decolorizing carbon). Treatment of **5d**·hydrochloride (1 g.) with 1 *N* sodium hydroxide (30 ml.) and crystallization from 95% ethanol gave the free base (0.56 g., 60% yield).

C. Synthesis of 1,3-Diaminobenzo[*f*]quinazolines.

1. Cyanamide-Pyridine Hydrochloride Fusion (Table I, Method A).

a. 1,3-Diamino-8-bromobenzo[*f*]quinazoline (**2r**).

A mixture of 6-bromo-1-cyano-2-naphthylamine (5.4 g., 0.022 mole), crystalline cyanamide (24) (5.4 g., 0.13 mole), and pyridine hydrochloride (23 g., 0.18 mole) was heated by means of an oil bath maintained at 175°. After an initial increase to 148°, the internal temperature of the reaction mixture gradually decreased to 132° over a twenty minute period. The semisolid mass was cooled to 80°, triturated with 95% ethanol (100 ml.) and filtered. Digestion of the ethanol- and ether-washed product with boiling water (3000 ml. total), basification of the combined aqueous digests with 10% sodium carbonate, and crystallization of the gelatinous precipitate from 95% ethanol (decolorizing carbon) gave **2r** (21 g., 33% yield). Analytically pure, colorless material was obtained by vacuum sublimation at 190-200° (0.1 mm).

2. Two-Step Bisarylbiguanide Cyclization (Table I, Method B).

a. Example 1. 1,3-Diamino-9-chlorobenzo[*f*]quinazoline (**2n**).

A rapidly stirred mixture of **5c**·hydrochloride (2.8 g., 0.0061 mole) in diphenyl ether (80 ml.) was heated to 250°, and maintained at 248-250° (internal) for 2.5 minutes. Dilution of the cooled mixture with 1:1 ethanol-ether (100 ml.) gave an off-white solid which was digested with several portions of boiling water (500 ml. total). Basification of the filtered digest to *p*H 10 with 10% sodium carbonate gave **2n** (0.48 g., 47% yield). Analytically pure, colorless needles were obtained after three crystallizations from 95% ethanol.

b. Example 2. 1,3-Diamino-8-methoxybenzo[*f*]quinazoline (**2t**).

A rapidly stirred mixture of **5e**·hydrochloride (5 g., 0.011 mole) in diphenyl ether (125 ml.) was heated to 250°. After 2 minutes at 248-251° (internal), the mixture was cooled, diluted with ether (125 ml.) and filtered. The greenish-gray solid (2.5 g.) was washed free of diphenyl ether with generous portions of ether, and then digested with boiling water (2 x 50 ml.) containing a trace of hydrochloric acid. Basification of the filtered digest to *p*H 10 with sodium carbonate afforded a greenish yellow solid (1.4 g., 53% yield). Analytically pure **2t** was obtained in the form of pale yellow prisms after two crystallizations from 95% ethanol (decolorizing carbon).

3. One-Step Bisarylbiguanide Cyclization (Table I, Method C).

a. Example 1. 1,3-Diamino-8-chlorobenzo[*f*]quinazoline (**2m**).

A mixture of 6-chloro-2-naphthylamine hydrochloride (25) (25 g., 0.11 mole), sodium dicyanamide (25 g., 0.28 mole), and 1-octanol (500 ml.) was stirred under reflux for 18 hours and filtered while hot. Washing of the solid with dichloromethane (600 ml.), digestion with boiling water (1000 ml.), and crystallization from 95% ethanol afforded 2.5 g. of **2m** directly. Filtration of the combined 1-octanol filtrate and dichloromethane wash after refrigeration yielded another 1.1 g. Finally, passage of dry hydrogen chloride gas through the 1-octanol and dichloromethane mother liquor for 15 minutes, digestion of the precipitated **2m**·hydrochloride with boiling water (2500 ml.), and basification of the digest to *p*H 12 with 40% sodium hydroxide (40 ml.) yielded an additional 1.2 g. The total yield of **2m** in this experiment was 4.8 g. (18%). The analytical sample was prepared by vacuum sublimation at 185° (0.01 mm).

b. Example 2. 1,3-Diamino-7,8-dichlorobenzo[*f*]quinazoline (**2o**).

