Quinazolines. XI. Synthesis of 2,4-Diamino-5,10-dihydrobenzo[*g*]quinazolines (1,2)

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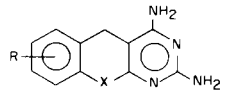
An unequivocal synthesis of 2,4-diamino-5,10-dihydrobenzo[*g*]quinazolines is described, starting from methyl 2-tetralone-3-carboxylates. Condensation with guanidine yielded 2-amino-4-hydroxy derivatives, which were thiated with phosphorus pentasulfide and *S*-alkylated with dimethyl sulfate. The resultant 2-amino-4-methylthio compounds were converted into 2,4-diamino derivatives by amination at elevated temperature and pressure. Attempted synthesis from 3-cyano-1,4-dihydro-2-methoxynaphthalene and guanidine was unsuccessful.

In connection with a larger synthetic program involving new types of polycyclic 2,4-diaminopyrimidines as potential antimalarial and antitumor agents (3), tricyclic ring systems of general structure **1** were viewed with interest because of their structural relationship to 2,4-diamino-5-benzylpyrimidines **2** (4). The latter non-bridged compounds have been shown to possess significant antifolate activity (5), and one of them, trimethoprim (**2**, R = 3′,4′,5′-$(MeO)_3$), has attracted considerable attention as an effective drug against resistant strains of malaria (6).



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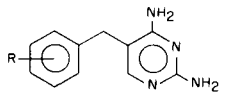

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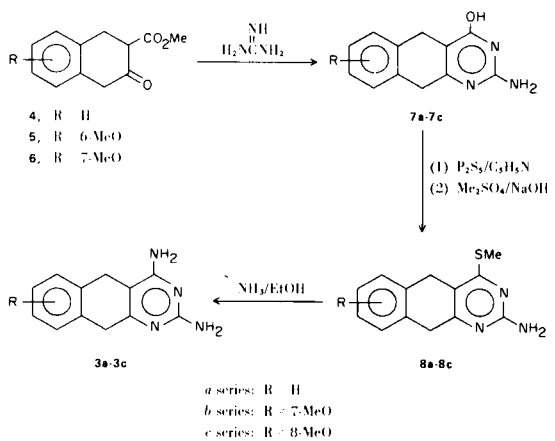
In this paper we should like to describe the synthesis of three members of the heretofore unreported 2,4-diamino-5,10-dihydrobenzo[*g*]quinazoline series (**1**, X = CH_2) *via* the route summarized in Scheme I. These linear compounds (**3a-3c**) are isomers of the angular 1,3-diamino-5,6-dihydrobenzo[*f*]quinazolines obtained earlier in this laboratory from 2-tetralones and cyanoguanidine (7).

Methyl 2-tetralone-3-carboxylate (**4**) was prepared from 2-hydroxy-3-naphthoic acid by electrolytic reduction to 2-tetralone-3-carboxylic acid (8a) followed by esterification with diazomethane (8b). The same acid and ester were also prepared for comparison by condensation of 2-tetralone with methyl magnesium carbonate and treatment with diazomethane (9). The latter route was followed for the synthesis of methyl 6-methoxy-2-tetralone-3-carboxylate (**5**) and methyl 7-methoxy-2-tetralone-3-carboxylate (**6**). Neither these two esters nor the corresponding acids have been described previously.

SCHEME I



The 2-tetralone-3-carboxylic acids were found to be capable of existence in either the keto or enol tautomeric form. In the solid state infrared absorption peaks characteristic of enolic β-keto acids were seen at 1670 and 1610-1630 cm^{-1}. Nmr spectra taken in deuteriopyridine, on the other hand, contained a complex array of methylene peaks between τ 6.0 and τ 8.0 suggesting a considerable amount of keto tautomer under these conditions. Nmr spectra of the corresponding esters in deuteriochloroform solution showed only a pair of singlets at τ 6.2 and τ 6.4 attributable to the methyl ester and ring methylene protons of the enol form. Infrared absorption bands in the 1660-1670 cm^{-1} and 1620-1640 cm^{-1} regions were

likewise typical of enolic β-keto esters.

