Analogs of 3-Amino-7-chloro-1,2,4-benzotriazine 1-Oxide as Antimalarial Agents[1]

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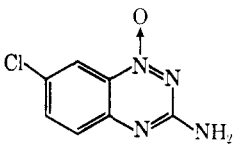
A series of substituted 1,2,4-benzotriazines, quinazolines, quinoxalines, quinolines, and other related heterocycles has been prepared for evaluation as antimalarial agents. Substituent patterns of candidate compounds were chosen to provide maximum steric resemblance to 3-amino-7-chloro-1,2,4-benzotriazine 1-oxide, a known antimalarial compound. Slight favorable effects against experimental *Plasmodium berghei* infections in mice were noted, but significant activity was not encountered. When assayed *in vitro*, five of the compounds were inhibitory to a series of eight other microorganisms.

A revival of interest in malaria chemotherapy has resulted from the emergence of strains of *Plasmodium falciparum* that are resistant to some or all of the synthetic drugs in current use.[2] To avoid cross-resistance, it is desirable that the structures of new candidate antimalarials differ significantly from those of antimalarials now in use. Thus, there is renewed interest in reexamining old leads with novel structures that were dropped when the currently used drugs were developed. This paper reports a structure–activity study on a group of compounds derived from such a known lead, the antimalarial benzotriazines.

In 1954 Wolf and co-workers[3] reported that the title compound, **1**, protected chicks against *Plasmodium*



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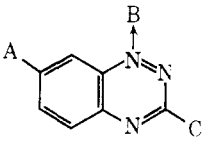
gallinaceum infection when incorporated in their diet at 0.01% or higher. The corresponding desoxy compound (**2**, Table I) and the bromo and iodo analogs were equally effective. Analogs were inactive when the halogen was absent, present in another ring position, or replaced by methyl or methoxy groups. Coatney and associates[4] found that **2** was effective at 4 mg/kg in a somewhat different *P. gallinaceum* assay, although in this work the compound was toxic at 20 mg/kg. In a second paper on benzotriazines,[5] Wolf, *et al.*, reported a series of substituted derivatives of **1** in which various alkyl and aryl groups were attached to the 3-amino function. All such substitutions produced inactive or much less active compounds.

In the present study, this prior work was extended in two ways. Additional benzotriazines bearing new substituents in the benzo ring were prepared after the title compound (**1**) and its desoxy derivative (**2**) had been resynthesized. The second type of modification involved replacement of one or two of the triazine ring nitrogens of **2** with carbon, thus giving different heterocyclic ring systems that retained the chloro and amino functions in the same steric relationship. Other heterocyclic ring systems only approximately derivable by this logic were also prepared.

TABLE I

1,2,4-BENZOTRIAZINES. CHEMICAL AND BIOLOGICAL DATA



No.	A	B	C	Ref for prepn or mp, °C[a]	Antimalarial act. (toxicity deaths)[b] 40	160	640
1	Cl	O	NH_2	*c*	0.4	1.4	3.8 (1.5)
2	Cl		NH_2	*c*	0.0	0.0	0.2
3	H	O	NH_2	*d*	0.0	0.4	0.6
4	H		NH_2	*d*	0.5	0.9 (2/5)	(5/5)
5	H	O	$NHCOCH_3$[e]	190–191	0.5	0.7	(5/5)
6	Cl	O	OH	*f*	0.7	1.2	(5/5)
7	Cl		OH	*g*	1.0	2.3 (2/5)	(5/5)
8	Cl	O	Cl	*h*	1.7	2.7 (2/5)	(5/5)
9	NO_2	O	NH_2	*i*	0.0	0.2	0.2
10	C_6H_5	O	NH_2	>275	0.7[j]	0.7	0.7
Quinine					1.2	3.4	6.5
Chloroquine					4.6	10.0	(5/5)

[a] Where a melting point is given, the compound has not been described previously. [b] Results are expressed as increase of survival time (days) of treated mice (at dosages of 40, 160, and 640 mg/kg) beyond that of untreated controls. See ref 18 for a complete description of the test procedure. [c] Reference 3. [d] F. Arndt, *Chem. Ber.*, **46**, 3522 (1913). [e] *Anal.* ($C_9H_8N_4O_2$) C, H, N. [f] Reference 5. [g] Merck and Co., U. S. Patent 2,489,357 (1947). [h] Merck and Co., U. S. Patent 2,489,489 (1949). [i] Prepared by a modification of the procedure described in ref 22; see Experimental Section. [j] Tested at 20, 80, and 320 mg/kg. *Anal.* ($C_{13}H_{10}N_4O$) C, H, N.

