at 100° with 10 ml of 6 *N* sodium hydroxide for 15 min. During the course of this heating, the solid disappeared and an oil separated. After cooling to room temperature, the aqueous layer was extracted three times with 20 ml of ether. After drying, evaporation of the ether yielded 250 mg of a white solid, mp 100–102.5°. A portion of this was recrystallized twice from hexane to give an analytical sample of the amino alcohol, mp 102–104°.

Anal. Calcd for $C_{20}H_{24}BrNO_2$: C, 61.53; H, 6.21; N, 3.58. Found: C, 61.48; H, 6.34; N, 3.71.

A solution of 100 mg of the above amino alcohol in 5 ml of methanol was treated with a solution of 110 mg of sodium metaperiodate in 7 ml of water. Enough methanol and water was added to make the solution homogeneous, bringing the final volume to 20 ml. The reaction was allowed to stand at room temperature under nitrogen ebullition for 5 hr. The inorganics were then removed by filtration and the methanol was evaporated *in vacuo*. The remaining aqueous layer was extracted twice with 15 ml of ether. After drying, evaporation of the ether *in vacuo* left a solid residue, mp 63–66°. Two recrystallizations from hexane yielded 15 mg, mp 70–72° (lit.[11] mp 73–74°).

Authentic 5-bromo-2-benzyloxybenzaldehyde was prepared from salicylaldehyde according to the procedure of Raiford and Tanzer.[11] A mixture melting point of the authentic sample with the material from the cleavage reaction was undepressed.

Acknowledgment.—A portion of this work was supported by Parke, Davis & Co. until October 1, 1963, and after that date a portion was supported by the National Science Foundation Grant GP-205. This financial assistance is gratefully acknowledged. The authors wish to thank Melvin Clark and John Stoddard for the synthesis of three compounds.

Quinazolines. III. Synthesis of 1,3-Diaminobenzo[*f*]quinazoline and Related Compounds[1-3]

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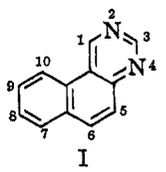
The title compound was prepared by condensation of 1-cyano-2-naphthylamine with cyanamide in the presence of pyridine hydrochloride, or by amination of 1,3-dichlorobenzo[*f*]quinazoline at elevated temperature and pressure. Similarly, reaction of formamide, urea, and thiourea with 1-cyano-2-naphthylamine afforded 1-amino-, 1-amino-3-hydroxy-, and 1-amino-3-mercaptobenzo[*f*]quinazoline, respectively. A novel reaction between guanidine and 2-hydroxy-1-naphthaldehyde resulted in the formation of 3-aminobenzo[*f*]quinazoline. A number of other previously unknown benzo[*f*]quinazolines, including the unsubstituted parent member of the series, were prepared by acid hydrolysis, thiation with phosphorus pentasulfide, and nickel-catalyzed dethiation reactions. The nuclear magnetic resonance spectrum of benzo[*f*]quinazoline is presented.

As a logical extension of earlier work[4] involving, in part, certain derivatives of benzo[*f*]quinazoline (I), a more thorough investigation of this ring system was undertaken. A review of the literature[5-15] revealed that only a few systematic studies dealing with benzo-



I

[*f*]quinazolines had been carried out previously. A major objective of the present study was to prepare 1,3-diaminobenzo[*f*]quinazoline (II) as a planar, tricyclic analog of the antifolic and antimalarial agent pyrimethamine (III).[16,17] The hypothesis that this type of structural modification might lead to enhanced biological activity is consistent with our earlier observation that the sterically related 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazine molecule exhibits optimal anti-

(1) This investigation was supported in part by Research Grant C6516 and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(2) A preliminary report of this work has been presented: A. Rosowsky, N. Papathanasopoulos, M. E. Nadel, S. K. Sengupta, and E. J. Modest, Abstracts of Papers, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 28, 1966.

(3) Paper II: A. Rosowsky, H. Kangur Protopapa, and E. J. Modest, *J. Org. Chem.*, **30**, 285 (1965).

(4) A. Rosowsky, H. Kangur Protopapa, P. J. Burke, and E. J. Modest, *ibid.*, **29**, 2881 (1964).

(5) T. Bhattacharyya, P. K. Bose, and J. N. Ray, *J. Indian Chem. Soc.*, **6**, 279 (1929).

(6) R. C. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936).

(7) K. Dziewonski, L. Sternbach, and A. Strauchen, *Bull. Intern. Acad. Polon. Sci., Classe Sci. Math. Nat.*, 493 (1936); *Chem. Abstr.*, **31**, 3053 (1937).

(8) L. A. Krol, F. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **71**, 545 (1952).

(9) A. H. deCat, G. M. Sevens, and A. E. vanDormael, U. S. Patent 2,668,112; *Chem. Abstr.*, **48**, 5699 (1954).

(10) H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig, *Ber.*, **89**, 224 (1956).

(11) H. Bretschneider and K. Hohenlohe-Oehringen, *Monatsh.*, **89**, 358 (1958).

(12) W. Dymek and D. Sybistowicz, *Roczniki Chem.*, **36**, 1639 (1962); *Chem. Abstr.*, **59**, 8742 (1963).

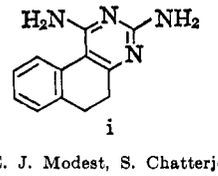
(13) W. Dymek and D. Sybistowicz, *Roczniki Chem.*, **37**, 547 (1963); *Chem. Abstr.*, **59**, 10040 (1963).

(14) R. Gompper, H. Noppel, and H. Schaefer, *Angew. Chem.*, **75**, 918 (1963).

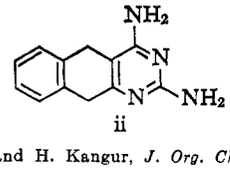
(15) For the preparation of 7,8,9,10-tetrahydrobenzo[*f*]quinazoline derivatives, the following references may also be consulted: (a) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17**, 149 (1952); (b) G. H. Hitchings, A. E. Falco, and K. W. Ledig, U. S. Patent 2,945,859; *Chem. Abstr.*, **54**, 24820 (1960).

(16) P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951); E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. Rollo, and P. B. Russell, *Brit. J. Pharmacol.*, **6**, 185 (1951); G. H. Hitchings, E. A. Falco, H. Vander Werff, P. B. Russell, and G. B. Elion, *J. Biol. Chem.*, **199**, 43 (1952).

(17) An attempt to synthesize another tricyclic pyrimethamine analog, 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline (i), by condensation of dicyandiamide with 2-tetralone[18] led only to the linear isomer, 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline (ii).[19]



i

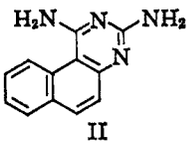


ii

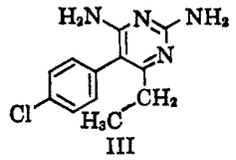
(18) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(19) S. K. Sengupta, S. Chatterjee, H. Kangur, and E. J. Modest, Abstracts of Papers, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 3, 1963, p 37-L.

folic activity when a planar configuration can be acheived.[20] This paper describes the synthesis of II, as well as the parent compound I and other related benzo[*f*]quinazolines.



