Chemical and Biological Studies on Dihydro-*s*-triazines. XVI. Nmr Evidence for the Formation of 2-Guanidino-4-methylquinazolines as Anomalous Byproducts in the Three-Component Synthesis (1a,b)

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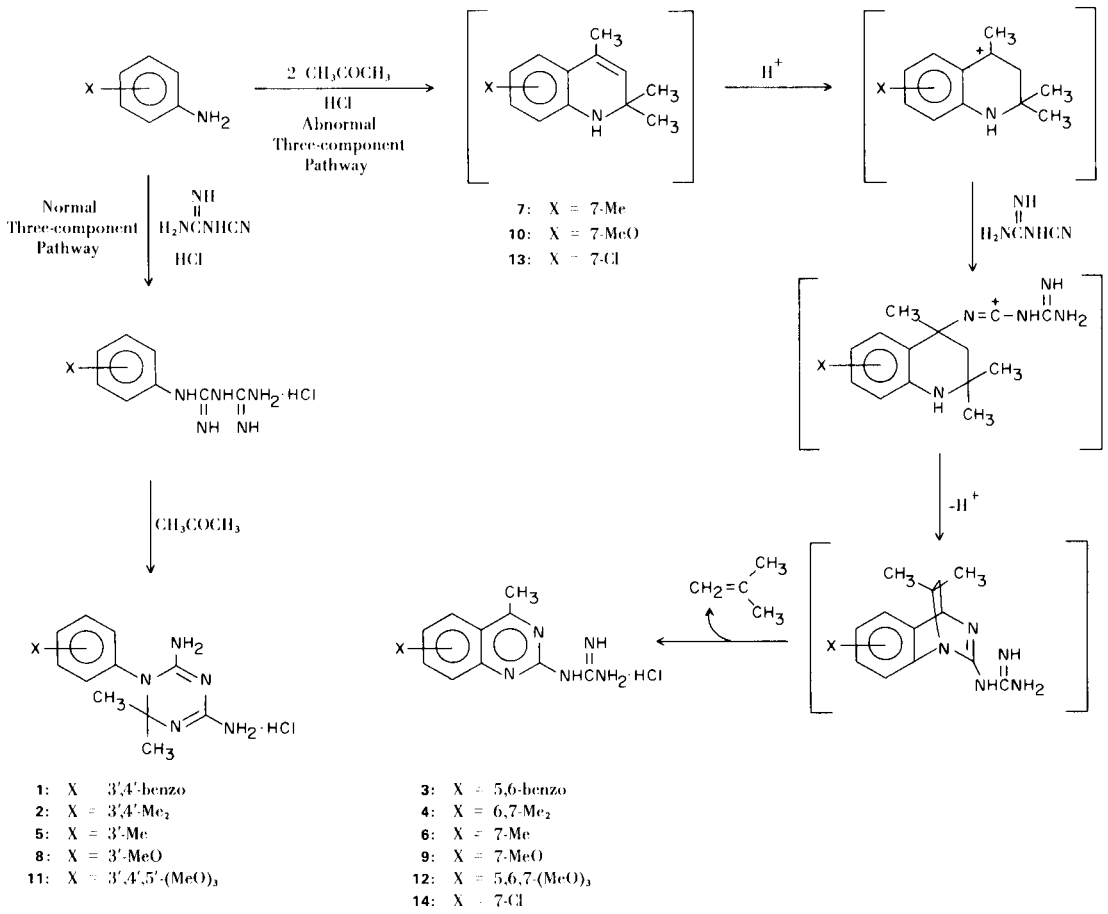
The three-component synthesis of 4,6-diamino-1-aryl-1,2-dihydro-2,2-dimethyl-*s*-triazines from arylamines, cyanoguanidine, and acetone has been studied by nmr spectral analysis in trifluoroacetic acid solution. The presence of 2-guanidino-4-methylquinazoline contaminants can be discerned clearly at concentrations as low as 1%. Arylamines most likely to give significant proportions of guanidinoquinazoline byproducts are 2-naphthylamines and anilines containing one or more electron-donating *meta*-substituents.

4,6-Diamino-1-aryl-1,2-dihydro-*s*-triazines (2), a class of compounds endowed with a broad spectrum of biological properties including antibacterial, antiparasitic, and experimental antitumor activity, can be prepared *via* a "three-component synthesis" involving condensation of equimolar amounts of an arylamine salt, cyanoguanidine (dicyandiamide), and a ketone or aldehyde (3,4). Alternatively, a "two-component synthesis" may be employed, involving reaction of an arylbiguanide salt with a ketone or aldehyde (5) or reaction of a protonated Schiff base with cyanoguanidine (6). Of these three general routes, the most direct and, therefore, most popular (7) has been the three-component synthesis.