Chemistry.—The 1,2,4-benzotriazines (Table I) were prepared from derivatives of *o*-nitroaniline by the known procedures, or minor modifications thereof, that are cited in Table I or in the Experimental Section.

The monoamino quinazolines (**11–13**, **17**, Table II) were prepared by condensation of *o*-aminobenzaldehydes with guanidine hydrochloride in the presence of sodium carbonate and decalin after the method of Tsuda, *et al.*[6] We found that this procedure does not require the pure substituted *o*-aminobenzaldehyde; the polymers to which these compounds spontaneously de-

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This paper is Contribution No. 352 from the Army Research Program on Malaria.

(2) Some leading references: (a) Resistance of Malaria Parasites to Drugs, Report of a WHO Scientific Group, *World Health Organ. Tech. Rept. Ser.*, **296**, 1 (1965); (b) C. G. Huff, *Military Med.*, **131**, 505 (1966); (c) R. D. Powell, *Clin. Pharmacol. Therap.*, **7**, 48 (1966); (d) L. J. Legters, D. K. Wallace, R. D. Powell, and S. Pollack, *Military Med.*, **130**, 168 (1965); (e) P. J. Bartelloni, F. W. Sheehy, and W. D. Tigertt, *J. Am. Med. Assoc.*, **199**, 141 (1967).

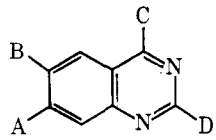
(3) F. J. Wolf, K. Pfister, 3rd, R. M. Wilson, and C. A. Robinson, *J. Am. Chem. Soc.*, **76**, 3551 (1954).

(4) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, Washington, D. C., 1953, p 207.

(5) F. J. Wolf, R. M. Wilson, Jr., K. Pfister, 3rd, and M. Tishler, *J. Am. Chem. Soc.*, **76**, 4611 (1954).

(6) K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, and T. Miyadera, *Chem. Pharm. Bull.* (Tokyo), **10**, 863 (1962).

TABLE II
QUINAZOLINES. CHEMICAL AND BIOLOGICAL DATA



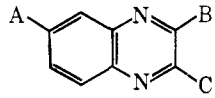
No.	A	B	C	D	Ref for prepn or mp, °C[a]	Antimalarial act. (toxicity deaths)[b] 40	160	640
11	H	H	H	NH_2	*c*	0.1	0.3	0.3
12	H	F	H	NH_2	241–243[d]	0.1	0.1	0.1
13	H	Cl	H	NH_2	258–259 dec[e]	0.3	0.3	0.5
14	H	Cl	NH_2	NH_2	268–273 dec[f]	0.5	0.7	4.9 (3/5)
						0.2	0.6	2.8 (4/5)
15	H	Cl	OH	OH	*g*			
16	H	Cl	Cl	Cl	*g*	0.1	0.1	0.1
17	Cl	Cl	H	NH_2	>275 dec[h]	0.1	0.1	0.3

[a,b] See corresponding footnotes of Table I. [c] M. J. S. Dewar, *J. Chem. Soc.*, 619 (1944). [d] *Anal.* ($C_8H_6FN_3$) C, H, N. [e] *Anal.* ($C_8H_6ClN_3$) C, H, N. [f] *Anal.* ($C_8H_7ClN_4 \cdot H_2O$) C, H, Cl, N. [g] Reference 12. [h] *Anal.* ($C_8H_5Cl_2N_3$) C, H, N.

grade[7,8] provided the 2-aminoquinazolines nearly as well. Diaminoquinazoline **14** has been cited several times in the literature,[9-11] but data on method of synthesis or characterization were not provided. Compound **14** was readily obtained by treatment of 2,4,6-trichloroquinazoline[12] (**16**) with ammonia in a sealed tube at 150°.