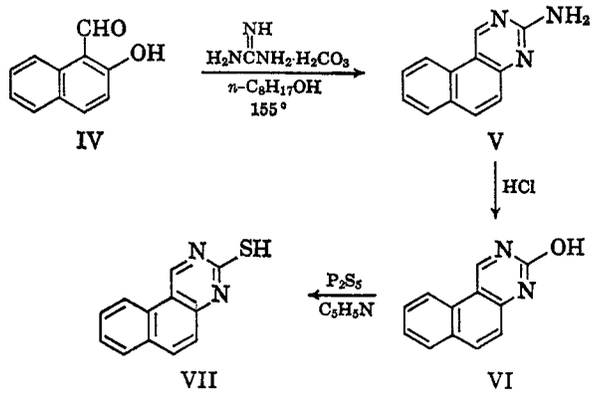
II



III

The discovery of a novel condensation reaction between 2-hydroxy-1-naphthaldehyde (IV) and guanidine[21] led to the preparation of several previously unreported 3-substituted benzo[*f*]quinazoline derivatives (Chart I). Heating a mixture of IV and guanidine

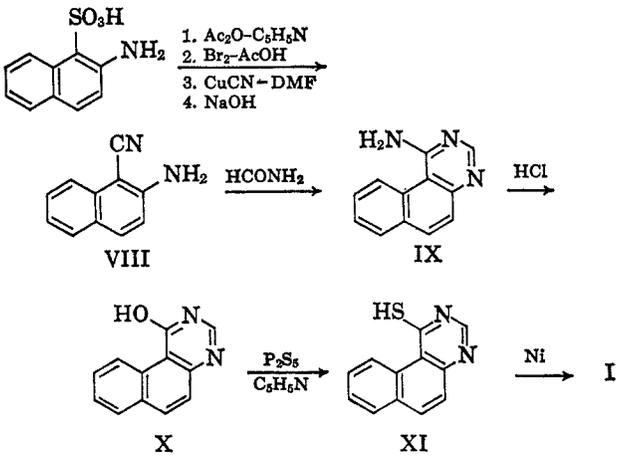
CHART I



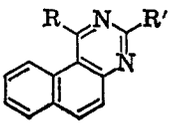
carbonate in *n*-octanol led to the formation of 3-aminobenzo[*f*]quinazoline (V). Hydrolysis of V with 6 *N* hydrochloric acid afforded a sparingly soluble hydrochloride salt, which gave 3-hydroxybenzo[*f*]quinazoline (VI) on neutralization. Thiation of VI with phosphorus pentasulfide in pyridine furnished 3-mercaptobenzo[*f*]-quinazoline (VII).

1-Cyano-2-naphthylamine (VIII)[8,11] was found to be an excellent starting material for the synthesis of 1-substituted benzo[*f*]quinazolines (Chart II). For the preparation of VIII, 2-aminonaphthalene-1-sulfonic acid was treated with acetic anhydride in pyridine, and the resulting pyridinium salt of 2-acetylamino-1-naphthalenesulfonic acid was converted into 2-acetylamino-1-bromonaphthalene by bromination in aqueous acetic acid.[22] Treatment of the latter with cuprous cyanide in dimethylformamide[23] yielded 2-acetylamino-1-cyanonaphthalene,[8,11] from which VIII was readily obtained upon removal of the N-acetyl blocking group by brief alkaline hydrolysis.[8,11,24] In an alternative approach, 1-bromo-2-naphthylamine was acetylated, and the resulting 2-diacetylamino-1-bromonaphthalene was converted into VIII by reaction with cuprous cyanide in dimethylformamide, followed by alkaline hydrolysis. Condensation of VIII with formamide afforded 1-aminobenzo[*f*]quinazoline (IX). Overnight treatment of IX with excess nitrous acid in acetic or hydrochloric acid at room temperature gave only a moderate yield of 1-hydroxybenzo[*f*]quinazoline (X), together with unidentified salmon-colored by-products. For preparative purposes, much higher yields of X and a substantially shorter reaction time were achieved by omitting the diazotization step and simply heating IX in 6 *N* hydrochloric acid. As in the conversion of V into VI, a sparingly soluble hydrochloride salt formed, from which X resulted on neutralization.[25] Thiation of X with phosphorus pentasulfide in pyridine afforded 1-mercaptobenzo[*f*]quinazoline (XI).

CHART II



The ultraviolet absorption spectrum of VI was nearly identical with that of a compound previously obtained in this laboratory by another route and formulated as 3-hydroxy-1-methylbenzo[*f*]quinazoline (XII).[4] The spectrum of X was found to resemble closely that of 1-hydroxy-3-methylbenzo[*f*]quinazoline (XIII), a sample of which was prepared from 2-acetylaminonaphthalene and urethane in the presence of phosphorus pentoxide.[4,5] The present unequivocal syntheses of VI and X from 1,2-disubstituted naphthalenes, and the similarity in the spectra of VI and XII, and of X and XIII, support the formulation of XII and XIII as angular rather than linear structures.



XII, R = CH_3; R′ = OH
XIII, R = OH; R′ = CH_3

The unsubstituted parent member of the series, benzo[*f*]quinazoline (I), was obtained on dethiation of XI with Davison sponge nickel in refluxing ethanol.[26] The product was a colorless to very pale yellow solid melting at 107–108° after repeated vacuum sublimation. Although benzo[*f*]quinazoline has been reported

(20) E. J. Modest, S. Farber, and G. E. Foley, *Proc. Am. Assoc. Cancer Res.*, **1**, 33 (1954).

(21) This reaction was originated and carried out by Mr. Nickolas Papathanasopoulos in these laboratories.

(22) M. C. Kloetzel, W. King, W. J. Wasserman, C. K. Warren, and P. A. Larssen, *J. Org. Chem.*, **26**, 607 (1961).

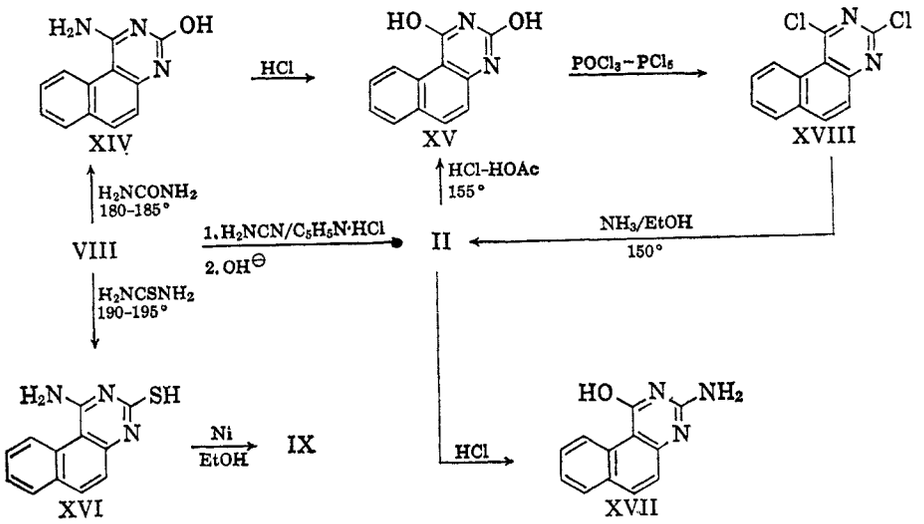
(23) L. Friedman and H. Shechter, *ibid.*, **26**, 2522 (1961).