Condensation of **4** with guanidine (Scheme I) proceeded rapidly and in high yield, giving 2-amino-5,10-dihydro-4-hydroxybenzo[*g*]quinazoline (**7a**), a high-melting material with very low solubility in all but the most polar solvents and with infrared and ultraviolet absorption features consistent with its 2-amino-4-hydroxypyrimidine structure. Direct chemical proof for the linear structure was provided *via* palladium-catalyzed dehydrogenation, which yielded a product indistinguishable from 2-amino-4-hydroxybenzo-[*g*]quinazoline derived from 2-amino-3-naphthoic acid and guanidine (10,11). Condensation of the methoxy analogs **5** and **6** likewise occurred readily, with formation of tricyclic compounds **7b** and **7c**.

Initial efforts to convert **7a** into **3a** *via* a chlorination-amination sequence were blocked when **7a** proved completely resistant to a variety of reagents, including phosphorus oxychloride, phosphorus pentachloride, and thionyl chloride. Despite repeated attempts under many different conditions, only high-melting insoluble products of undetermined structure were isolated, along with considerable amounts of tar. On the other hand, thiation with phosphorus pentasulfide in pyridine readily afforded a 2-amino-4-mercapto derivative which could be *S*-alkylated directly with dimethyl sulfate in the presence of base to 2-amino-5,10-dihydro-4-methylthiobenzo[*g*]quinazoline (**8a**). The overall yield of **8a** was 67% and similar results were obtained with the monomethoxy analogs. In contrast to the 4-mercapto compounds, which were difficult to purify because of their extremely low solubility, the 4-methylthio derivatives could be recrystallized from moderately polar solvents such as tetrahydrofuran.

The structure of **8a** was supported by the nmr spectrum in deuteriopyridine solution, which showed the aromatic and 2-amino protons as singlets at τ 2.71 and τ 3.0 (broad), the *S*-methyl protons as a sharp singlet at τ 7.46, and the methylene protons at $C_{(5)}$ and $C_{(10)}$ as a finely resolved 6-peak A_2B_2 pattern centered at τ 6.08. The latter appears to be a characteristic feature of the linear 5,10-dihydrobenzo[*g*]quinazoline system and is suggestive of a fairly rigid molecule.

On treatment of **8a** with ethanolic ammonia in a stainless steel autoclave at elevated temperature, nucleophilic replacement of the 4-methylthio group led to the formation of **3a** in approximately 50% yield. The identity of **3a** was apparent on the basis of its microanalysis and spectral data. The ultraviolet spectrum resembled closely those reported for 2,4-diamino-5-benzylpyrimidine and 2,4-diamino-5-benzyl-6-methylpyrimidine (12), with a maximum in ethanol at about 285 nm. The nmr spectrum in deuteriopyridine solution showed the aromatic protons as a singlet at τ 2.73, the 2- and 4-amino protons as broad singlets at τ 3.08 and 3.55, and the $C_{(5)}$ and $C_{(10)}$ methylene protons as a 6-peak A_2B_2 multiplet centered at τ 6.02. In addition, palladium-catalyzed dehydrogenation afforded a product identical with an authentic sample of 2,4-diaminobenzo[*g*]quinazoline prepared previously either by ammonolysis of 2,4-dichlorobenzo[*g*]-quinazoline (10,11) or by direct amination of 4-mercaptobenzo[*g*]quinazoline (13). Amination of **8b** and **8c** proceeded similarly, giving **3b** and **3c** in about 60% yield.

Because of our earlier experience in the synthesis of 1,3-diamino-5,6-dihydrobenzo[*f*]quinazoline from 1-cyano-3,4-dihydro-2-methoxynaphthalene and guanidine (7b), an extension of this approach was attempted with the isomeric 3-cyano-1,4-dihydro-2-methoxynaphthalene (**9**).

