Chemical and Biological Studies on Dihydro-s-triazines. XVII.
Modifications of the Three-Component Synthesis Favoring the
Formation of 2-Guanidino-4-methylquinazoline Byproducts (1,2)

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A modified three-component reaction of arylamines, cyanoguanidine, and acetone is described, wherein formation of anomalous guanidinoquinazoline byproducts is greatly enhanced at the expense of the normal dihydro-s-triazines. Four new guanidinoquinazolines and four new dihydro-s-triazines were synthesized via this modification, starting from 2,4-, 2,5-, 3,4-, and 3,5-dimethoxyaniline. The guanidinoquinazoline to dihydro-s-triazine ratio was much higher with 3,4- and 3,5-dimethoxyaniline than with 2,4-dimethoxyaniline. 2,5-Dimethoxyaniline gave an unexpectedly low yield of guanidinoquinazoline, apparently because of steric hindrance. The modified three-component synthesis was also examined in detail with 2-naphthylamine.

As shown in the accompanying paper (2), the three-component synthesis of 4,6-diamino-1-aryl-1,2-dihydro-2,2-dimethyl-s-triazines from arylamines, cyanoguanidine, and acetone (3) is sometimes complicated by the formation of difficultly separable byproducts, which have been identified as 2-guanidino-4-methylquinazolines (4). Inasmuch as these anomalous byproducts sometimes possess significant biological activity of their own, their presence can lead to erroneous bioassay results for the dihydro-s-triazines (5).

On the basis of the work reported to date (2,4), it is apparent that at least two independent and competing processes can occur when an arylamine hydrochloride is allowed to react simultaneously with cyanoguanidine and acetone. In one process (Path A), the first step is arylbiguanide formation; in the other (Path B), it is the formation of a 1,2-dihydro-2,2,4-trimethylquinoline ("acetone anil") (6). Condensation of the arylbiguanide with acetone leads to a dihydro-s-triazine, whereas further reaction of the dihydroquinoline intermediate with cyano-

Path A (Normal Three-Component Synthesis):
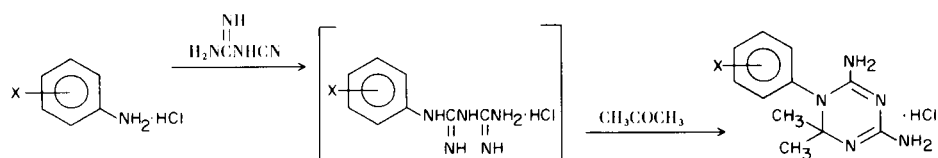
Path B (Abnormal Three-Component Synthesis):
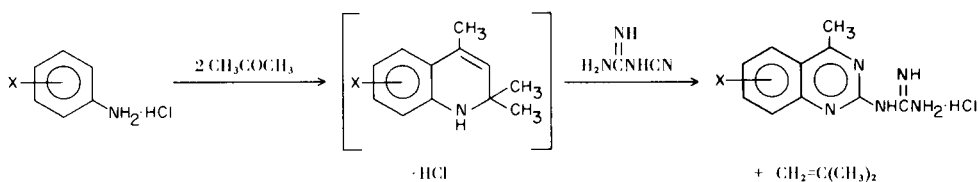
guanidine (7) gives a guanidinoquinazoline.

In the present paper, we should like to report some experiments carried out in order to gain additional information about the competition between pathways A and B in the three-component synthesis.

The basis for this work was an accidental observation during a three-component synthesis with m-anisidine (2). In one run, m-anisidine was dissolved in excess acetone and one molar equivalent of cyanoguanidine was added; however, only one-tenth of the calculated one molar equivalent of hydrochloric acid was used. The reaction mixture was stirred under reflux for 1 hour before this calculation error was detected. Upon addition of another 0.9 molar equivalent of acid, vigorous isobutylene evolution was observed. The mixture became homogeneous and lighter in color, and almost immediately thereafter a copious white precipitate appeared. After another 30