Several years ago we reported that the three-component synthesis proceeded anomalously with 2-naphthylamine (8a) and 3,4-dimethylaniline (8b). With acetone as the carbonyl component, the dihydro-*s*-triazine products **1**·HCl and **2**·HCl were contaminated with varying amounts of guanidinoquinazoline salts **3**·HCl and **4**·HCl, respectively. A possible mechanism was proposed (Chart I) (8b) which involved initial formation of a 1,2-dihydro-2,2,4-trimethylquinoline (9) and subsequent reaction of this intermediate with cyanoguanidine (10). It was suggested (8b) that formation of difficultly separable guanidinoquinazoline byproducts could be more prevalent in the three-component synthesis than had been heretofore recognized. In this paper we should like to report additional experiments aimed at a more precise delineation of the scope and limitations of the three-component synthesis.

Nmr spectrometry in trifluoroacetic acid (TFA) solution provided a convenient and highly sensitive assay for the detection of guanidinoquinazolines in the three-component synthesis mixture (11). For example, the spectrum of an incompletely purified sample of **1**·HCl showed, in addition to the expected *gem*-dimethyl doublet at τ 8.12 (12), a smaller singlet at τ 6.35 corresponding to the 4-methyl group of **3**·HCl. Quantitative estimation of relative peak areas after deliberate addition of a known amount of authentic **3**·HCl established that the original impure sample of dihydro-*s*-triazine contained a small amount, probably about 10%, of guanidinoquinazoline byproduct. Similar analyses were then carried out for the dihydro-*s*-triazines from *m*-toluidine and *p*-toluidine, which had been synthesized routinely in this laboratory several years before (3b) with no indications of any byproducts being formed. A sample of unpurified 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(*m*-tolyl)-*s*-triazine hydrochloride (**5**·HCl) in TFA solution (300 mg./ml.) showed strong *gem*-dimethyl and aromatic methyl signals at τ 8.20 (6 protons) and τ 7.50 (3 protons) (see Table I for complete nmr data for **5**·HCl and **6**·HCl and other pairs of dihydro-*s*-triazines and guanidinoquinazolines discussed in this paper). In addition, two small but clearly visible peaks (the visual sensitivity of the assay is illustrated in Figure 1) at τ 7.22 and τ 6.70 corresponded exactly to the 7-methyl and 4-methyl groups of 2-guanidino-4,7-dimethylquinazoline hydrochloride (**6**·HCl), an authentic sample of which was synthesized from 1,2-dihydro-2,2,4,7-tetra-

CHART I



methylquinoline (**7**) (9b), cyanoguanidine, and hydrochloric acid. The amount of **6**·HCl in the crude three-component synthesis product was estimated to be no greater than 2%, which would explain the fact that this byproduct had previously escaped detection. In contrast, the TFA spectrum (300 mg./ml.) of an unpurified sample of 4,6-diamino-1,2-dihydro-2,2-dimethyl-(1-*p*-tolyl)-*s*-triazine hydrochloride showed *gem*-dimethyl and aromatic methyl peaks at τ 8.22 (6 protons) and τ 7.52 (3 protons) but no trace of absorption at τ 7.28 and τ 6.67 corresponding to the 4-methyl and 6-methyl protons of a separately prepared sample of 2-guanidino-4,6-dimethylquinazoline hydrochloride (10b).

The fact that *m*-toluidine and 3,4-dimethylaniline both gave discernible amounts of byproduct, whereas *p*-toluidine did not, suggested that the position *ortho* to the amino group was being activated toward electrophilic attack as a result of hyperconjugative participation by a methyl group. According to this view, the arylamines most likely to give guanidinoquinazoline byproducts would be those containing electron-releasing substituents *meta* to the amino group. The formation of 1,2-dihydroquinolines from arylamines and acetone has been shown to proceed *via* intramolecular electrophilic substitution (13), and evidence has been presented for the probable intermediacy of 1,2-dihydroquinolines in the abnormal three-component pathway (Chart I) (8). With arylamines containing an especially reactive *ortho* position, the rate of dihydroquinoline formation could be sufficiently rapid, relative to the rate of biguanide formation, to permit the isolation of significant quantities of guanidinoquinazoline byproduct.

In order to establish the validity of the above hypothesis, we chose to examine two highly activated arylamines, *m*-anisidine and 3,4,5-trimethoxyaniline, neither of which had been used previously in this laboratory for the preparation of dihydro-*s*-triazines (14).