(24) Acid hydrolysis was not used for this purpose because acid had previously been shown to cause facile cyclization of VIII to XIII.[8,11] It is of interest to note, however, the recent contradictory report[13] that alkaline hydrolysis of 2-acetylamino-1-cyanonaphthalene in dilute aqueous ethanolic sodium hydroxide results in cyclization to XIII, while vigorous treatment with 40% hydrobromic acid yields VIII without giving any cyclized product.

(25) An alternate synthesis of X from 2-naphthylamine and N-ethoxymethylene urethane was reported recently.[14]

(26) H. N. Schlein, M. Israel, S. Chatterjee, and E. J. Modest, *Chem. Ind.* (London), 418 (1964).

CHART III



by Dymek and Sybistowicz,[27] *via* an alternate route, the characteristics of I and its salts prepared in our laboratories differ markedly from the values given by these authors. In the present study, the structure of I was supported by its ultraviolet absorption spectrum, which closely resembled that of benzo[*f*]quinoline,[28] and by its nmr spectrum (Figure 1). In addition to the typical aromatic proton absorption pattern in the τ 1.5–2.5 region, the nmr spectrum of I contained two sharp isolated signals at τ 0.65 and 0.10. Armarego and Willette[29] recently observed that in quinazoline itself the protons at positions 2 and 4 absorb at τ 0.63 and 0.49, respectively. The τ 0.65 signal in the spectrum of I was therefore assigned to the C-3 proton, and the τ 0.10 signal was assigned to the C-1 proton. The large downfield shift of the C-1 proton of I, relative to the corresponding proton of quinazoline, apparently results from the deshielding effect of the additional benzene ring in I.

1-Cyano-2-naphthylamine (VIII) was also used as a key intermediate for the synthesis and interconversions of several new 1,3-disubstituted benzo[*f*] quinazolines (Chart III). When heated with urea, VIII afforded 1-amino-3-hydroxybenzo[*f*]quinazoline (XIV). An attempt to prepare XIV from VIII and urethane led only to the isolation of cyanuric acid. Acid hydrolysis of XIV yielded 1,3-dihydroxybenzo[*f*]quinazoline (XV), identified by comparison with an authentic sample prepared by a known two-step sequence from 2-naphthylamine and thiourea.[7] The same compound has also been obtained by a modified two-step route starting from N-(2-naphthyl)-N′-phenylguanidine and phenyl isothiocyanate,[12] and the present unambiguous synthesis from a 1,2-disubstituted naphthalene corroborates earlier assignments of an angular structure for this substance. Condensation of VIII with thiourea furnished 1-amino-3-mercaptobenzo[*f*]quinazoline (XVI). Dethiation of XVI with Davison sponge nickel[26] occurred readily and gave a good yield of pure IX, identical with the material prepared from VIII and formamide.

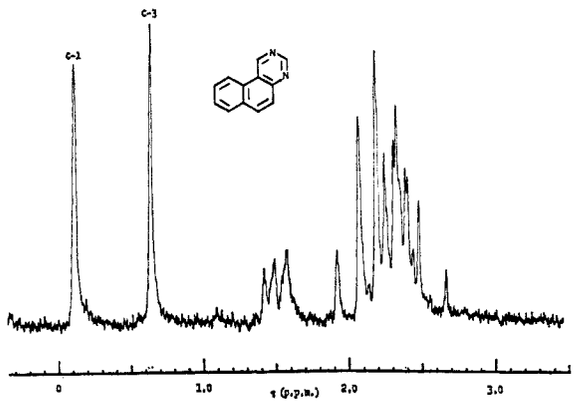


Figure 1.—Nmr spectrum of benzo[*f*]quinazoline in deuteriochloroform.

Several approaches were explored for the synthesis of II, the compound of greatest interest in the present study. In one of these, the condensation of VIII with cyanamide in the presence of pyridine hydrochloride[30] gave II, a pale yellow to nearly colorless solid melting at 200–202°. Since II gave a negative Sakaguchi test, indicating the absence of a guanidino group, and showed no nitrile absorption in the infrared, the possibility that II might be uncyclized 1-cyano-2-guanidinonaphthalene was eliminated. Acid hydrolysis of II led to the precipitation of a hydrochloride salt. Neutralization of this salt with ammonia afforded a very high melting isomer of XIV which was formulated as 1-hydroxy-3-aminobenzo[*f*]quinazoline (XVII). When the hydrolysis of II was carried out under more vigorous conditions, both amino groups were lost and XV was formed in good yield.

A second synthesis of II was based on a published claim[12] that treatment of 1,3-dichlorobenzo[*f*]quina-

(27) By dehalogenation of XVIII with red phosphorus and 40% hydriodic acid and re-oxidation of the resulting overreduced product with potassium ferricyanide, Dymek and Sybistowicz[12] obtained a compound to which they assigned structure I. This substance melted at 142–143°, and its picrate and hydrochloride salts melted at 257–258° and 307–308°, respectively.

(28) W. S. Johnson, E. Woroch, and F. J. Mathews, *J. Am. Chem. Soc.*, **69**, 566 (1947).

(29) W. L. F. Armarego and R. E. Willette, *J. Chem. Soc.*, 1258 (1965).

(30) L. F. Theiling and R. L. McKee [*J. Am. Chem. Soc.*, **74**, 1834 (1952)] reported that the dry fusion of *o*-aminoacetophenone hydrochloride and dicyandiamide gave higher yields of 2-guanidino-4-methylquinazoline hydrochloride when pyridine hydrochloride was included.

zoline (XVIII)[7] with ammonium hydroxide in refluxing methanol gives a compound allegedly possessing structure II.[31] Repetition of this amination under the prescribed conditions failed to give any II; instead, there was formed another product, the structure of which is presently under investigation. When the amination was conducted in a sealed tube at 150° for 48 hr, however, II could be isolated, provided that water was rigorously excluded.[32] The material obtained by this route was identical with II prepared by the condensation of VIII with cyanamide.