Compound **18** (Table III), a quinoxaline analog of **2**, was prepared *via* known precursors **19** and **20**.[13] The aminoquinolines of Table IV were also prepared from known chloro precursors.[14]

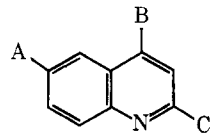
TABLE III
QUINOXALINES. CHEMICAL AND BIOLOGICAL DATA



No.	A	B	C	Ref for prepn or mp, °C[a]	Antimalarial act.[b] 40	160	640
18	Cl	H	NH_2	213–217 dec[c]	0.7	0.9	1.1
19	Cl	H	Cl	*d*	0.7	1.1	2.1
20	Cl	$CONHCONH_2$	OH	*d*	1.2	1.4	1.8

[a,b] See corresponding footnotes of Table I. [c] *Anal.* ($C_8H_6ClN_3$) C, H, N. [d] Reference 13.

TABLE IV
QUINOLINES. CHEMICAL AND BIOLOGICAL DATA



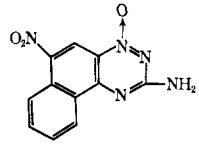
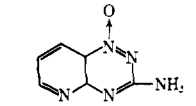
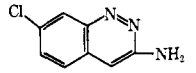
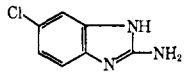
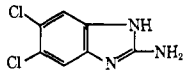
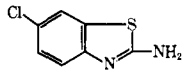
No.	A	B	C	Ref for prepn or mp, °C[a]	Antimalarial act. (toxicity deaths)[b] 40	160	640
21	Cl	H	NH_2	*c*	0.4	(5/5)	(5/5)
22	Cl	H	Cl	*d*	0.1	0.1	0.1
23	Cl	Cl	H	*d*	0.1	0.1	0.1
24	Cl	NH_2	H	*c*	0.3	0.5	0.9 (3/5)

[a,b] See corresponding footnotes of Table I. [c] See Experimental Section. [d] Reference 14.

(7) A. Albert and H. Yamamoto, *J. Chem. Soc., B*, 956 (1966).
(8) L. Smith and J. Opie, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 58.
(9) E. Falco, L. Goodwin, G. Hitchings, I. Rollo, and P. Russell, *Brit. J. Pharmacol.*, **6**, 185 (1951).
(10) G. Hitchings, *Trans. N. Y. Acad. Sci.*, **23**, 700 (1961).
(11) Wellcome Foundation Ltd., British Patent 806,772 (1958); *Chem. Abstr.*, **53**, 4675 (1959).

Table V gives data on miscellaneous heterocycles that were prepared for this study. Compounds **25** and **26** were obtained by base-catalyzed ring closure of 1-guanidino-2,4-dinitronaphthalene and 2-guanidino-3-nitropyridine, respectively. Compound **26**, known from the patent literature,[15] served as a model for an unsuccessful attempt to prepare an isomer where the pyridine ring nitrogen occupies the position corresponding to that bearing the chlorine in **1**. This attempt failed when it was found impossible to replace the chloro of 3-nitro-4-chloropyridine with guanidino, a reaction analogous to that which easily provided the guanidino precursor to **26**.[16] Cinnoline **27** was prepared from 2-amino-4-chlorobenzaldehyde and nitromethane according to the procedure of Baumgarten, *et al.*[17] Standard methods provided the other compounds listed in Table V.

TABLE V
MISCELLANEOUS NITROGEN HETEROCYCLES. CHEMICAL AND BIOLOGICAL DATA

No.	Structure	Ref for prepn or mp, °C[a]	Antimalarial act. (toxicity deaths)[b] 40	160	640
25		291–292 dec[c]	0.4	0.4	1.0
26		*d*	0.0	0.0	0.6
27		*e*	0.3	0.5	0.7
28		*f*	0.2	0.2	(5/5)
29		260–262 dec[g]	0.3	0.3	0.7
30		*h*	0.2	0.8 (2/5)	(5/5)

[a,b] See corresponding footnotes of Table I. [c] *Anal.* ($C_{11}H_7N_5O_3$) C, H, N. [d] Reference 15. [e] Reference 17. [f] N. J. Leonard, D. Y. Curtin, and K. M. Beck, *J. Am. Chem. Soc.*, **69**, 2459 (1947). [g] Prepared according to the general procedure described in footnote *f*; see Experimental Section. [h] P. N. Bhergava and B. F. Baliga, *J. Indian. Chem. Soc.*, **35**, 807 (1958).