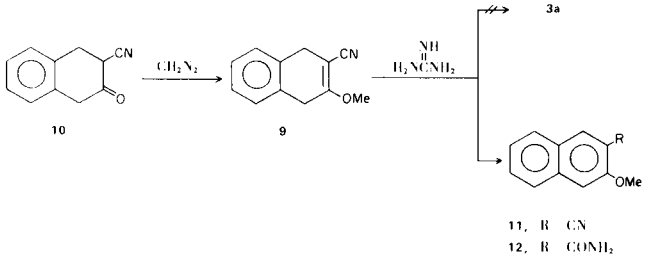
3-Cyano-2-tetralone (**10**) was synthesized according to a modification of the reported preparation of 3-cyano-5-methoxy-2-tetralone (9). In our hands formylation of 2-tetralone with ethyl formate could not be achieved satisfactorily with sodium methoxide or sodium hydride as the basic catalyst (14) but was effected in moderate yield with metallic sodium. Direct reaction of the crude hydroxymethylene derivative with hydroxylamine hydrochloride in acetic acid yielded a non-homogeneous product whose nmr spectrum revealed two major and two minor peaks in the τ 1.30-1.75 region where -N=CH- and O-CH=C- protons would be expected to absorb. In addition two complex methylene multiplets were seen at τ 5.7-6.0 and τ 6.8-6.9. Although the nmr data clearly suggested the presence of more than one isoxazole isomer in the mixture, further treatment with sodium methoxide nonetheless led to the isolation of a single crystalline end product, to which structure **10** was assigned.

In contrast to 1-cyano-2-tetralone, which totally lacks infrared carbonyl absorption and is thus entirely enolic (7b,15), compound **10** exhibited in chloroform solution a carbonyl band at 1740 cm^{-1} as well as a strong conjugated nitrile band at 2220 cm^{-1}. It was concluded that **10** can exist as a keto-enol equilibrium mixture in chloroform solution but that the unconjugated nitrile band of the keto tautomer is too weak to be visible at normal concentrations (16). In accord with this view, the nmr spectrum of **10** in deuteriochloroform solution showed a total of seven peaks in the τ 6.25-6.75 region corresponding to the various types of methylene protons expected in such a tautomer mixture.

Despite the incompletely enolic character of **10**, reaction with diazomethane resulted in kinetically controlled selective *O*-methylation. That the sole product was the desired **9** was shown by the nmr spectrum, which contained only a singlet at τ 6.02 corresponding to the *O*-methyl protons and a second singlet at τ 6.40 ascribable to the methylene groups at $C_{(1)}$ and $C_{(4)}$. The infrared spectrum contained the expected unsaturated nitrile

band at 2220 cm^{-1}.

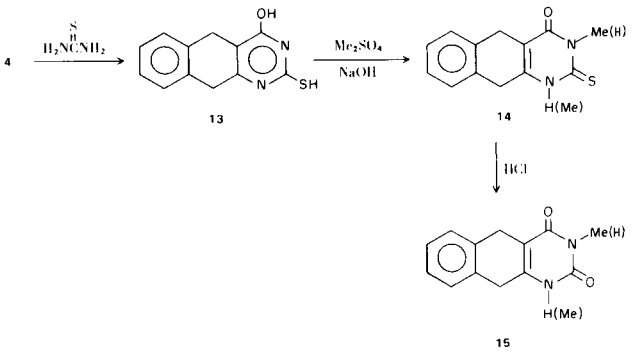
Unfortunately, attempted condensation of **9** with guanidine failed to give **3a**. Instead a complex mixture was obtained, consisting predominantly of 3-cyano-2-methoxynaphthalene (**11**) and 2-methoxynaphthalene-3-carboxamide (**12**). While the possibility could not be excluded that one of the trace components of the mixture might be the desired **3a**, the results discouraged us from further pursuit of this approach.



10 9

11, R = CN
12, R = $CONH_2$

A second unsuccessful alternative route to **3a** began with the condensation of **4** with thiourea instead of guanidine. It was intended for the resultant 5,10-dihydro-4-hydroxy-2-mercaptobenzo[*g*]quinazoline (**13**) to be converted *via* two additional steps into a 4-chloro-2-methylthio derivative which would then be aminated with simultaneous replacement of the 2- and 4-substituents. This strategy likewise had to be abandoned because reaction of **13** with dimethylsulfate in the presence of base gave *N*-alkylation instead of *S*-alkylation. The product showed intense amide carbonyl absorption in the infrared at 1670 cm^{-1} and was converted on acid hydrolysis into a sulfur-free compound retaining a methyl group. The infrared spectrum of the latter compound showed strong amide bands at 1750 and 1650 cm^{-1}, the higher wavenumber peak being due presumably to the newly formed 4-oxo moiety. The nmr spectrum in deuteriopyridine solution showed the aromatic protons as a singlet at τ 2.77, the $C_{(5)}$ and $C_{(10)}$ protons as a singlet at τ 6.15, and the *N*-methyl protons as a singlet at τ 6.52. The data supported the formulation of the alkylation product as **14** and the subsequent hydrolysis product as **15**.