The three-component synthesis with *m*-anisidine was performed according to a slightly modified procedure (see Experimental) involving periodic interruption to col-

lect crops of product for nmr analysis. Although the first crop consisted entirely of the dihydro-*s*-triazine **8**·HCl (*gem*-dimethyl at τ 8.20, *m*-methoxy at τ 6.10), all subsequent crops were found to contain varying proportions of the guanidinoquinazoline **9**·HCl (4-methyl at τ 6.72, 7-methoxy at τ 5.75). An authentic specimen of the latter was synthesized independently from 1,2-dihydro-7-methoxy-2,2,4-trimethylquinoline hydrochloride (**10**·HCl) (9b) and cyanoguanidine. On the basis of averaged relative peak areas from all the crops, the amount of **9**·HCl in the mixture was calculated to be about 4%. Thus, to a first approximation, *m*-anisidine did give a somewhat greater proportion of abnormal product than *m*-toluidine, in accord with the greater electron-releasing capacity of the methoxy group. Similarly, nmr analysis of two crops from the three-component reaction with 3,4,5-trimethoxyaniline (Figures 2a and 2b) revealed the first crop to be dihydro-*s*-triazine **11**·HCl (*gem*-dimethyl at τ 8.15, 3′-methoxy and 5′-methoxy at τ 6.05, 4′-methoxy at τ 5.96), and the second to be guanidinoquinazoline **12**·HCl (4-methyl at τ 6.70, 5-methoxy at τ 5.68, 7-methoxy at τ 5.79, 6-methoxy at τ 5.91). The

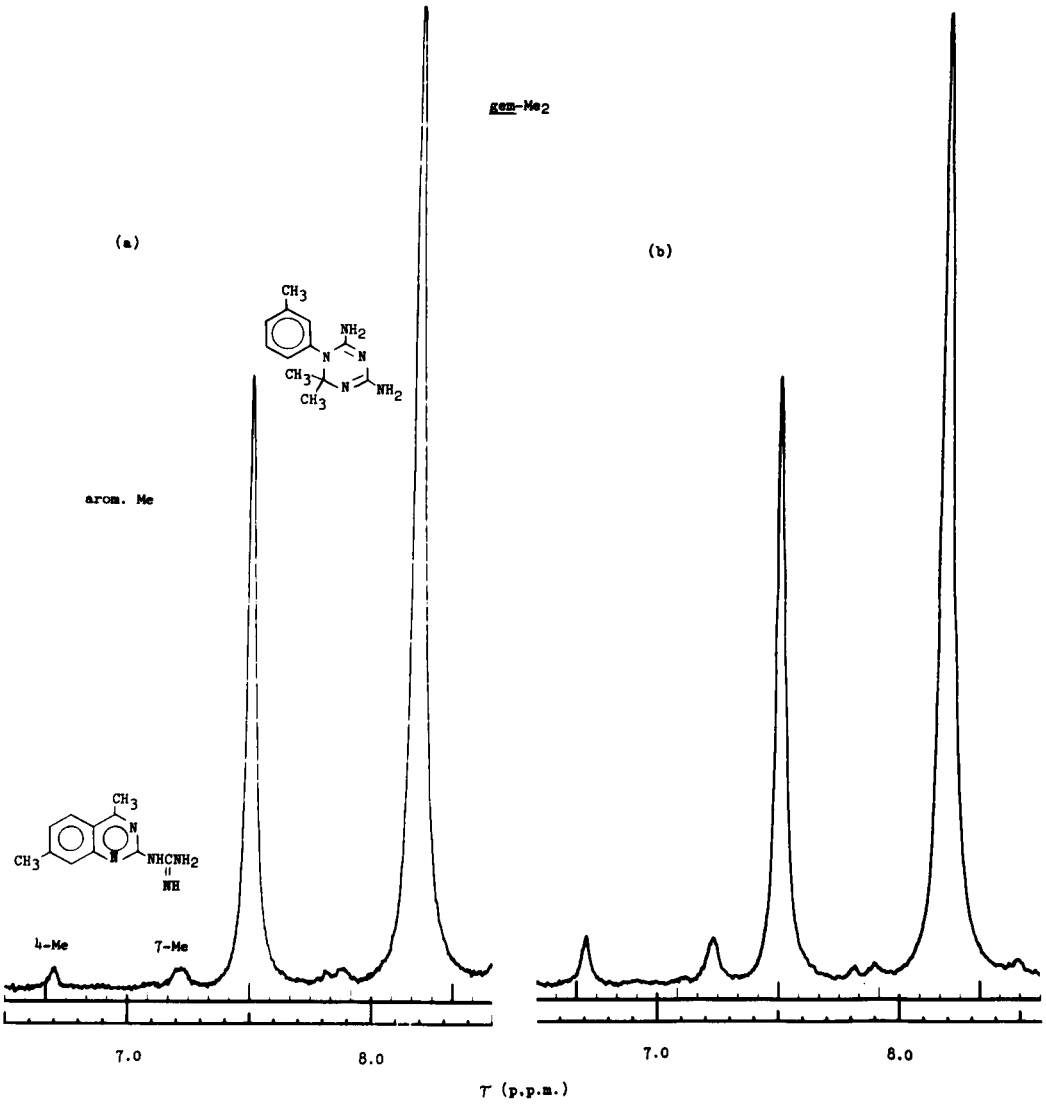
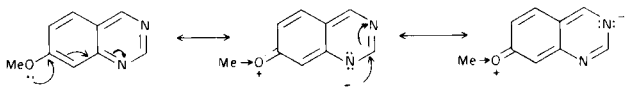