Bioassay Results.—Compounds were tested against lethal, blood-induced *Plasmodium berghei* infections in mice as part of the Walter Reed Army Institute of Research malaria program.[18] Tables I–V summarize testing data on the compounds examined in this study. Quinine and chloroquine are included for comparison.

The lead benzotriazines (**1** and **2**, Table I), although of equivalent effect in the original work with *P. gal-*

(12) F. Curd, J. Landquist, and F. Rose, *J. Chem. Soc.*, 1762 (1948).
(13) H. G. Petering and G. J. Van Giessen, *J. Org. Chem.*, **26**, 2820 (1961).
(14) G. B. Bachman and D. E. Cooper, *ibid.*, **9**, 308 (1944).
(15) Abbott Laboratories, British Patent 989,397 (1963).
(16) Abbott Laboratories, German Patent 1,200,301 (1963).
(17) H. E. Baumgarten, D. L. Pedersen, and M. W. Hunt, *J. Am. Chem. Soc.*, **80** 1978 (1958).
(18) Thanks are due to Dr. David P. Jacobus for providing test results from this program. The bioassays were performed by Dr. Leo Rane of the University of Miami. For a description of the test, see F. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

linaceum,[3] acted quite differently in the *P. berghei* test employed in this work. The N-oxide (**1**) provided moderate prolongation of survival time at the 640 mg/kg dose level, but the desoxy compound (**2**) was completely inactive. Slight activity appeared to be present in two other benzotriazines (**7** and **8**), but these were also quite toxic. The remaining members of this class were inactive and/or toxic. One quinazoline (**14**, Table II) was significantly active, but only at a toxic level. This compound was reported previously to have a slight protective effect in a different *P. berghei* assay[9] and is a known folic acid antagonist in bacterial systems.[10]

The quinoxaline group (Table III) appeared to give slight protection without toxicity. None of the quinolines or miscellaneous heterocycles (Table IV and V) had an appreciable antimalarial effect. The quinoline analog of **2**, compound **21**, was notably toxic.

Several of these compounds (**2**, **11**, **17**, **20**, **28**) were assayed for antischistosomal activity as well. They did not prolong the survival time of mice infected with lethal numbers of *Schistosoma mansoni* cercariae.[19]

All of the compounds listed in the tables also were submitted to *in vitro* screening against eight microorganisms. Those showing appreciable inhibitory activity in a paper-disk, agar-diffusion assay were further examined by a serial, tenfold, tube dilution technique.[20] Table VI presents results from the latter assay on compounds showing appreciable activity. Moderate, broad-spectrum activity was fairly common in the series, compound **8** being the most potent. Diaminoquinazoline **14**, the known folic acid antagonist,[10] displayed inhibitory action, as expected. The structural similarity of the compounds suggests that all might be acting by folic acid inhibition.

TABLE VI

In Vitro ANTIMICROBIAL ACTIVITY[a]

	Min inhib concn, μg/ml						
Compd	SA[b]	EC	SM	KA	SC	PN	SS
8	10	10	10	10	1	0.1	0.1
14	100	100	10	1000	100	1000	10
21	100	1000	1000	1000	100	10	100
29	100	100	100	100	1000	1000	100
30	1000	1000	100	1000	100	100	100
Furazolidone	0.1	1	0.1	0.1	1000	10	0.1

[a] See ref 20 for test description. [b] SA = *Staphylococcus albus*, EC = *Escherichia coli*, SM = *Serratia marcescens*, KA = *Klebsiella aerobacter*, SC = *Saccharomyces cerevisiae*, PN = *Penicillium notatum*, SS = *Sporobolomyces salmoncolor*.

Experimental Section[21]

3-Acetylamino-1,2,4-benzotriazine 1-Oxide (5).—3-Amino-1,2,4-benzotriazine 1-oxide[3] (**3**) (3.2 g, 0.02 mole) was refluxed for 8 hr with 10.2 g (0.10 mole) of Ac_2O and 32 ml of pyridine. The clear solution was stirred at 25° for 60 hr and then concentrated under reduced pressure. The residual solid was triturated with H_2O and collected to yield 2.56 g of product, mp 190–191.5°. Additional product (2.95 g) was isolated from the wash solution to give a 73% yield. A sample was recrystallized from EtOH for analysis. *Anal.* ($C_9H_8N_4O_2$) C, H, N.