Several other routes to II were investigated and found to be unsatisfactory. Although anthranilonitrile has been reported to yield 2,4-diaminoquinazoline by reaction with dicyandiamide in boiling dilute hydrochloric acid,[33] treatment of VIII under identical conditions led only to the recovery of unchanged starting material. Dry fusion of VIII with dicyandiamide likewise gave only unchanged VIII, a surprising observation in view of the report that several alkyl-substituted anthranilonitriles yield alkyl-substituted 2,4-diaminoquinazolines under similar conditions.[15b] Attempts to condense VIII with guanidine in refluxing 2-ethoxyethanol,[34] or in the higher boiling solvent, 2-[(2′-ethoxy)ethoxy]ethanol, were also unsuccessful. The unexpected lack of reactivity of VIII toward dicyandiamide and guanidine probably stems from the general deactivating effect of the naphthalene ring and the weakly basic character of the 2-amino group. Consistent with this was the observation that VIII HCl could be prepared only by passing dry hydrogen chloride gas into a solution of VIII in anhydrous ether. When VIII HCl prepared in this way was added to water or alcohol, the free base VIII was regenerated instantaneously.

Several other approaches to the synthesis of mono- and disubstituted benzo[*f*]quinazolines were explored without success. Efforts to prepare VI and VII by the condensation of IV with urea and thiourea, respectively, led only to the isolation of other, as yet unidentified, products. Condensation of 2-amino-1-naphthoic acid or 2-hydroxy-1-naphthoic acid with urea and related compounds failed, apparently because these acids undergo facile decarboxylation in preference to any of the desired reactions. Similarly, an attempt to condense 2-hydroxy-1-naphthamide with guanidine led only to the formation of 2-naphthol, presumably with the attendant loss of a molecule of formamide.

Further work on the chemistry of the benzo[*f*]-quinazoline ring system is currently in progress and will be reported at a later date.

(31) This compound was reported[12] to melt at 291°, however, and is therefore probably not II.

(32) It was recognized that scrupulously anhydrous conditions are mandatory for this reaction only after several unsuccessful amination experiments gave XV instead of II. Apparently, traces of moisture can cause rapid hydrolysis of XVIII. Even when crystallized from chloroform, dried under reduced pressure, and stored in a closed container, XVIII was found to undergo some decomposition after just a few weeks. For this reason, XVIII was sublimed immediately prior to use, and both the absolute ethanol and the ammonia gas used in the amination were thoroughly dried. Only in this manner was it possible to obtain any II from XVIII, and even with the most elaborate precautions to exclude moisture, some XV was still produced. This may be due, in part, to the generation of a trace of water from the high temperature condensation of ethanol and ammonia.

(33) W. Zerweck and W. Kunze, German Patent 737,931; *Chem. Abstr.*, **38**, 3993 (1944).

(34) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5711 (1960).

Experimental Section

The ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Spectra at pH 1 were taken in ethanolic 0.1 *N* hydrochloric acid and at pH 10 in ethanolic 0.05 *M* sodium carbonate–sodium borate buffer. Infrared spectra were measured in potassium bromide or potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer (sodium chloride prism). Nmr spectra were recorded on a Varian A-60 instrument using deuteriochloroform solutions and tetramethylsilane as the internal reference standard.

Melting points were determined in Pyrex capillary tubes in a modified Wagner–Meyer apparatus[35] and are corrected wherever possible. Melting points were taken under standardized conditions at a uniform heating rate of 2°/min.[4]

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Unless otherwise specified, analytical samples were dried *in vacuo* (0.01 mm) over phosphorus pentoxide at 70–100° for 17 hr in a drying tube.

Materials.—2-Hydroxy-1-naphthaldehyde was obtained from L. Light and Co. Ltd., Colnbrook, Bucks, England, and from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, and was used without preliminary purification. 1-Bromo-2-naphthylamine was obtained from L. Light and Co. Ltd., and from Aceto Chemical Co., Inc., Flushing, New York. The Davison sponge nickel was obtained from W. R. Grace and Co., Baltimore, Maryland, and has been described in detail in an earlier publication from this laboratory.[26] The phosphorus pentasulfide used for thiation experiments was a special reactive grade supplied by Monsanto Chemical Co., St. Louis, Missouri, and was purified by extraction with carbon disulfide in a Soxhlet apparatus; the extract was reduced in volume, and the solid which crystallized out was collected, dried, and stored in the freezer until needed. For the preparation of crystalline cyanamide, a 50% aqueous solution obtained from American Cyanamid Co., New York, New York, was lyophilized to near dryness, the residue extracted with ethyl acetate, and the extract dried over anhydrous sodium sulfate, reduced in volume, and diluted with petroleum ether; the crystalline material prepared in this manner melted at 45° and was free of dicyandiamide.

2-Acetylamino-1-cyanonaphthalene.—2-Amino-1-naphthalenesulfonic acid was converted into pyridinium 2-acetylamino-1-naphthalenesulfonate, and the latter into 2-acetylamino-1-bromonaphthalene (mp 141–142°, lit.[22] mp 140–141°), by the method of Kloetzel and co-workers.[22] A suspension of 2-acetylamino-1-bromonaphthalene (44.1 g, 0.167 mole) and cuprous cyanide (16.2 g, 0.180 mole) in 150 ml of dimethylformamide was refluxed with magnetic stirring for 4 hr. After standing at room temperature for 15 hr, the mixture was warmed to about 70° and transferred to a separatory funnel with the aid of liberal amounts of benzene and water. Three 100-ml portions of 10% sodium cyanide solution were added, the funnel being shaken vigorously for 10 min after each addition. The aqueous extracts were withdrawn, and a small quantity of gummy solid which remained suspended in the benzene layer was removed by suction filtration. The benzene solution was treated with a generous portion of Darco,[36] dried over anhydrous sodium sulfate, concentrated to a small volume under reduced pressure, and diluted with *n*-heptane. The precipitated solid was collected and dried *in vacuo:* yield 27.5 g (79%). After crystallization from aqueous alcohol, the product melted at 160.5–162° (lit.[11] mp 164°).

2-Diacetylamino-1-bromonaphthalene.—A mixture of 1-bromo-2-naphthylamine (10.4 g, 0.0468 mole) and acetic anhydride (50 ml) was refluxed with stirring for 45 min, cooled to room temperature for 1 hr, and poured into 300 ml of crushed ice. After standing overnight, the solid was collected, washed thoroughly with water, and crystallized from 250 ml of 50% aqueous ethanol with the aid of Darco: yield 10.3 g (78%), mp 102–105°. The analytical sample was prepared by a second crystallization from aqueous ethanol.

Anal. Calcd. for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; Br, 26.10; N, 4.58. Found: C, 55.00; H, 4.04; Br, 26.22; N, 4.61.

A small quantity of 2-acetylamino-1-bromonaphthalene was recovered from the mother liquor of the first crystallization.

1-Cyano-2-naphthylamine (VIII). A.—Hydrolysis of 2-acetyl-

(35) E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938).