13 14 15

The singlet produced by the middle-ring protons in **15** is noteworthy because the corresponding protons in **3a** and **8a** gave rise to A_2B_2 multiplets. In **15**, *N*-alkylation has obviously disrupted the aromatic character of the pyrimidine ring, thereby altering the overall geometry of the molecule. The tendency of **13** to undergo *N*-alkylation is likewise of interest, inasmuch as it appears to contradict Brown's generalization that alkylation of mercaptopyrimidines invariably leads to *S*-alkyl derivatives (17). Although unequivocal proof is lacking, we favor the $N_{(3)}$-methyl structure for both **14** and **15** because of the very narrow half-peak width (*ca.* 1 Hz) and complete lack of fine structure in the *N*-methyl proton signal of **15**, and because of the published observation that treatment of 1,2,3,4-tetrahydro-4-oxo-2-thioquinazoline with dimethyl sulfate leads to alkylation at $N_{(3)}$ preferentially (18).

Biological Results.

Compounds **3a** and **3b** were assayed for antimetabolite activity against *Streptococcus faecium ATCC #8043* as described earlier (19). At a folate level of 0.001 μg./ml., 50% inhibition of cell growth was observed at concentrations of 1.5 μg./ml. and 0.28 μg./ml., respectively. Compound **3a** was also tested for antimalarial activity against *Plasmodium berghei* in the mouse (20). At a single dose of 640 mg./kg. the mean survival time of treated animals was 10.0 days as compared with 6.2 days for the untreated controls.

EXPERIMENTAL (21)

7-Methoxy-2-tetralone-3-carboxylic Acid.

Anhydrous methanol (200 ml.), dimethylformamide (30 ml., previously dried over Linde 4A molecular sieves), and magnesium metal (10 g., 0.43 mole) were placed in a 500 ml. three-neck flask equipped with a gas inlet tube, two long reflux condensers, an efficient magnetic stirrer, and a cold water bath. Dry carbon dioxide was bubbled through the vigorously stirred mixture at a rate sufficient to cause gentle reflux and a moderately rapid dissolution of the magnesium (22). When a clear solution was obtained (*ca.* 40 minutes) a second portion of dry dimethylformamide was added, the reflux condensers were replaced with a distillation head, and the flask was heated by means of an oil bath, a carbon dioxide atmosphere being maintained as much as possible during this and subsequent operations until the end of the reaction. When the vapor temperature reached 140°, indicating complete removal of the methanol, the solution was cooled, 7-methoxy-2-tetralone (22 g., 0.13 mole) (23) was added with stirring, and heating was resumed at 130° (bath temperature) with the distillation head still in place. After about 4 hours the mixture was poured into ice-cold 10% hydrochloric acid (600 ml.), and the product was extracted with ether (3 x 300 ml.). Washing of the combined ether layers with water, drying, and evaporation left a solid. This was washed with 4:1 hexane-ether in order to remove unreacted 7-methoxy-2-tetralone (12 g., 55% recovery), and the residue (5.2 g., 19% yield) was recrystallized from tetrahydrofuran-hexane; m.p. 133-134° dec.; ν max (potassium

chloride) 2940 and 2660 (broad), 1680, 1630 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.58; H, 5.69.

Methyl 7-Methoxy-2-tetralone-3-carboxylate (**6**).

A suspension of the foregoing acid (5 g., 0.023 mole) in ice-cold ether (250 ml.) was treated with ethereal diazomethane (80 ml.) obtained in the usual manner from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (24). After overnight storage at room temperature excess diazomethane was destroyed by addition of acetic acid (5 ml.) and the solution was washed with saturated sodium bicarbonate, rinsed with water, dried, and evaporated to a reddish oil which solidified on contact with a small amount of 95% ethanol. Recrystallization from 80% ethanol afforded 3.4 g. (65% yield) of pale yellow needles; m.p. 85-86° (ethanol); ν max (potassium chloride) 3510, 3080-2900 (4 peaks), 1675, 1640 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.95; H, 6.30.