3-Amino-7-nitro-1,2,4-benzotriazine 1-Oxide (9).—Intermediate 2,4-dinitrophenylguanidine was prepared according to Dolman, *et al.*[22] However, use of the conditions employed by these workers for ring closure of the guanidine to the benzotriazine (heating with 2 *N* NaOH solution for 4 min, 50% yield) resulted in complete decomposition of the product in our hands. The following modified procedure gave an 83% yield.

A suspension of 1.0 g (4.45 mmoles) of 2,4-dinitrophenylguanidine in 100 ml of H_2O containing 7.0 g of Na_2CO_3 was heated to reflux to effect solution. Heating was stopped and, after 0.5 hr at 25°, the mixture was cooled and the precipitated product was collected by filtration. The solid was washed with H_2O and dried to yield 762 mg, mp 289–291° dec, lit.[22] mp 289–290° dec.

3-Amino-7-phenyl-1,2,4-benzotriazine 1-Oxide (10).—The standard procedure of Wolf, *et al.*,[3] for the preparation of 3-amino-1,2,4-benzotriazine 1-oxides was applied to 3-amino-4-nitrobiphenyl to obtain this compound in 34% yield. It was recrystallized from methyl Cellosolve and melted at >275°. *Anal.* ($C_{13}H_{10}N_4O$) C, H, N.

5-Fluoro-2-nitrobenzaldehyde was prepared in 86% yield by nitration of *m*-fluorobenzaldehyde according to the method of Pelchowicz, *et al.*[23] An alternate method given by Pelchowicz (chromic acid oxidation of 5-fluoro-2-nitrotoluene) gave much lower yields.

2-Amino-5-fluorobenzaldehyde.—5-Fluoro-2-nitrobenzaldehyde (1.85 g, 0.011 mole) in 25 ml of MeOH was slowly added over 25 min to a stirred and refluxing solution of 11.4 g (0.066 mole) of $Na_2S_2O_4$ and 5.8 g (0.055 mole) of Na_2CO_3 in 22.5 ml of H_2O. After an additional 1 hr of reflux, the solution was cooled to 0° and extracted with Et_2O. The Et_2O solution was dried and concentrated to yield 0.6 g of solid. The ir spectra did not contraindicate the desired structure and, due to the instability common to this class of compounds,[7,8] it was used in the crude state for the next reaction without characterization.

2-Amino-6-fluoroquinazoline (12).—A mixture of 0.60 g (4.3 mmoles) of 2-amino-5-fluorobenzaldehyde, 0.75 g (8.0 mmoles) of guanidine hydrochloride, and 0.43 g (4.0 mmoles) of Na_2CO_3 in 10 ml of decalin was heated at 200° for 1 hr. The hot supernatant was decanted and cooled, and the oily precipitate was dissolved in 3 *N* HCl. The solution was filtered through Celite and the filtrate was made basic. The resulting precipitate was collected and recrystallized from EtOH to give 100 mg (15%) of yellow solid melting at 241–243°. It was recrystallized once more for analysis. *Anal.* ($C_8H_6FN_3$) C, H, N.

In a larger run, 2.5 g of aminoaldehyde yielded 38% of product melting at 236–240°.

2-Amino-5-chlorobenzaldehyde.—To a hot, stirred solution of 26.0 g (0.027 mole) of $Na_2S_2O_4$, 12.8 g (0.12 mole) of Na_2CO_3, and 500 ml of H_2O was added slowly a solution of 5.0 g (0.027 mole) of 5-chloro-2-nitrobenzaldehyde in 100 ml of MeOH. The addition required 25 min. The solution was then refluxed for 2 hr, cooled to 25°, and extracted with Et_2O. The Et_2O solution was washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure to yield 2.35 g (56%) of yellow, solid 2-amino-5-chlorobenzaldehyde, mp 67–70°. Repeated recrystallizations from hexane gave the analytical sample, mp 72°. *Anal.* (C_7H_6ClNO) C, H, N.

This product was found to undergo self-condensation within a few hours at room temperature. Such samples lost aldehyde carbonyl absorption (5.93 μ) in their ir spectra and changed their melting point to 104–105°.