Fig. 1. Partial nmr spectra of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(*m*-tolyl)-*s*-triazine·HCl containing 2-guanidino-4,7-dimethylquinazoline·HCl as a contaminant: (a) Unpurified dihydro-*s*-triazine from "three-component synthesis" (300 mg. in 1 ml. of TFA); (b) Same sample as in (a), but with 10 mg. of guanidinoquinazoline added.

latter was calculated to comprise about 6% of the total product.

Support for the methoxy group assignments in **12**·HCl was provided by nmr spectra of the model compounds 2-guanidino-6-methoxy-4-methylquinazoline hydrochloride (10b) and **9**·HCl, which showed methoxy signals at τ 5.88 and τ 5.75, respectively. A possible interpretation for the difference in chemical shift of the methoxy protons in these model compounds is that, in the 7(or 5)-methoxy derivative, resonance structures can be written in which the positive charge on oxygen tends to pull electrons away from the methyl group by induction, as shown below; in 6(or 8)-methoxy derivatives, this type of resonance interaction is not possible, and higher values can, therefore, be expected because of increased shielding of the methyl protons.



The extent to which the abnormal three-component pathway (Chart I) can compete with the normal reaction probably depends upon a combination of sometimes quite subtle electronic effects. One of these is the reactivity

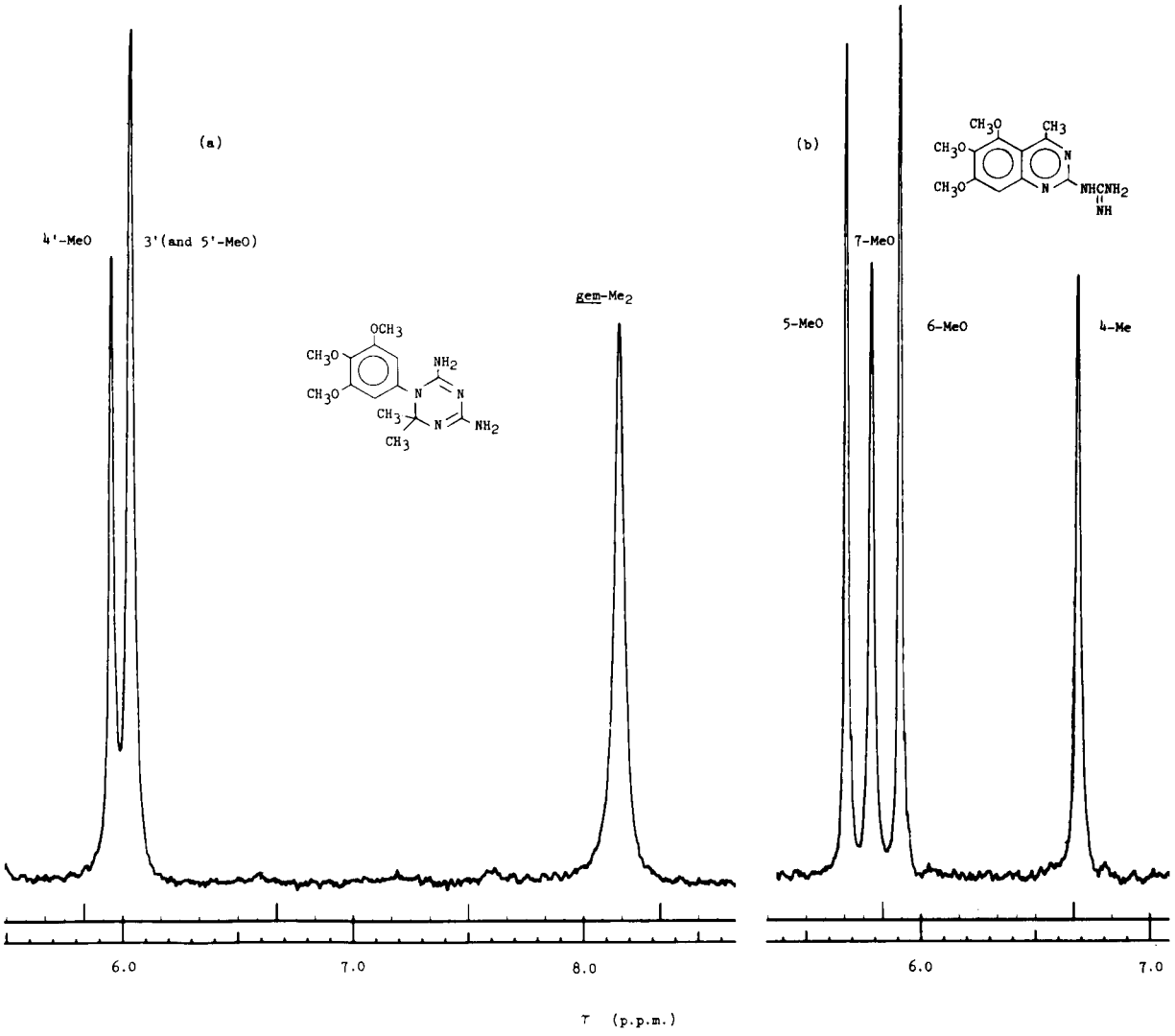


Fig. 2. (a) Partial nmr spectrum of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(3′,4′,5′-trimethoxyphenyl)-*s*-triazine·HCl (80 mg./ml. in TFA); (b) Partial nmr spectrum of 2-guanidino-5,6,7-trimethoxy-4-methylquinazoline·HCl (100 mg./ml. in TFA).

TABLE I

Nmr Spectral Data of Three-Component Synthesis Products (a)

	Dihydro *s*-triazines			Guanidinoquinazolines		
Starting Arylamines	*gem*-Me_2	Arom. Me	Arom. MeO	Hetero-arom. Me	Arom. Me	Arom. MeO
2-Naphthylamine	8.12			6.35		
6-Chloro-2-naphthylamine	8.12			6.37		
m-Toluidine	8.20	7.50 (3′-Me)		6.70	7.22 (7-Me)	
p-Toluidine	8.22	7.52 (4′-Me)		6.67	7.28 (6-Me)	
m-Chloroaniline	8.20			6.69		
p-Chloroaniline	8.20			6.70		
m-Anisidine	8.20		6.10 (3′-MeO)	6.72		5.75 (7-MeO)
p-Anisidine	8.22		6.03 (4′-MeO)	6.70		5.88 (6-MeO)
3,4,5-Trimethoxyaniline	8.15		6.05 (3′ and 5′-MeO)	6.70		5.68 (5-MeO)
			5.96 (4′-MeO)			5.79 (7-MeO)