Methyl 6-Methoxy-2-tetralone-3-carboxylate (**5**).

Condensation of 6-methoxy-2-tetralone (25) with methyl magnesium carbonate as described for the 7-methoxy isomer gave a 60% yield of light yellow 6-methoxy-2-tetralone-3-carboxylic acid; m.p. 106-107° dec. (THF-hexane); ν max (potassium chloride) 3390, 3080, 2630 (broad), 1670, 1610 cm^{-1}. Esterification with ethereal diazomethane as described in the preceding experiment gave a 46% yield of pale yellow needles; m.p. 98-99° (80% ethanol); ν max (potassium chloride) 3410, 3080-2900 (4 peaks), 1665, 1640, 1600 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.97; H, 6.18.

2-Amino-5,10-dihydro-4-hydroxybenzo[*g*]quinazoline (**7a**).

A mixture of methyl 2-tetralone-3-carboxylate (**4**) (8a,b) (1.0 g., 0.0049 mole), guanidine carbonate (1.0 g., 0.0056 mole), and absolute ethanol (20 ml.) was stirred under reflux for 16 hours. The solvent was evaporated under reduced pressure, water (20 ml.) was added to the greenish yellow residue, and the *p*H was adjusted to 6.5 with glacial acetic acid (3 ml.). The solid was collected, washed with water, and redissolved in warm 1*N* sodium hydroxide (100 ml.). Treatment of the solution with decolorizing carbon and neutralization to *p*H 7 with acetic acid afforded a light yellow solid (1.1 g., 54% yield) which was purified by crystallization from dimethylformamide; m.p. >350°; ν (potassium chloride) 3350, 3220, 1670, 1615 cm^{-1}; λ max (ethanol) (nm) 265 (ϵ 8900), 273 (ϵ 10,100), 287 (ϵ 7600); λ max (*p*H 1, ethanol) (nm) 257 (ϵ 14,400), 262 (ϵ 15,700); λ max (*p*H 10, ethanol) (nm) 230 (ϵ 9500), 243 (ϵ 11,400), 270 (ϵ 9600).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.60; H, 5.20; N, 19.71. Found: C, 67.36; H, 5.32; N, 19.50.

2-Amino-5,10-dihydro-4-hydroxy-7-methoxybenzo[*g*]quinazoline (**7b**).

Condensation of **5** (3.0 g., 0.014 mole) with guanidine carbonate (3.0 g., 0.017 mole) as in the preceding experiment gave 3.1 g. (86% yield) of pale yellow powder; m.p. >300° (DMF); ν max (potassium chloride) 3390, 3220, 1670, 1660, 1640 cm^{-1}; λ max (ethanol) (nm) 223 (ϵ 18,200), 285 (ϵ 8700); λ max (*p*H 1, ethanol) (nm) 226 (ϵ 18,400), 265 (ϵ 7700); λ max (*p*H 10, ethanol) (nm) 277 (ϵ 7900).

Anal. Calcd. for $C_{13}H_{12}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.38; H, 5.31; N, 16.95.

2-Amino-5,10-dihydro-4-hydroxy-8-methoxybenzo[*g*]quinazoline (**7c**).

Condensation of **6** (3.1 g., 0.014 mole) with guanidine carbonate (3.1 g., 0.017 mole) as described above afforded 3.4 g. (*ca.* 100% yield) of pale yellow powder; m.p. >300° (DMF); ν max (potassium chloride) 3450, 3220, 1655, 1630 cm^{-1}; λ max (ethanol) (nm) 267 (ϵ 8600, inflection), 277 (ϵ 11,600), 287 (ϵ 9300, inflection), 300 (ϵ 4900, inflection); λ max (*p*H 1, ethanol) 227 (nm) (ϵ 15,400), 268 (ϵ 8800, inflection); λ max (*p*H 10, ethanol) 230 (nm) (ϵ 13,900, inflection), 268 (ϵ 8800, inflection), 278 (ϵ 10,700, inflection).

Anal. Calcd. for $C_{13}H_{12}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.49; H, 5.48; N, 17.04.

2-Amino-5,10-dihydro-4-methylthiobenzo[*g*]quinazoline (**8a**).