2-Amino-6-chloroquinazoline (13).—A mixture of 2-amino-5-chlorobenzaldehyde (100 mg, 0.65 mmole, mp 70–71°), guanidine hydrochloride (122 mg, 1.30 mmoles), and Na_2CO_3 (69 mg, 0.65 mmole) was covered with 2 ml of decalin and quickly heated to reflux. After 30 min at 185°, the hot decalin was decanted from the insoluble solid. The solid was extracted with an additional 1 ml of hot decalin, and the extracts were combined and cooled overnight. The yellow, solid product was collected in 25% crude yield and recrystallized from benzene for analysis; mp 258–259° dec; uv, $\lambda_{max}^{0.1\ N\ HCl}$ 236 mμ (ε 25,950), 247 (21,650), 282 (4525), 360 (2120). *Anal.* ($C_7H_6ClN_3$) C, H, N.

In a larger run, 7.0 g of polymerized 2-amino-5-chlorobenzaldehyde was treated as above. After refluxing in decalin for 4 hr, 17% of crude product was isolated. Precipitation from warm 0.1 *N* HCl solution with dilute NaOH solution gave material with a melting range of 254–257° dec.

(19) Colonel William E. Rothe of the Walter Reed Army Institute of Research kindly provided this information.

(20) W. T. Colwell, J. H. Lange, and D. W. Henry, *J. Med. Chem.*, **11**, 282 (1968).

(21) All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within 0.4% of the calculated values.

(22) H. Dolman, H. Peperkamp, and H. Moed, *Rec. Trav. Chim.*, **83**, 1307 (1964).

(23) Z. Pelchowicz, A. Kaluszyner, and M. Bentov, *J. Chem. Soc.*, 5420 (1961).

2,4-Diamino-6-chloroquinazoline (**14**).—2,4,6-Trichloroquinazoline[12] was heated at 150° with alcoholic NH_3 for 17 hr in a bomb tube. The solution was cooled and concentrated, and the resulting yellow solid was dissolved in dilute HCl. The suspension was filtered and the filtrate was adjusted to pH 12. The solid **14** was collected in 79% yield, mp 268–273° dec. *Anal.* ($C_8H_7ClN_4 \cdot H_2O$) C, H, Cl, N.

4,5-Dichloro-2-nitrobenzaldehyde.—The following procedure was suggested by Ruggli and coworkers.[24] Red fuming HNO_3 (62.5 ml, *ca.* 1.0 mole) was placed in a beaker, cooled in a water bath, and stirred while concentrated H_2SO_4 (56. ml, 1.0 mole) was added. The mixed acids were cooled to 30° and 3,4-dichlorobenzaldehyde (70 g, 0.4 mole) was slowly added. This addition required 45 min when the temperature was maintained near 30°. In previous experiments reaction at higher temperatures resulted in increased amounts of 3,4-dichlorobenzoic acid. The mixture was stirred at room temperature for 1 hr and poured into 1 l. of cold H_2O. The mixture was stirred for 30 min, the H_2O was decanted, and the residual yellow oil was washed with H_2O and then weak $NaHCO_3$ solution. When the wash solution became basic (pH paper), the oil was dissolved in Et_2O and the solution was washed with H_2O. The ethereal solution was dried and concentrated, and the warm residual oil was slowly poured into 800 ml of vigorously stirred cyclohexane. After 1 hr, the solid was collected and recrystallized from 100 ml of 4:1 cyclohexane–benzene to yield 27 g of a yellow solid, mp 62–65°, lit.[25] mp 73°. The ir spectrum was in agreement with the assigned structure.

2-Amino-6,7-dichloroquinazoline (**17**).—4,5-Dichloro-2-nitrobenzaldehyde (5.0 g, 0.023 mole) was reduced to 2-amino-4,5-dichlorobenzaldehyde with $Na_2S_2O_4$ and Na_2CO_3 in aqueous MeOH in the same manner as the 6-fluoro and 6-chloro isomers. The sensitive aminoaldehyde (2.17 g) was not analyzed but was immediately combined with 2 molar proportions of guanidine hydrochloride (2.15 g), 1.17 g of Na_2CO_3, and 25 ml of decalin. This mixture was heated at 200° for 1 hr and the clear hydrocarbon solvent was decanted. The residual solid was heated with two additional 10-ml portions of decalin and the solvents were combined and cooled. The deposited yellow product was collected, triturated with benzene, then reprecipitated from 3 *N* HCl to yield 500 mg of solid, mp >310°. An analytical sample was prepared by recrystallization from methyl Cellosolve. *Anal.* ($C_8H_5Cl_2N_3$) C, H, N.