minutes, the solid (crop A) was filtered, washed with acetone, and dried. Nmr spectral analysis in trifluoroacetic acid (TFA) solution (2) showed this material to be pure 2-guanidino-7-methoxy-4-methylquinazoline hydrochloride, with no evidence of dihydro-s-triazine. The combined mother liquor and acetone washings were returned to the reaction flask, and reflux was resumed for 48 hours, during which another solid (crop B) had deposited. Nmr spectral analysis showed crop B to consist mainly of 4,6-diamino-1-(m-anisyl)-1,2-dihydro-2,2-dimethyl-s-triazine hydrochloride, with only a small amount of guanidinoquinazoline. The most significant aspect of this experiment was that the yield of guanidinoquinazoline (crop A) was 45% (compared to about 4% in the standard three-component synthesis), whereas the yield of dihydro-s-triazine (crop B) was only 22% (compared to the usual 68%). Thus, we had altered the normal product ratio

TABLE I

Modified Three-Component Synthesis with Methoxy-Substituted
Anilines, Cyanoguanidine, and Acetone

Run	Substituted Aniline	Reaction Conditions	Recovered Starting Material	% Yields Guanidino-quinazoline	Dihydro-s-triazine
1	o-Anisidine	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (16 hr. contin. reflux)	0	0	62
2	o-Anisidine	0.1 mole HCl (5 hr. reflux) + 0.9 mole HCl (21 hr. contin. reflux)	0	0	73
3	m-Anisidine	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (30 min. reflux, filtn., addnl. 48 hr. reflux)	0	45	22
4	p-Anisidine	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (30 min. reflux, filtn., addnl. 18 hr. reflux)	0	3	60
5	2,4-Dimethoxy-aniline	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (15 min. reflux, filtn., addnl. 16 hr. reflux)	23	2	54
6	2,5-Dimethoxy-aniline	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (5-10 min. reflux, filtn., addnl. 16 hr. reflux)	54	4	31
7	3,4-Dimethoxy-aniline	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (5 min. reflux and filtn. only)	58 (est.)	35	
8	3,5-Dimethoxy-aniline	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (25 min. reflux, filtn., addnl. 18 hr. reflux)	0	54	34
9	3,4,5-Trimethoxy-aniline	0.1 mole HCl (1 hr. reflux) + 0.9 mole HCl (30 min. reflux, filtn., addnl. 15 hr. reflux)	8	36	26

in the reaction, and had actually transformed the "by-product" into the *principal* product.

A limitation of the nmr method described in the preceding paper (2) was that the extremely small guanidino-quinazoline to dihydro-s-triazine ratios observed in the standard three-component synthesis made any assessment of substituent effects subject to considerable uncertainty. It was felt that the magnified importance of Path B in the "modified three-component synthesis" might overcome this limitation. Accordingly, a series of seven methoxy-substituted anilines was subjected to the modified three-component synthesis (Table I).

Anilines giving the highest yields of guanidinoquin-azolines were found to be m-anisidine, 3,4- and 3,5-dimethoxyaniline, and 3,4,5-trimethoxyaniline. In the reactions of m-anisidine, 3,5-dimethoxyaniline, and 3,4,5-trimethoxyaniline, where the second addition of acid was followed by approximately 30 minutes of reflux, yields of guanidinoquinazolines were 45%, 54%, and 36%, respectively. The corresponding yields of dihydro-s-triazines were only 22%, 34%, and 26%, and no unchanged starting materials were recovered. In the reaction of 3,4-dimethoxy-aniline, in which the second addition was followed by only 5 minutes of reflux prior to filtration, the yield of guanidinoquinazoline was still 35%; now, however, a substantial quantity of unchanged starting material was also

recovered, in the form of the hydrochloride salt. Apparently, refluxing should be continued for at least 30 minutes after addition of the second 0.9 mole of acid in order to insure complete utilization of the aniline.

Yields of guanidinoquinazolines from o- and p-anisidine and 2,4-dimethoxyaniline were extremely low, as anticipated. In the reactions of o- and p-anisidine, since reflux was continued for 16-21 hours after the second addition of acid, yields of dihydro-s-triazines were typical for a standard three-component synthesis. With 2,4-dimethoxy-aniline, reflux was interrupted only 15 minutes after the second addition of acid, and consequently some unchanged starting material was recovered.