A mixture of **7a** (2.0 g., 0.0094 mole), freshly purified phosphorus pentasulfide (26) (2.0 g., 0.0089 mole), and dry pyridine (20 ml.) was stirred under reflux for 1 hour. After removal of the solvent under reduced pressure the residue was treated with 60% methanol-water (50 ml.) on the steam bath for 30 minutes, the volume was reduced to 20 ml., water (50 ml.) was added, and the solid was collected; yield 1.4 g. (65%). The combined crude product from two runs (3.0 g., 0.014 mole) was dissolved in warm 10% sodium hydroxide (20 ml.) and the solution was decolorized with charcoal, filtered through Celite, cooled to 0°, and treated dropwise with dimethyl sulfate (3 ml.). After 25 minutes of stirring, the precipitate was collected, washed with water, and dried; yield 2.4 g. (67%). Crystallization from tetrahydrofuran-hexane (charcoal) furnished analytically pure **8a** in the form of long light-yellow needles; m.p. 207-210° dec.; ν max (potassium chloride) 3510, 3330, 3170, 1625 cm^{-1}; λ max (ethanol) (nm) 234 (ϵ 16,900), 245 (ϵ 13,700, inflection), 303 (ϵ 8000); λ max (*p*H 1, ethanol) (nm) 233 (ϵ 10,500), 273 (ϵ 11,300), 310 (ϵ 9900).

Anal. Calcd. for $C_{13}H_{13}N_3S$: C, 64.17; H, 5.38; N, 17.27; S, 13.18. Found: C, 64.27; H, 5.47; N, 17.42; S, 13.12.

2-Amino-5,10-dihydro-7-methoxy-4-methylthiobenzo[*g*]quinazoline (**8b**).

Thiation and methylation of **7b** as described in the preceding experiment afforded a 53% yield of pale yellow solid; m.p. 204-208° dec. (THF); ν max (potassium chloride) 3570, 3450, 3360, 3230, 1620 cm^{-1}; λ max (ethanol) (nm) 230 (ϵ 21,700), 245 (ϵ 14,700, inflection), 292 (ϵ 7300), 305 (ϵ 8800); λ max (*p*H 1, ethanol) (nm) 277 (ϵ 13,600), 307 (ϵ 11,300).

Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.67; H, 5.73; N, 15.12; S, 11.81.

2-Amino-5,10-dihydro-8-methoxy-4-methylthiobenzo[*g*]quinazoline (**8c**).

Thiation and methylation of **7c** as described above afforded a 59% yield of pale yellow solid; m.p. 198-201° dec. (THF); ν max (potassium chloride) 3580, 3510, 3350, 3230, 1640 cm^{-1}; λ max (ethanol) (nm) 235 (ϵ 21,000), 247 (ϵ 16,300, inflection), 291 (ϵ 6700, inflection), 305 (ϵ 8500); λ max (*p*H 1, ethanol) 232 (ϵ 12,800), 276 (ϵ 15,000), 303 (ϵ 11,800).

Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.54; H, 5.72; N, 15.54; S, 11.38.

2,4-Diamino-5,10-dihydrobenzo[*g*]quinazoline (**3a**).

A mixture of **8a** (0.5 g., 0.0021 mole) and ethanolic ammonia (5 ml., 20% w/w) was heated in a stainless steel autoclave at 180-200° (jacket temperature) for 16 hours (27). After cooling

and filtration the brownish-yellow solid (0.28 g.) was recrystallized from ethanol; yield 0.22 g. (50%). For the preparation of analytically pure material a 0.1 g. sample was dissolved in dimethylformamide (5 ml.) and the solution was placed on a silica gel column (1.5 x 20 cm.). Successive elution with chloroform (200 ml.) and 4:1 chloroform-ethanol (300 ml.), evaporation of the pooled chloroform-ethanol eluates, and crystallization of the residue from ethanol afforded small yellow prisms, m.p. 261-263° dec.; ν max (potassium chloride) 3450, 3380, 3180, 1650, 1610, 1575 cm^{-1}; λ max (ethanol) (nm) 282 (ϵ 7200); λ max (pH 1, ethanol) (nm) 267 (ϵ 7800), 271 (ϵ 7900).

Anal. Calcd. for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.53; H, 5.70; N, 26.56.

2,4-Diamino-5,10-dihydro-7-methoxybenzo[*g*]quinazoline (**3b**).