						5.91 (6-MeO)

(a) τ values in trifluoroacetic acid solution with Me_4Si as the reference.

of the arylamine toward electrophilic attack at the *ortho* position; another is the susceptibility of the initially formed dihydroquinoline intermediate toward further reaction with cyanoguanidine. According to Brown (10b), the acid-catalyzed reaction of 1,2-dihydro-2,2,4-trimethylquinolines with cyanoguanidine is an example of the Ritter reaction. As indicated in Chart I, protonation gives rise to a carbonium ion which is attacked rapidly by the nitrile nitrogen of cyanoguanidine, with concomitant cyclization to a bridged intermediate resembling a Diels-Alder adduct. Expulsion of isobutylene from this intermediate leads to the observed product.

Support for the foregoing mechanism comes from our finding that the yields of guanidinoquinazolines obtained from 7-substituted dihydroquinolines **7**, **10**, and **13** upon reaction with cyanoguanidine were 65%, 73%, and 21%, respectively. These values indicate that the reaction does proceed *via* a mechanism involving substantial carbonium ion character at the 4-position of the quinoline ring system.

Several other arylamines were investigated in order to assess the importance of substituent effects in the abnormal three-component pathway. As expected, the reactivity of the aniline ring was decreased by halogen substitution. An authentic sample of 6-chloro-2-guanidino-4-methylquinazoline hydrochloride was prepared according to Brown (10b), and the hitherto unreported 7-chloro isomer, **14**·HCl, was synthesized from **13** (9b). Unpurified samples of the dihydro-*s*-triazines prepared from *m*- and *p*-chloroaniline *via* the standard three-component synthesis were subjected to careful nmr analysis in TFA solution; no trace of guanidino compounds could be discerned in either instance. The behavior of 6-chloro-2-naphthylamine was also examined, in order to estimate the effect of halogen substitution in the naphthalene system. Although it afforded much less abnormal product than 2-naphthylamine itself, the 6-chloro derivatives was still reactive enough to produce an isolable quantity of byproduct (see Experimental); 1-naphthylamine, on the other hand, yielded only the normal dihydro-*s*-triazine, as reported earlier (8a).