(36) Darco G-60 activated carbon, Atlas Chemical Industries, Inc., Wilmington, Del.

amino-1-cyanonaphthalene in 1 *N* sodium hydroxide in the prescribed manner[8,11] gave an 80% yield of VIII, mp 135–137° (lit.[11] mp 132–133°) after one crystallization from aqueous ethanol.

B. Treatment of 2-diacetylamino-1-bromonaphthalene with cuprous cyanide in dimethylformamide according to the procedure used for the preparation of 2-acetylamino-1-cyanonaphthalene, followed directly by alkaline hydrolysis in 1 *N* sodium hydroxide, likewise gave VIII.

3-Aminobenzo[*f*]quinazoline (V).[21]—A mixture of 2-hydroxy-1-naphthaldehyde (IV) (4.5 g, 0.026 mole) and guanidine carbonate (10 g, 0.055 mole) in 15 ml of *n*-octanol was heated to 155° under nitrogen for 2 hr. After cooling to room temperature, 150 ml of benzene was added and stirring was continued for 1 hr. The solid was collected, washed liberally with water, and rinsed with dichloromethane. Crystallization of the crude product from *n*-butanol with the aid of Darco afforded 1.1 g (22%) of analytically pure V as a yellow microcrystalline solid, mp 258–259.5°, after being dried for 48 hr at 110° (0.01 mm). Alternately, V could be purified by sublimation at 170° (0.05 mm), from which it was obtained as a pale yellow solid: λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 237 (35.1), 247 (33.5), 264 (26.6), 272 (26.9), 286 (14.9, sh), 360 (3.1), 370 (3.1); (EtOH, pH 1) 215 (24.3), 237 (57.5), 267 (15.9), 291 (10.9), 331 (6.0), 364 (6.6), 377 (6.0); (EtOH, pH 10) 236 (36.4), 245 (30.5, infl), 264 (25.2), 272 (25.0), 286 (14.2, sh), 360 (3.2).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 74.03; H, 4.80; N, 21.60.

Replacement of *n*-octanol in the above procedure by *t*-butyl alcohol (3-day reflux), toluene (24-hr reflux), or 2-[(2′-ethoxy)-ethoxy]ethanol (1 hr at 170°) resulted only in very low yields of impure product.

3-Hydroxybenzo[*f*]quinazoline (VI).—A mixture of V (100 mg, 0.513 mmole) and 25 ml of 6 *N* hydrochloric acid was stirred under reflux for 18 hr. The reaction mixture was cooled, and the fibrous, pale yellow needles of VI HCl that had formed were collected and treated with concentrated ammonia at room temperature. The resulting colorless solid was collected, washed, and crystallized from acetic acid with the aid of Darco: yield 45 mg (45%) of VI; mp 330–332° dec (softening at 320°), after being dried for 48 hr at 80° (0.01 mm.); λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 214 (19.6), 237 (50.7), 246 (43.9), 263 (7.7), 269 (7.4), 282 (5.9), 292 (4.8), 321 (3.2), 337 (2.2, infl), 364 (1.8), 377 (1.6); (EtOH, pH 1) 211 (20.2), 232 (58.2), 247 (13.0, infl), 255 (12.1), 263 (9.9), 280 (5.7), 285 (5.4), 292 (8.5), 366 (7.2); (EtOH, pH 10) 236 (36.4), 246 (35.5), 262 (23.6), 270 (22.2), 287 (12.0), 360 (3.5), 370 (3.5).

Anal. Calcd for $C_{12}H_8N_2O$: C, 73.45; H, 4.11; N, 14.28. Found: C, 73.32; H, 4.21; N, 14.40.

An attempt to prepare VI by condensing IV with urea under the conditions used for V was unsuccessful.

3-Mercaptobenzo[*f*]quinazoline (VII).—A mixture of VI (100 mg, 0.5 mmole) and purified phosphorus pentasulfide (230 mg, 1 mmole) was suspended in pyridine (7 ml) and stirred under reflux for 1.5 hr. The red solution was stirred overnight at room temperature and the solvent was removed under reduced pressure. Water (5 ml) was added to the dark red oily residue, and the mixture was heated on the steam bath for 15 min. The yellow solid which formed was filtered and washed several times with hot water. Two crystallizations from aqueous ethanol, once with the aid of Darco, gave 79 mg (73%) of VII, yellow prisms: mp 250–252° dec; λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 215 (30.0), 238 (16.2), 272 (34.9), 295 (17.5), 307 (18.9), 324 (7.7, infl), 338 (4.0, infl); (EtOH, pH 1) 217 (29.8), 263 (14.4), 268 (14.4), 315 (35.8), 374 (4.7); (EtOH, pH 10) 220 (23.9), 233 (20.8), 249 (13.6, infl), 261 (17.0), 297 (34.7), 317 (21.1, infl), 375 (2.3).

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.89; H, 3.80; N, 13.20; S, 15.11. Found: C, 67.76; H, 3.99; N, 13.12; S, 15.07.

An attempt to prepare VII by condensing IV with thiourea under the conditions used for V was unsuccessful.

1-Aminobenzo[*f*]quinazoline (IX). A.—A solution of VIII (25.0 g, 0.149 mole) in 250 ml of 99% formamide was stirred under reflux for 1 hr. The dark brown reaction mixture was cooled to room temperature and diluted with 850 ml of water. The olive green precipitate which formed on cooling was collected and washed with small portions of water. Crystallization from absolute ethanol yielded 19.6 g (67%) of IX, yellow prisms, mp 238–238.5°. A portion of IX purified for analysis by two vacuum sublimations at 160° (0.05 mm) gave nearly colorless material: mp 235–238°; λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 213 (31.5, infl), 233 (11.4, infl), 245 (14.1, infl), 251 (16.2, infl), 269 (34.7), 292 (10.5, infl), 320 (1.6), 334 (2.3), 349 (2.5); (EtOH, pH 1) 211 (40.0, infl), 278 (30.0), 303 (8.1, infl), 320 (5.3, infl), 334 (4.0), 350 (3.8); (EtOH, pH 10) 234 (11.6, infl), 244 (12.9, sh), 252 (16.0, infl), 269 (34.9), 290 (10.2, infl), 319 (1.8, infl), 333 (2.3), 348 (2.4).

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.62; H, 4.80; N, 21.46.

B.—Davison sponge nickel (7 ml of settled suspension in 95% ethanol) was added to a solution of XVI (100 mg, 0.441 mmole) in 100 ml of hot 95% ethanol, an additional 25 ml of 95% ethanol being used to effect transfer of the nickel. The mixture was stirred under reflux for 0.5 hr, at which time the initial yellow color of the solution had disappeared. The nickel was separated by suction filtration and washed with 95% ethanol. The combined filtrate and wash solution were evaporated nearly to dryness under reduced pressure, and water was added with cooling. The crude product was collected, washed with water, and dried *in vacuo* at 60°: yield 41 mg (48%) of IX, mp 228–231°. Vacuum sublimation at 145–160° (0.5 mm) gave nearly colorless material, mp 235–238°. The infrared and ultraviolet absorption spectra of this product were identical with the spectra of IX obtained by procedure A. A mixture melting point was not depressed.