Amination of **8b** was carried out as in the preceding experiment, the temperature being maintained at 200° for 20 hours. The deep orange reaction mixture was cooled and filtered, the filtrate was evaporated to dryness under reduced pressure, and the residue was filtered and washed with ether; 60% yield. For microanalysis a portion of this material was recrystallized from *n*-butylamine (charcoal); m.p. 212° dec.; ν max (potassium chloride) 3570, 3440, 3230, 1640, 1590 cm^{-1}; λ max (ethanol) (nm) 263 (ϵ 6300, inflection), 283 (ϵ 8500); λ max (pH 1, ethanol) (nm) 266 (ϵ 9600).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.67; H, 5.72; N, 22.98.

2,4-Diamino-5,10-dihydro-8-methoxybenzo[*g*]quinazoline (**3c**).

Amination of **8c** as described above gave a 60% yield of crude **3c**, which was recrystallized twice from *n*-butylamine (charcoal); m.p. 216° dec.; ν max (potassium chloride) 3440, 3280, 1665, 1640 cm^{-1}; λ max (ethanol) (nm) 230 (ϵ 12,400, inflection), 282 (ϵ 8200); λ max (pH 1, ethanol) (nm) 227 (ϵ 14,300), 277 (ϵ 8100).

Anal. Calcd. for $C_{13}H_{14}N_4O \cdot 0.75C_4H_9NH_2$: C, 64.73; H, 7.47; N, 22.41. Found: C, 64.63; H, 7.04; N, 21.96.

3-Cyano-2-tetralone (**10**).

Metallic sodium (1.3 g., 0.057 g.-atom) was added in small pieces to a stirred solution of ethyl formate (12 ml.) in ether (100 ml.) under a nitrogen atmosphere. A solution of 2-tetralone (7.3 g., 0.05 mole) was then added, and the orange solution was stirred overnight at room temperature. After addition of water the layers were separated and the aqueous layer was acidified to pH 5 with dilute hydrochloric acid, saturated with sodium chloride, and extracted repeatedly with ether. Drying and evaporation of the combined ether extracts gave 4.7 g. of crude 3-hydroxymethylene-2-tetralone as a dark amber-colored oil; ν max (carbon tetrachloride) 1667 and 1613 cm^{-1} (-CO-C(=CHOH)-). This was dissolved directly in glacial acetic acid (70 ml.) and powdered hydroxylamine hydrochloride (2.3 g.) was added. After 25 minutes of stirring at 115° under nitrogen the mixture was evaporated to dryness under reduced pressure and the residue was partitioned between carbon tetrachloride and water (a small amount of insoluble black tar was discarded). Evaporation of the carbon tetrachloride and passage of the residue through acid-washed Merck alumina (25 g.) with benzene as the eluant gave 2.1 g. of isoxazole mixture (see Discussion). This was dissolved in benzene (50 ml.) and treated with a solution of sodium (0.65 g.) in methanol (40 ml.) under nitrogen. After 3 hours at room temperature, ice-cold water and ether were added and the aqueous layer was separated, acidified to pH 6 with dilute hydrochloric acid, saturated with sodium chloride, and extracted twice with ether. Drying and evaporation of the combined organic layers afforded an oil from which 0.65 g. of crystalline product was obtained on crystallization from a small volume of ether. Analytically pure **10** was prepared by repeated recrystallization, once from ether and once from dichloromethane-ether; m.p. 107-108°; ν max (potassium chloride) 3250 (OH), 2220 (conjugated nitrile), 1680 (C=O), 1590 cm^{-1}; ν max (chloroform) 2230 (conjugated nitrile), 1740 (C=O), 1610 cm^{-1}.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.14; H, 5.36; N, 8.16.

3-Cyano-1,4-dihydro-2-methoxynaphthalene (**9**).

Treatment of the foregoing cyano ketone **10** (0.53 g., 0.0031 mole) with ethereal diazomethane yielded 0.46 g. (80%) of the enol ether; m.p. 96-97° (ethanol); ν max (potassium chloride) 2220 (conjugated nitrile), 1640 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.56; H, 6.16; N, 7.80.

Attempted Condensation of **9** with Guanidine.