Sodium dicyanamide (17 g., 0.2 mole), 5,6-dichloro-2-naphthylamine hydrochloride (25) (20 g., 0.08 mole), and 1-octanol (400 ml.) were stirred under reflux for 36 hours. The hot reaction mixture was filtered, the solid was washed with dichloromethane (400 ml.), the wash solution was combined with the 1-octanol mother liquor, and ether (500 ml.) was added. Upon addition of concentrated hydrochloric acid (20 ml.), a solid (14 g.) consisting of **2o**·hydrochloride and some unreacted 5,6-dichloro-2-naphthylamine hydrochloride was deposited. This was digested with boiling water (4 x 1500 ml.) and 0.1 *N* hydrochloric acid (1000 ml.), and the combined aqueous digests were basified with sodium carbonate (37 g.). Filtration of the solid and washing with ether (100 ml.) to effect complete removal of unreacted 5,6-dichloro-2-naphthylamine furnished 2.5 g. (11% yield) of pure **2o**. Repeated vacuum sublimation at 190° (0.1 mm) provided the analytical specimen.

4. Selenium Dioxide Dehydrogenation (Table I, Method D).

a. Example 1. 1,3-Diamino-8-ethylbenzo[*f*]quinazoline (**2f**).

A mixture of 1,3-diamino-8-ethyl-5,6-dihydrobenzo[*f*]quinazoline (5) (6.1 g., 0.025 mole) and selenium dioxide (2.8 g., 0.025 mole) in glacial acetic acid (240 ml.) was stirred under reflux for 18 hours, filtered through a Celite pad while hot, and concentrated to dryness under reduced pressure. The residue was washed with water and digested with 1 *N* hydrochloric acid (four portions totaling 870 ml.). Overnight refrigeration of the combined acid digests gave crystals of **2f**·hydrochloride (3.2 g., 47% yield). This material was re-dissolved in water (1200 ml.), the solution was decolorized with charcoal, and the *p*H was adjusted to 10 with 40% sodium hydroxide (20 ml.). The free base (1.1 g., 17% yield) was obtained in analytically pure state by crystallization from 95% ethanol.

b. Example 2. 1,3-Diamino-7,9-dichlorobenzo[*f*]quinazoline (**2p**).

A mixture of 1,3-diamino-7,9-dichloro-5,6-dihydrobenzo[*f*]-quinazoline (5) (9 g., 0.032 mole), selenium dioxide (3.6 g., 0.032 mole), and glacial acetic acid (300 ml.) was refluxed with stirring for 18 hours and filtered while hot, and the filtrate allowed to stand until precipitation occurred. The solvent was partly evaporated and the solid filtered, washed with water, and digested repeatedly with boiling water. The insoluble material consisted of 4 g. of crude **2p**. Basification of the cold water wash with sodium hydroxide afforded another 1.3 g. Repeated crystallization of these crops from 95% ethanol (decolorizing carbon) furnished **2p** in the form of a beige powder (2.1 g., 23% yield). Vacuum sublimation at 210° (0.01 mm) was required for the preparation of the analytical sample.

c. Example 3. 1,3-Diamino-8,9-dichlorobenzo[*f*]quinazoline (**2q**).

A mixture of 1,3-diamino-8,9-dichloro-5,6-dihydrobenzo[*f*]-quinazoline (5) (4.7 g., 0.017 mole), selenium dioxide (1.7 g., 0.019 mole), and glacial acetic acid (200 ml.) was refluxed with stirring for 18 hours. Dilution of the charcoal-treated filtrate with water (1000 ml.), basification with concentrated ammonia, and repeated crystallization from 95% ethanol gave **2q** (1.5 g., 32% yield).

d. Example 4. 1,3-Diamino-7-methoxybenzo[*f*]quinazoline (**2s**).

A mixture of 1,3-diamino-5,6-dihydro-7-methoxybenzo[*f*]-quinazoline (5) (6.9 g., 0.029 mole), selenium dioxide (3.2 g., 0.029 mole), and glacial acetic acid (300 ml.) was stirred under reflux for 20 hours and filtered while hot. The filtrate was diluted with water (700 ml.) and basified to *p*H 10 with concentrated ammonia. The filtered solid was digested with boiling 1 *N* hydrochloric acid (4 x 250 ml.), and the combined digests were treated with decolorizing carbon and refrigerated until crystals of **2s**·hydrochloride were formed. Treatment of this material with base and crystallization from 95% ethanol (decolorizing carbon) furnished the free base (0.8 g., 12% yield).

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