1-Hydroxybenzo[*f*]quinazoline (X).—A mixture of IX (5.0 g, 0.026 mole) and 220 ml of 6 *N* hydrochloric acid was stirred under reflux for 1 hr. The reaction mixture was cooled, and the long, pale yellow, fibrous needles of X HCl were collected, washed with small portions of water, and dried. The solid was pulverized and added to 1 l. of 10% sodium hydroxide, and the mixture was heated on the steam bath until a clear solution was obtained. The solution was cooled and carefully adjusted to pH 7.6 with concentrated hydrochloric acid. The colorless precipitate which formed was collected, washed with water, and dried: yield 4.8 g (96%) of X, mp 265–266° dec. A sample of X was purified for analysis by four crystallizations from 25% acetic acid, once with the aid of Darco, yielding material which melted at 263–265° dec (lit.[37] mp 263° dec) after being dried for 48 hr at 90° (0.01 mm): λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 221 (12.1, infl), 243 (18.1, infl), 255 (29.5, infl), 261 (39.1), 270 (35.3), 287 (5.2, sh), 298 (5.2), 307 (4.0, infl), 315 (3.8), 323 (2.7), 329 (4.2), 338 (2.2), 344 (5.0); (EtOH, pH 1) 235 (10.6), 270 (28.4), 312 (5.1, sh), 327 (4.1, infl), 342 (2.3, infl); (EtOH, pH 10) 241 (15.2, infl), 247 (18.4, infl), 265 (39.5), 290 (8.8), 315 (2.1), 329 (2.8), 344 (3.0).

Anal. Calcd. for $C_{12}H_8N_2O$: C, 73.45; H, 4.11; N, 14.28. Found: C, 73.43; H, 4.20; N, 14.11.

1-Mercaptobenzo[*f*]quinazoline (XI).—A mixture of X (5.0 g, 0.026 mole) and purified phosphorus pentasulfide (11.3 g, 0.051 mole) in 325 ml of pyridine was stirred under reflux for 7 hr. The dark orange-brown solution was cooled to room temperature and the pyridine removed by means of a rotary evaporator. The gummy residue was digested on the steam bath with 175 ml of water for 10 min. The crude greenish yellow product was collected, washed thoroughly with water, and crystallized from 95% ethanol: yield 4.6 g (85%) of XI. For the preparation of the analytical sample, XI was crystallized several times from 95% ethanol and dried for 48 hr at 80° (0.01 mm): mp 267–271° dec; λ_{max} in mμ ($\epsilon \times 10^{-3}$) (95% EtOH) 217 (43.2), 253 (11.1, sh), 260 (11.1), 270 (9.3), 309 (17.7), 327 (8.7, infl), 379 (6.0); (EtOH, pH 1) 212 (42.6), 223 (34.1, infl), 270 (10.4, infl), 312 (16.6), 378 (8.5); (EtOH, pH 10) 231 (18.8), 239 (19.1, infl), 247 (22.1, infl), 259 (31.4), 291 (8.9, sh), 329 (3.1, infl), 339 (2.6, infl), 345 (2.7).

Anal. Calcd for $C_{12}H_8N_2S$: C, 67.89; H, 3.80; N, 13.20; S, 15.11. Found: C, 67.73; H, 3.76; N, 13.30; S, 15.24.

Benzo[*f*]quinazoline (I).[27]—A solution of XI (500 mg, 2.4 mmole) in 300 ml of hot 95% ethanol was added to Davison sponge nickel (4.6 ml of settled suspension) previously transferred into 100 ml of 95% ethanol. The mixture was stirred mechanically and refluxed for 0.5 hr, then filtered. The nickel was washed with hot 95% ethanol. The combined filtrate and wash solution were concentrated to dryness by means of a rotary evaporator (water-bath temperature <40° to minimize loss of product by sublimation). The greenish yellow residue weighing 350 mg was sublimed twice at 84–87° (0.05 mm), giving 210 mg (50%) of colorless I, mp 107–108°, after being dried for 24

(37) R. Gompper, personal communication.

hr at 60° (0.01 mm) in a closed apparatus to minimize loss by sublimation: λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 212 (33.7), 225 (33.7, infl), 229 (38.3), 263 (19.7), 300 (6.2), 328 (2.6), 343 (2.0); (EtOH, pH 1) 208 (28.9), 229 (26.4), 245 (15.2, infl), 253 (20.8), 262 (22.2), 314 (3.2, infl), 329 (2.5), 345 (1.4); (EtOH, pH 10) 229 (37.8), 264 (20.1), 304 (6.1), 329 (2.9, sh), 344 (2.1).

Anal. Calcd for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.55. Found: C, 79.86; H, 4.60; N, 15.46.

The **hydrochloride salt I HCl** was prepared by passing dry hydrogen chloride gas through a solution of purified I (50 mg, 0.28 mmole) in 20 ml of ether. The colorless solid was washed with ether and dried for 24 hr at 25° (0.01 mm): yield 47 mg (78%); mp 196–206° dec, with softening at 185°.

Anal. Calcd for $C_{12}H_8N_2 \cdot HCl$: C, 66.52; H, 4.19; N, 12.93; Cl, 16.35. Found: C, 66.08; H, 4.43; N, 13.03; Cl, 16.23.

The **picrate salt** was prepared from 50 mg (0.28 mmole) of I and 68 mg (0.30 mmole) of picric acid, crystallized three times from 95% ethanol, and dried for 22 hr at 70° (0.01 mm): yield 52 mg (47%); mp 195–196°.

Anal. Calcd for $C_{12}H_8N_2 \cdot C_6H_3N_3O_7 \cdot C_2H_5OH$: C, 52.75; H, 3.76; N, 15.38. Found: C, 53.08; H, 3.98; N, 15.79.

1-Amino-3-hydroxybenzo[*f*]quinazoline (XIV).—A mixture of VIII (1.1 g, 0.0067 mole) and urea (2.0 g, 0.033 mole) was immersed in a wax bath preheated to 140°, and the temperature raised to 180° (internal) over a period of 15 min. The internal temperature was maintained at 180–185° for 1 hr, at which time the initial melt had resolidified completely. The solid was cooled, pulverized, and triturated with 95% ethanol to remove any remaining unchanged VIII. The ethanol-insoluble material (1.1 g, 80%) was dissolved in 250 ml of boiling dimethylformamide, the solution treated with Darco, and 100 ml of water added. The precipitated solid was collected, washed thoroughly with water and 95% ethanol, rinsed with ether, and dried. The analytical sample of XIV was obtained by a second precipitation from fresh dimethylformamide, and was dried for 24 hr at 100° (0.01 mm), giving a white powder darkening above 320° without melting below 350°: λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 217 (30.5), 238 (30.7), 255 (37.1), 293 (6.0), 305 (7.2), 335 (2.5, infl), 345 (3.8), 359 (3.7); (EtOH, pH 1) 213 (26.4), 229 (32.5), 259 (24.8), 322 (7.9), 352 (5.3), 365 (4.7, infl); (EtOH, pH 10) 237 (29.2), 255 (33.1), 297 (6.0, infl), 305 (6.7), 344 (3.8), 358 (3.7).