The outcome of the 2,5-dimethoxyaniline reaction was unexpected, in that the yield of guanidinoquinazoline was only 4%. Since this compound contains a meta-methoxy substituent, we had assumed that guanidinoquinazoline formation would be favored. A reasonable explanation for this finding is that the 2-methoxy substituent exerts some steric hindrance.

In order to gain more information about the effect of varying conditions upon the yields of guanidino-quinazolines and dihydro-s-triazines, the reaction of 2-naphthylamine, cyanoguanidine and acetone (4a) was reinvestigated in detail (Table II).

TABLE II

Modified Three-Component Synthesis with 2-Naphthylamine, Cyanoguanidine, and Acetone

	Run	Molar Equivs. of HCl Added Initially	Hrs. of Stirring at Room Temp.	Hrs of Reflux Before 2nd Addn. of HCl	% Yields Guanidino-quinazoline	% Yields Dihydro-s-triazine
Series A	1	0.1	0	0.5	54	18
	2	0.1	0	1	56	24
	3	0.1	0	2	60	17
	4	0.05	0	1	58	21
	5	0.2	0	1	61	16
	6	0.4	0	1	44	31
	7	0.8	0	1	25	57
Series B	8	0.1	17	2	72	5
	9	0.1	15	4	71	6
	10	0.1	13	6	71	--
	11	0.1	11	8	60	8
	12	0.2	18	1	69	--
	13	0.2	17	2	69	2
	14	0.2	15	4	68	5

The effect of varying the length of reflux prior to the second addition of acid is indicated in runs 1-3, where the yield of guanidinoquinazoline increased from 54% at 30 minutes to 60% at 2 hours. A more pronounced effect was observed when the initial amount of acid was varied. With up to 0.2 molar equivalents of acid (runs 1-5), yields of guanidinoquinazoline remained essentially unaffected. However, as the amount of acid was increased to 0.4 and 0.8 molar equivalents (runs 6 and 7), the yield of guanidinoquinazoline fell sharply and the yield of dihydro-s-triazine rose proportionately. With 0.1 molar equivalent of acid and immediate refluxing for 2 hours (run 3), the yield of guanidinoquinazoline was 60%. Under the same conditions, but with 17 hours of stirring at room temperature, the yield increased to 72%. Correspondingly, the yield of dihydro-s-triazine dropped from 17% to 5%.

On the basis of the experiments reported here and in the preceding paper, it appears that, in the presence of limited quantities of acid, the preferred course of the three-component reaction of 2-naphthylamines or anilines containing one or more electropositive meta-substituents is via a 1,2-dihydro-2,2,4-trimethylquinoline (path B). The formation of arylbiguanides from arylamines and cyanoguanidine normally requires at least one molar equivalent of acid (8), and conversion of arylbiguanides into dihydro-s-triazines is known to proceed best in the presence of 1.5-2.0 molar equivalents of acid (9). The reaction of 1,2-dihydro-2,2,4-trimethylquinolines with cyanoguanidine likewise requires at least one equivalent of acid, and proceeds better when a slight excess of acid is used (7b). The synthesis of 1,2-dihydro-2,2,4-trimethylquinolines from anilines and acetone, on the other hand, can be performed with catalytic amounts of acid (10), and was in fact originally carried out with iodine rather than a proton acid as the catalyst (6). In all probability, therefore, use of only 0.1 molar equivalent of acid in the initial stage of the modified three-component synthesis retards arylbiguanide formation and allows the formation of a relatively large amount of dihydroquinoline. When the second portion of acid is added, bringing the total amount of acid in the reaction mixture to 1.0 molar equivalent, both the normal process of arylbiguanide and dihydro-s-triazine formation and the condensation of the dihydroquinoline with cyanoguanidine can proceed to completion. Guanidinoquinazoline salts are significantly less soluble than dihydro-s-triazines and tend to precipitate rapidly from the reaction mixture even at reflux temperatures. In contrast, formation of dihydro-s-triazines requires longer heating, and cooling or reduction in volume may be required to bring the products out of solution.

EXPERIMENTAL (11)

Reaction of 2,4-Dimethoxyaniline with Cyanoguanidine and Acetone.