2-Amino-6-chloroquinoxaline (**18**).—A 40-ml, stainless steel Parr bomb was cooled in Dry Ice and 200 mg (0.001 mole) of 2,6-dichloroquinoxaline[13] was introduced. Liquid NH_3 (20 ml) was added and the bomb was sealed. The contents were stirred magnetically for 17 hr at room temperature. The bomb was cooled and opened, and the excess NH_3 was expelled by stirring at room temperature. The yellow residue was triturated with H_2O and collected by filtration to give the crude product in quantitative yield. The products from five separate runs (mp 196–202° dec) were combined and dissolved in 0.1 *N* HCl. The solution was filtered and the purified product was precipitated by the slow addition of 5 *N* NaOH solution to pH 10 (mp 202–205° dec). An analytical sample was obtained by recrystallizations from EtOH, mp 213–217° dec, with softening at 210°. *Anal.* ($C_8H_6ClN_3$) C, H, N.

2-Amino-6-chloroquinoline (**21**).—2,6-Dichloroquinoline[14] was treated with excess methanolic NH_3 at 105° in a bomb for 17 hr. The cooled reaction mixture was concentrated to dryness and triturated with dilute NH_4OH. The insoluble product was purified by solution in dilute HCl followed by precipitation with NH_4OH solution. It was recrystallized finally from *n*-BuCl and melted at 151.5–153°. Fischer[26] prepared this compound in 1902 by another procedure and found mp 152°.

4-Amino-6-chloroquinoline (**24**) was prepared from 4,6-dichloroquinoline[14] in the same manner as the 2-amino analog except that heating was continued for 3 days. Precipitation from acid solution with NH_4OH gave material melting at 225–227° dec, lit.[27] mp 233–234° dec.

1-(2,4-Dinitro-1-naphthyl)guanidine.—Sodium *t*-butoxide was prepared by treating 2.9 g (0.06 mole) of NaH (50% suspension in oil) with 240 ml of *t*-BuOH. Guanidine hydrochloride (6.2 g, 0.066 mole) was added and the mixture was stirred at 40° for 30 min. The separated NaCl was removed by filtration and the clear filtrate was added over 45 min to a stirred mixture of 1-chloro-2,4-dinitronaphthalene (7.6 g, 0.03 mole) in 180 ml of *t*-BuOH at 75°. After an additional 15 min at 75°, the clear alkaline solution was cooled to 25° and adjusted to pH 3 with 6 *N* ethanolic HCl. The precipitate was partitioned between 0.5 *N* HCl and $CHCl_3$. The acid phase was washed well with Et_2O, cooled in ice, and made alkaline with 5 *N* NaOH. The precipitate was collected and recrystallized once from *i*-PrOH to give a 26% yield of orange product, mp 203–205°. *Anal.* ($C_{11}H_9N_5O_4$) C, H, N.

2-Amino-6-nitronaphtho[1,2-*e*]-*as*-triazine 4-Oxide (**25**).—1-(2,4-Dinitro-1-naphthyl)guanidine (2.40 g, 8.70 mmoles) was suspended in 50 ml of 1 *N* NaOH solution. The mixture was heated to boiling, then held at 90–100° for 15 min. During this time the insoluble orange solid became brown. The hot mixture was cooled to 25° and the solid was collected and washed with H_2O to give 1.7 g of product, mp 271° dec. The solid was recrystallized from methyl Cellosolve and washed with EtOH to give 1.0 g (45%), mp 291–292° dec. *Anal.* ($C_{11}H_7N_5O_3$) C, H, N.

2-Amino-5,6-dichlorobenzimidazole (**29**).—Crude 4,5-dichloro-*o*-phenylenediamine (8.85 g) and damp, crude BrCN (*ca.* 10 g) were combined with 100 ml of H_2O. The mixture was stirred on the steam bath for 1 hr and the dark solution was passed through a mixture of Celite and charcoal. The filtrate was made basic with 5 *N* NaOH, and the crude **29** was collected and recrystallized from EtOH–H_2O to yield 2.15 g (22%), mp 260–262° dec. *Anal.* ($C_7H_5Cl_2N_3$) C, H, N.

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