Anal. Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.04; H, 4.41; N, 19.83.

1,3-Diaminobenzo[*f*]quinazoline (II). A.—A mixture of VIII (0.49 g, 0.00314 mole), cyanamide (0.5 g, 0.0123 mole), and pyridine hydrochloride (2.1 g, 0.019 mole) was heated in a wax bath maintained at 165°. The internal reaction temperature rose to 160°, then subsided to 153°. After 15 min the nearly resolidified melt was cooled to room temperature and triturated with small portions of 95% ethanol (20 ml total) until the solid was no longer gummy. The mixture was cooled in an ice bath and filtered. The yellow filter cake was washed with ether (10 ml) and transferred to 20 ml of 95% ethanol containing 0.5 ml of concentrated ammonia. The suspension was heated to boiling, and a small amount of solid remaining undissolved was separated by decantation. The decantate was cooled and water was added gradually until crystals formed. The solid was collected, washed with water, rinsed with ether, and dried; yield 0.25 g (38%). For analysis, a sample of II was crystallized twice from aqueous ethanol with the aid of Darco, giving nearly colorless needles, mp 200–202°, after being dried for 72 hr at 70° (0.01 mm): λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 214 (23.6), 218 (23.7), 250 (22.6, infl), 266 (44.0), 280 (15.4, infl), 292 (11.0), 352 (3.0), 365 (2.9); (EtOH, pH 1) 217 (34.0), 237 (24.2), 260 (27.7), 308 (6.1), 341 (3.5), 356 (3.2); (EtOH, pH 10) 248 (20.7, infl), 266 (41.4), 291 (10.0, infl), 353 (2.9), 363 (2.8).

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.55; H, 4.80; N, 26.25. Found: C, 68.71; H, 4.77; N, 26.41.

B.—A 20-cm Carius combustion tube containing 42 mg (0.17 mmole) of freshly sublimed XVIII in 2 ml of absolute ethanol saturated with dry ammonia was protected from moisture,[32] cooled to −40°, and sealed. A freshly sublimed sample of XVIII was used, in order to ensure that no XV was present at the start of the reaction. The absolute ethanol was freshly prepared by distillation from calcium hydride, followed by redistillation from sodium. The dry ammonia gas was generated by adding a small amount of sodium to liquid ammonia drawn from a commercial cylinder, and then allowing the ammonia to distil directly into the absolute ethanol in the Carius tube until the saturation point was reached. The sealed tube was heated at 150° for 48 hr in an autoclave, then cooled, and opened. A small crop of solid which had crystallized out upon cooling was collected, washed with water, and dried: yield 15 mg of crude XV, identified by spectroscopic comparison with an authentic sample. The ethanolic mother liquor was concentrated to dryness under reduced pressure, yielding 25 mg (71%) of II as colorless needles. The infrared and ultraviolet spectra of this material were identical with those of II prepared by procedure A, and the mixture melting point was not depressed.

1,3-Dihydroxybenzo[*f*]quinazoline (XV). A.—A mixture of XIV (19.3 g, 0.0915 mole), ethylene glycol (250 ml), and concentrated hydrochloric acid (250 ml) was stirred under reflux for 24 hr. The reaction mixture was cooled and filtered. The filter cake was washed thoroughly with water and dissolved in 350 ml of dimethylformamide near the boiling point. The solution was treated with Darco and diluted to 800 ml with water. The precipitated solid was collected, washed with water, rinsed with ether, and dried *in vacuo* at 125°: yield 13.5 g (70%) of XV. For analysis, XV was crystallized three times from acetic acid and dried for 24 hr at 100° (0.01 mm): mp 344–345°, not depressed on admixture with XV prepared by the method of Dziewonski and co-workers;[7] λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 225 (24.1, infl), 240 (33.4, infl), 245 (37.2), 252 (38.8), 262 (19.8), 282 (3.5, infl), 294 (4.7), 307 (5.5), 337 (3.8), 352 (3.7); (EtOH, pH 1) 212 (26.8), 224 (25.6), 232 (27.7), 241 (31.4, infl), 246 (34.9), 252 (36.9), 262 (19.2, infl), 299 (5.0, infl), 308 (5.9), 337 (3.7), 350 (3.5); (EtOH, pH 10) 238 (22.4, infl), 254 (39.1), 261 (40.2), 282 (7.9, infl), 291 (6.0, infl), 303 (4.2), 337 (3.2, infl), 351 (4.3), 369 (2.8, infl).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.74; H, 3.88; N, 13.31.

B.—A mixture of II (200 mg, 0.953 mmole), glacial acetic acid (15 ml), and concentrated hydrochloric acid (15 ml) was heated in an autoclave at 155° for 5 hr. Water (200 ml) was added to the cooled reaction mixture, and the precipitated solid was collected, washed with water, and crystallized twice from acetic acid, once with the aid of Darco: yield 65 mg (32%). The melting point and infrared and ultraviolet spectra of this sample were identical with those of XV prepared by procedure A.

1-Amino-3-mercaptobenzo[*f*]quinazoline (XVI).—A mixture of VIII (1.48 g, 0.00882 mole) and thiourea (3.0 g, 0.04 mole) was immersed in a wax bath preheated to 190°, and the internal temperature was maintained at 190–195° for 3.5 hr. The melt was cooled, pulverized, and triturated with dimethylformamide (10 ml). Water (100 ml) was added, and the precipitated solid was collected, washed with water, and dried *in vacuo*, yielding 1.75 g (88%) of crude XVI. For analysis, XVI was crystallized three times from 1:1 dimethylformamide–water with the aid of Darco, giving a yellow powder, mp 296–298° dec, after being at 110° (0.01 mm) for 72 hr: λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 256 (19.1, infl), 264 (22.1, infl), 274 (30.7), 301 (35.0), 359 (2.8); (EtOH, pH 1) 220 (23.0, infl), 258 (13.8), 272 (16.7), 303 (46.9), 380 (2.8, infl); (EtOH, pH 10) 232 (16.7), 257 (20.4, infl), 279 (37.9), 297 (26.1, infl), 343 (3.0, infl), 357 (3.0).

Anal. Calcd for $C_{12}H_9N_3S$: C, 63.41; H, 3.99; N, 18.49; S, 14.11. Found: C, 63.60; H, 4.09; N, 18.49; S, 14.13.