In summary, the formation of small amounts of guanidinoquinazoline byproducts can indeed occur when the three-component synthesis is carried out with certain types of arylamines. The occurrence of this side reaction becomes particularly important when dihydro-*s*-triazines are being synthesized for biological evaluation, inasmuch as some guanidinoquinazolines possess significant biological activity by themselves (15). On the basis of these findings, it seems well advised to use the two-component synthesis whenever the arylamine is activated toward

electrophilic attack *ortho* to the amino group, and to reserve the three-component synthesis for those arylamines in which such activation is lacking.

EXPERIMENTAL (16)

Condensation of *m*-Anisidine Hydrochloride, Cyanoguanidine, and Acetone.

A mixture of *m*-anisidine (50 g., 0.41 mole), cyanoguanidine (35 g., 0.42 mole), acetone (200 ml.), and concentrated hydrochloric acid (35 ml.) was stirred under reflux for about 1 hour. The dense solid (crop A) was collected, washed until colorless with acetone, rinsed with ether, and dried; yield 32 g. (28%), consisting entirely of **8**·HCl according to nmr analysis. The combined mother liquor and acetone washings were returned to the reaction flask, and heating was resumed for 4 hours. The precipitated solid (crop B) was isolated as described above; yield 35.5 g. (31%). The mother liquor was returned to the reaction flask, heating was resumed for another 4 hours, and the precipitate (crop C) was collected; yield 8.5 g. (7.4%). An additional 10.6 g. (9%) of solid (crop D) was obtained upon further heating for 16 hours. Nmr analysis of crops B, C, and D showed each of them to contain mostly **8**·HCl, but also small amounts of **9**·HCl. Combined crops B, C, and D were suspended in 95% ethanol (800 ml.), the mixture was stirred and heated just to the boiling point, and the solid remaining undissolved was filtered off. This solid (0.2 g.) was identified as essentially pure **9**·HCl by comparison with the authentic specimen obtained from **10**·HCl and cyanoguanidine (see below). Repeated concentration and cooling of the ethanol digest (final volume 200 ml.) produced several crops of solid (total 46 g.) consisting entirely of **8**·HCl by nmr analysis. The overall yield, including crop A, was 78 g. (68%). One more crystallization from 95% ethanol (Darco) (17), afforded analytically pure **8**·HCl, m.p. 214-217° (softening above 190°).

Anal. Calcd. for $C_{12}H_{17}N_5O$·HCl: C, 50.79; H, 6.39; Cl, 12.50; N, 24.68. Found: C, 51.05; H, 6.37; Cl, 12.48; N, 24.90.

Condensation of 3,4,5-Trimethoxyaniline, Cyanoguanidine, and Acetone.

A mixture of 3,4,5-trimethoxyaniline (24.9 g., 0.136 mole), cyanoguanidine (11.5 g., 0.137 mole), acetone (450 ml.), and concentrated hydrochloric acid (12 ml.) was stirred under reflux for 20 hours. The dense white precipitate (crop A) was collected, washed with acetone, and air-dried; yield 38.5 g. (83%), consisting entirely of **11**·HCl by nmr analysis. Repeated crystallization from 95% ethanol afforded analytically pure **11**·HCl, m.p. 203-206°.

Anal. Calcd. for $C_{14}H_{21}N_5O_3$·HCl: C, 48.90; H, 6.45; Cl, 10.31; N, 20.37. Found: C, 49.16; H, 6.59; Cl, 10.32; N, 20.75.

The mother liquor remaining after filtration of crop A was concentrated under reduced pressure, and the precipitated solid (crop B) was collected, washed with a small volume of acetone, rinsed with ether, and air-dried; yield 2.55 g. (5.7%). Nmr analysis showed this fraction to consist entirely of guanidinoquinazoline. Three crystallizations from 95% ethanol (Darco) produced analytically pure **12**·HCl, m.p. 118-121°.

Anal. Calcd. for $C_{13}H_{17}N_5O_3$·HCl: C, 47.63; H, 5.53; Cl, 10.82; N, 21.37. Found: C, 47.48; H, 5.81; Cl, 10.45; N, 21.15.

Condensation of 6-Chloro-2-naphthylamine Hydrochloride, Cyanoguanidine, and Acetone.