A solution of **9** (0.46 g., 0.0025 mole), guanidine hydrochloride (0.29 g., 0.003 mole), and sodium methoxide (from 0.069 g., 0.003 mole, of sodium metal) in ethanol (5 ml. total volume) was refluxed under nitrogen for 4 days. After cooling and filtration to remove sodium chloride, the solvent was evaporated under reduced pressure. The residue, consisting largely of dark tarry material at this point, was purified partially by vacuum sublimation at 100° (bath temperature)/0.05 mm. The sublimate, m.p. 105-125°, was shown by tlc on silica gel (4:1 benzene-methanol) to contain two rapidly moving major components. Preparative tlc in combination with ir and mass spectral analysis allowed the first major product to be identified as 3-cyano-2-methoxynaphthalene (**11**); m/e 183 (parent ion); ν max (chloroform) 2275 (aromatic nitrile), 1645, 1610 cm^{-1}. The second, somewhat less abundant product was identified as 2-methoxy-3-naphthalenecarboxamide (**12**); m/e 201 (parent ion); ν max (chloroform) 3600 and 3460 (NH_2), 1675 (amide C=O), 1630, 1580 cm^{-1}. Several minor constituents probably comprising less than 5% of the mixture were not identified. No evidence for the formation of any **3a** was found either under the above conditions, or on heating at 135° for 15 hours in 2-ethoxyethanol under nitrogen.

5,10-Dihydro-4-hydroxy-2-mercaptobenzo[*g*]quinazoline (**13**).

A mixture of **4** (2.0 g., 0.0098 mole), thiourea (4.0 g., 0.053 mole), and absolute ethanol (20 ml.) was stirred under reflux for 5 hours and evaporated to dryness under reduced pressure. The residue was washed with water and recrystallized from ethanol; yield 1.6 g. (71%); m.p. >300°; ν max (potassium chloride) 3450, 3150, 2960, 1680 cm^{-1}; λ max (ethanol) (nm) 282 (ϵ 18,300).

Anal. Calcd. for $C_{12}H_{10}N_2OS$: C, 62.59; H, 4.38; N, 12.16. Found: C, 62.45; H, 4.41; N, 12.35.

1,2,3,4,5,10-Hexahydro-3(or 1)-methyl-4-oxo-2-thiobenzo[*g*]quinazoline (**14**).

An ice-cold solution of **13** (1.5 g., 0.0065 mole) in 10% sodium hydroxide (20 ml.) was treated dropwise with dimethyl sulfate (1.5 ml.). After 30 minutes of stirring the precipitate was filtered, washed with water, and recrystallized from ethanol in the form of colorless fibrous needles; yield 1.0 g. (63%); m.p. 230-233°; ν max (potassium chloride) 3510, 1660 cm^{-1}; λ max (ethanol) (nm) 240 (ϵ 8900), 282 (ϵ 8800).

Anal. Calcd. for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.46. Found: C, 64.14; H, 5.06; N, 11.32.

1,2,3,4,5,10-Hexahydro-3(or 1)-methyl-2,4-dioxobenzo[*g*]quinazoline (**15**).

A mixture of **14** (0.5 g., 0.002 mole) and concentrated hydrochloric acid (20 ml.) was stirred under reflux for 5 hours, diluted with water (50 ml.), cooled, and filtered. Recrystallization from ethanol gave colorless prisms (0.27 g., 61% yield); m.p. 274-275°; ν max (potassium chloride) 3510, 3230, 1750, 1670 cm^{-1}; λ max (ethanol) (nm) 264 (ϵ 6400).

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.27. Found: C, 68.03; H, 5.34; N, 12.47.

Dehydrogenation Experiments.

A. A mixture of **7a** (50 mg.) and 5% palladium-on-carbon (50 mg.) was heated for 2 hours in a Wood's metal bath maintained at 300-320°. Extraction with hot 95% ethanol yielded a product whose ultraviolet absorption spectrum was indistinguishable from that of 2-amino-4-hydroxybenzo[*g*]quinazoline (10,11).

B. Similar treatment of **3a** (0.5 g.) with 10% palladium-on-carbon (0.5 g.) under nitrogen at 180-200° (bath temperature) for 1.5 hours afforded a product whose infrared and ultraviolet spectra were identical with those of an authentic sample of 2,4-diaminobenzo[*g*]quinazoline (11).

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