1-Hydroxy-3-aminobenzo[*f*]quinazoline (XVII).—A solution of II (100 mg, 0.476 mmole) in 75 ml of 6 *N* hydrochloric acid was refluxed for 24 hr. The fibrous needles of XVII HCl which precipitated on cooling were collected, washed with water, treated with dilute ammonia, and crystallized from acetic acid: yield 60 mg (60%) of XVII; mp >360°; λ_{max} in mμ (ε × 10^{-3}) (95% EtOH) 213 (20.8), 237 (15.7), 255 (35.9, infl), 263 (46.1), 272 (27.0, infl), 284 (8.7, infl), 295 (6.4, sh), 307 (3.1), 333 (2.8, infl), 349 (4.6), 364 (4.0); (EtOH, pH 1) 213 (25.5), 225 (18.7, infl), 234 (19.9, infl), 255 (36.8), 263 (39.2), 299 (4.4, sh), 313 (5.6), 332 (3.7), 347 (3.2); (EtOH, pH 10) 230 (15.8), 263 (50.0), 280 (11.7, infl), 291 (10.6), 301 (3.0, infl), 348 (3.3), 360 (3.1).

All efforts to obtain a solvent-free analytical sample of XVII were unsuccessful. Variable amounts of acetic acid appeared to be retained tenaciously even after thorough washing with water and prolonged drying of the pulverized sample at elevated temperatures. The following analytical values are typical.

Anal. Calcd for $C_{12}H_9N_3O \cdot 0.5C_2H_4O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.94; H, 4.55; N, 17.39.

1,3-Dichlorobenzo[*f*]quinazoline (XVIII).—A mixture of XV (4.85 g, 0.0229 mole), redistilled phosphorus oxychloride (12.5

ml), and phosphorus pentachloride (18 g) was refluxed with stirring for 1 hr. The orange solution formed a nearly solid yellow mass on cooling to room temperature. Excess phosphorus oxychloride was removed by means of a rotary evaporator. The residue was cooled in an ice bath and crushed ice was added. When most of the ice had melted, the pale yellow solid was collected, washed with a little cold water, and taken up in 1 l. of vigorously boiling chloroform. A small amount of insoluble matter was removed by filtration. The chloroform solution was dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure: yield 5.15 g (90%) of XVIII, lemon yellow powder, mp 183–184° (lit.[7] mp 184°). Alternatively, XVIII could be purified effectively on a small scale by vacuum sublimation at 140° (0.05 mm). This compound appears to be highly unstable in the presence of traces of moisture. A carefully dried and spectroscopically pure sample of XVIII was observed to have generated hydrogen chloride (readily detectable by its odor) after storage for a few weeks in a screwcap bottle, and its infrared spectrum already indicated the presence of an appreciable quantity of XV at this time.

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Quinoxaline Derivatives. IX.[1a] An Unusual Chlorine Substitution in Quinoxaline N-Oxides. Its Scope and Limitations

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An oxygen function at C-3 in quinoxaline 1-oxides has been shown to control the nucleophilic chlorine substitution at C-6 observed[2] when these N-oxides are heated with acetyl chloride or ethanolic hydrogen chloride. In its absence the chlorine substitution (a) fails to take place as evidenced in the case of 2,3-diphenylquinoxaline 1-oxide (Ij) and 1,4-dioxide (IVj); (b) if it takes place as in the case of 2,3-dimethylquinoxaline 1-oxide (If) and 1,4-dioxide (IVf) is directed to the methyl groups; (c) takes place at a position adjacent to the N-oxide if it is previously unoccupied.

Newbold and Spring[3] observed that 3-ethoxy-2-methylquinoxaline 1-oxide (Ia) on treatment with boiling ethanolic hydrogen chloride instead of giving the expected 2-chloromethyl-3-hydroxyquinoxaline (IIb) gave 6-chloro-3-hydroxy-2-methylquinoxaline (IIIc). Similarly Clark-Lewis and Katekar[4] confirmed the observation of Usherwood and Whiteley[5] that 3,4-dihydro-4-methyl-2-(N-methyl-N-phenylcarbamoyl)-3-oxoquinoxaline 1-oxide (V) on reaction with ethanolic hydrogen chloride also gave a compound with chlorine substituted on the benzene ring. Clark-Lewis, *et al.*, deduced the structure of this chloro compound as VI. For the mechanism of this unusual chlorine substitution, the latter considered the protonated form[4,6] of the N-oxide responsible for the nucleophilic attack of the chloride anion on the benzene ring of the quinoxaline moiety. In support they have drawn an analogy between their mechanism[4] of this reaction and that of the mechanism of the formation of *p*-chloroaniline from phenylhydroxylamine as proposed by Ingold.[7]

(1) (a) Part VIII: Y. Ahmad, M. S. Habib, M. Iqbal, M. I. Qureshi, and Ziauddin. *Can. J. Chem.*, **43**, 3424 (1965). (b) To whom inquiries should be addressed. (c) Burroughs Wellcome and Co. (Pakistan) Ltd., D/43 S.I.T.E., Karachi.

(2) Y. Ahmad, M. S. Habib, Ziauddin, and N. Bashir, *Bull. Chem. Soc. Japan*, **38**, 1953 (1965).

(3) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 519 (1948); W. Dawson, G. T. Newbold, and F. S. Spring, *ibid.*, 2579 (1949).

(4) J. W. Clark-Lewis and G. F. Katekar, *ibid.*, 2825 (1959).

(5) E. H. Usherwood and M. A. Whitely, *ibid.*, **123**, 1069 (1923).

(6) Y. Ahmad, M. S. Habib, M. Iqbal, M. I. Qureshi, and Ziauddin, *Bull. Chem. Soc. Japan*, **38**, 1659 (1965).

(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p 621.

In part VI[2] of this series, it has been shown that a large number of quinoxaline N-oxides bearing an aryl substituent at C-2 and a hydroxy group at C-3 undergo chlorination at position 6, on treatment with ethanolic hydrogen chloride (or acetyl chloride). A mechanism[2] has been proposed which envisages that attack of the reagent on the oxygen function at C-3 (probably augmented by the protonation or acylation of the N-oxide function) directs the nucleophilic attack of the chloride anion to position 6 of the quinoxaline. This mechanism fully and satisfactorily accounts[3,4] for the observations of Newbold, *et al.*, and Clark-Lewis, *et al.*, cited above.

In the present investigation the scope of this mechanism has been examined in further detail, and its generality has been established.

2-Phenylquinoline 1-oxide (VII), 2,3-diphenylquinoxaline 1-oxide (Ij), and the 1,4-dioxide IVj, all failed to react with acetyl chloride or ethanolic hydrogen chloride. Even when these reactions were carried out in sealed tubes at 100° for 24 hr, the starting materials in each case were recovered unchanged. This indicated that the N-oxides of these heterocycles in their protonated (or acylated) forms alone were unable to undergo the type of nucleophilic chlorination discussed above.

3-Phenylquinoxaline 1-oxide (Ik), when heated under reflux with acetyl chloride, gave a chlorine-substituted derivative, which was hydrolyzed with alkali to 3-hydroxy-2-phenylquinoxaline (IIq), indicating that the chloro compound formed in this reaction must have been 3-chloro-2-phenylquinoxaline