A mixture of 6-chloro-2-naphthylamine hydrochloride (18) (5.4 g., 0.027 mole), cyanoguanidine (2.5 g., 0.03 mole), acetone (20 ml.), and 95% ethanol (20 ml.) was stirred under reflux for 45 minutes. A small amount of undissolved solid (0.2 g.) was removed by filtration, the filtrate was returned to the reaction flask, another 20 ml. of acetone was added, and stirring under reflux was resumed for an additional 5 hours. The precipitate (crop A) was collected, washed with acetone, and air-dried; yield 2.9 g. (32%), consisting entirely of the dihydro-*s*-triazine according to nmr analysis. The filtrate was returned again to the reaction flask, and stirring under reflux was continued for another 14 hours. Refrigeration afforded 0.3 g. of solid (crop B), whose nmr spectrum showed it to contain mainly the guanidinoquinazoline, together with a small amount of dihydro-*s*-triazine. Evaporation of the mother liquor under reduced pressure left a solid residue (crop C), which was triturated with acetone and air-dried; yield 1.9 g. (21%), consisting mainly of the dihydro-*s*-triazine according to nmr analysis. Three crystallizations of crop A, once from 95% ethanol (Darco), and twice from ethanol-ether, gave analytically pure 4,6-diamino-1-(6-chloro-2-naphthyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride, m.p. 202-203°.

Anal. Calcd. for $C_{15}H_{16}ClN_5$·HCl: C, 53.26; H, 5.07; Cl, 20.96; N, 20.71. Found: C, 53.51; H, 5.27; Cl, 20.74; N, 20.69.

Two crystallizations of crop B from ethanol-ether (Darco) afforded analytically pure 8-chloro-3-guanidino-1-methylbenzo[*f*]-quinazoline hydrochloride, m.p. 292.5-294° dec.

Anal. Calcd. for $C_{14}H_{12}ClN_5$·HCl: C, 52.19; H, 4.07; Cl, 22.01. Found: C, 52.03; H, 4.22; Cl, 22.28.

2-Guanidino-4,7-dimethylquinazoline Hydrochloride (**6**·HCl).

A mixture of **7** (9b) (13 g., 0.069 mole), cyanoguanidine (5.8 g., 0.069 mole), 50% ethanol (100 ml.), and concentrated hydrochloric acid (10 ml.) was stirred under reflux for 2 hours, and then allowed to stand overnight. The precipitated product was collected, washed with several small portions of 95% ethanol, rinsed with acetone, and dried; yield 10 g. (65%). One crystallization from 95% ethanol (Darco) produced analytically pure **6**·HCl as colorless needles, m.p. 320-321° dec.

Anal. Calcd. for $C_{11}H_{13}N_5$·HCl: C, 52.48; H, 5.60; Cl, 14.10; N, 27.81. Found: C, 52.24; H, 5.74; Cl, 14.35; N, 27.78.

For the preparation of the free base, **6**, an aqueous solution of **6**·HCl (100 mg.) was basified to *p*H 11 with 5 *N* sodium hydroxide, and the precipitate was filtered, washed with water, and recrystallized from 95% ethanol; yield 70 mg. (82%), pale yellow prisms, m.p. 238.5-240° dec.; λ max (ethanol/*p*H 1) 247 (ε, 65,500), 320 nm (ε, 3,600); λ max (ethanol/*p*H 10) 264 (ε, 45,800), 283 (inflection, ε, 16,300), 338 nm (ε, 3,900).

Anal. Calcd. for $C_{11}H_{13}N_5$: C, 61.36; H, 6.08; N, 32.56. Found: C, 61.16; H, 6.17; N, 32.51.

2-Guanidino-7-methoxy-4-methylquinazoline Hydrochloride (**9**·HCl).

A mixture of **10**·HCl (9b) (2.42 g., 0.01 mole) and cyanoguanidine (0.84 g., 0.01 mole) in 50% ethanol (40 ml.) containing concentrated hydrochloric acid (2 ml.) was stirred under reflux for 2 hours. After overnight refrigeration, the solid was collected, washed with acetone, and air-dried; yield 1.61 g. (60%). Concentration of the mother liquor produced another 0.34 g. (13%) of the same product; total 1.95 g. (73%). Analytically pure buff-colored prisms, m.p. 297-301° dec., were obtained upon recrystallization from water (Darco).

Anal. Calcd. for $C_{11}H_{13}N_5O$·HCl: C, 49.35; H, 5.27; Cl, 13.26; N, 26.15. Found: C, 49.70; H, 5.40; Cl, 13.15; N, 26.05.

The free base, **9**, was prepared from the hydrochloride salt in the manner described for the 7-methyl isomer; m.p. 227-231° dec.; λ max (ethanol/*p*H 1) 247 (ε, 62,700), 315 (inflection, ε, 7,300), 324 nm (ε, 8,500); λ max (ethanol/*p*H 10) 266 (ε, 51,200), 328 (ε, 6,400), 333 nm (inflection, ε, 6,400).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.11; H, 5.66; N, 30.31. Found: C, 57.09; H, 5.80; N, 30.30.

7-Chloro-2-guanidino-4-methylquinazoline Hydrochloride (**14**·HCl).

A mixture of **13** (9b) (2.6 g., 0.013 mole), cyanoguanidine (1.0 g., 0.013 mole), and 2.4 *N* hydrochloric acid (10 ml.) was stirred under reflux for 2.5 hours and then allowed to stand overnight. Filtration of the solid, followed by washing with acetone and crystallization from 30% ethanol (100 ml.) containing concentrated hydrochloric acid (3 ml.) afforded 0.6 g. (18%) of **14**·HCl as fine colorless needles, m.p. 304-306° dec. Refrigeration of the mother liquor gave another 0.09 g. (3%) of the same product; total 0.69 g. (21%). The analytical sample, m.p. 313-317° dec., was obtained in 85% recovery by dissolving 0.2 g. of crude product in boiling water (7 ml.), decolorizing the solution with Darco, adding a small volume of 95% ethanol and 1 drop of concentrated hydrochloric acid, and refrigerating overnight.

Anal. Calcd. for $C_{10}H_{10}ClN_5$·HCl: C, 44.11; H, 4.08; Cl, 26.10; N, 25.77. Found: C, 44.20; H, 4.23; Cl, 26.32; N, 25.92.

For the preparation of the free base, **14**, an aqueous solution of **14**·HCl was basified to *p*H 11 with 4 *N* sodium hydroxide, and the precipitated solid was crystallized three times from methanol (Darco); pale yellow prisms, m.p. 245-246° dec.; λ max (ethanol/*p*H 1) 247.5 (ε, 70,000), 321 (ε, 4,100), 326.5 nm (inflection, ε, 3,700); λ max (ethanol/*p*H 10) 264 (ε, 45,800), 284.5 (ε, 24,000), 348 nm (ε, 4,900).

Anal. Calcd. for $C_{10}H_{10}ClN_5$: C, 50.93; H, 4.28; Cl, 15.06; N, 29.73. Found: C, 50.99; H, 4.20; Cl, 15.20; N, 29.71.

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(11) It is tacitly assumed throughout this discussion that the species actually present in TFA solution are probably diprotonated structures. However, the exact sites of protonation were considered less significant than the fact that the two types of compounds could be differentiated unambiguously by this method.

(12) The appearance of a doublet for the *gem*-dimethyl moiety of this dihydro-*s*-triazine is attributable to magnetic non-equivalence of the methyl groups. This phenomenon has also been observed with 4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazines derived from *ortho*-substituted anilines, and may be taken as evidence that free rotation in these compounds is subject to steric hindrance (A. Rosowsky and E. J. Modest, unpublished).

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(14) The preparation of a dihydro-*s*-triazine from *m*-anisidine *via* the three-component synthesis has been reported [M. Furukawa, Y. Seto, and S. Toyoshima, *Chem. Pharm. Bull.* (Tokyo), 9, 914 (1961); *Chem. Abstr.*, 57, 16617 (1962)], but the formation of a guanidinoquinazoline byproduct was apparently overlooked.

(15) For example, against KB cells (human epidermoid carcinoma) in mammalian cell culture systems, dihydro-*s*-triazine **8**·HCl and guanidinoquinazoline **9**·HCl had ID_{50} values of 10+ and 2.8 μg./ml., respectively. In this particular case, in which the byproduct is at least three times as active as the principal product, there is the obvious possibility of erroneous bioassay data unless care is taken to exclude contamination of the dihydro-*s*-triazine. We are indebted to Dr. George E. Foley and coworkers of the Laboratories of Microbiology, Children's Cancer Research Foundation for performing these assays.

(16) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride or bromide disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined in trifluoroacetic acid (TFA) solution on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Analytical samples were dried over phosphorus pentoxide at 70-100° (0.05 mm.). Melting points were measured in Pyrex capillary tubes in a modified Wagner-Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, 10, 584 (1938)] at a heating rate of 2°/min., and are uncorrected. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, by Galbraith Laboratories, Knoxville, Tennessee, and by Werby Laboratories, Boston, Massachusetts.

(17) Darco G-60 activated carbon, Atlas Chemical Industries, Wilmington, Delaware.

(18) A. Rosowsky, J. Battaglia, K. K. N. Chen, N. Papathanasopoulos, and E. J. Modest, *J. Chem. Soc.* (C), 1376 (1969).