A mixture of 2,4-dimethoxyaniline (25 g., 0.16 mole), cyanoguanidine (14 g., 0.17 mole), concentrated hydrochloric acid (1.5 ml., 0.018 mole), and acetone (100 ml.) was stirred under reflux for 1 hour. A second portion of concentrated hydrochloric acid (14 ml., 0.17 mole) was added, and refluxing was resumed for 15 minutes. Filtration of the precipitate (crop A), followed by washing with acetone (50 ml.) and drying, gave 7.2 g. (23% recovery) of unchanged 2,4-dimethoxyaniline hydrochloride. The mother liquor from crop A and the acetone wash were returned to the reaction flask, and refluxing was continued for 16 hours. Filtration, washing with acetone (100 ml.), and drying afforded a solid (crop B) weighing 28 g. (54%). One recrystallization of crop B from 95% ethanol (Darco) (12) furnished analytically pure 4,6-diamino-1,2-dihydro-1-(2',4'-dimethoxyphenyl)-2,2-dimethyl-s-triazine hydrochloride, m.p. 220-224° (softening at 218°).

Anal. Calcd. for $C_{13}H_{19}N_5O_2 \cdot HCl$: C, 49.76; H, 6.42; Cl, 11.30; N, 22.32. Found: C, 49.81; H, 6.44; Cl, 11.41; N, 22.69.

The combined mother liquor and wash solution remaining after isolation of crop B were refrigerated, and the resulting solid (crop C) was filtered, washed with acetone, and dried; yield 1.0 g. (2%). One crystallization of crop C from 95% ethanol (Darco) afforded analytically pure 2-guanidino-6,8-dimethoxy-4-methylquinazoline hydrochloride, m.p. 280-282° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O_2 \cdot HCl$: C, 48.40; H, 5.42; Cl, 11.91; N, 23.52. Found: C, 48.36; H, 5.43; Cl, 12.03; N, 23.51.

Reaction of 2,5-Dimethoxyaniline with Cyanoguanidine and Acetone.

A mixture of 2,5-dimethoxyaniline (50 g., 0.33 mole), cyanoguanidine (28 g., 0.33 mole), concentrated hydrochloric acid (3 ml., 0.036 mole), and acetone (160 ml.) was stirred under reflux for 1 hour. A second portion of acid (27 ml., 0.32 mole) was added, stirring was continued for 5-10 minutes, and the solid (crop A) was filtered, washed with acetone (400 ml.), and dried; yield 26 g., unchanged 2,5-dimethoxyaniline hydrochloride. The combined mother liquor and wash solution deposited additional material (crop B), which was isolated as described above; yield 15 g. Crop B, which appeared to be a mixture of product and starting material, was dissolved in boiling water (450 ml.). The solution was basified with ammonia and extracted with ether (2 x 900 ml.), and the organic layer was evaporated to dryness; yield 6.7 g., unchanged 2,5-dimethoxyaniline. The ether-insoluble material was taken up in hot 95% ethanol (900 ml.), and the volume adjusted to 375 ml. Ether (1500 ml.) and concentrated hydrochloric acid were then added, and the solid was filtered, washed with ether, and dried; yield 4 g. (4%). Two crystallizations from 95% ethanol (Darco) furnished analytically pure 2-guanidino-5,8-dimethoxy-4-methylquinazoline hydrochloride, m.p. 284-286° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O_2 \cdot HCl$: C, 48.40; H, 5.42; Cl, 11.91; N, 23.52. Found: C, 48.19; H, 5.39; Cl, 11.97; N, 23.42.

The mother liquor and wash solution remaining after isolation of crop B was concentrated to 250 ml., and refluxing was resumed. After 16 hours, the solid (crop C) was filtered, washed with acetone and dried; yield 25 g. Two additional crops (D and E), weighing 7 g., were obtained upon storage of the mother liquor in the cold; total yield 32 g. (31%). Three crystallizations of crops C-E from 95% ethanol gave analytically pure 4,6-diamino-1,2-dihydro-1-(2', 5'-dimethoxy)-2,2-dimethyl-s-triazine hydrochloride, m.p. 213-214°.

Anal. Calcd. for $C_{13}H_{19}N_5O_2 \cdot HCl$: C, 49.76; H, 6.42; Cl,

11.30; N, 22.32. Found: C, 49.84; H, 6.10; Cl, 11.33; N, 22.45.

Reaction of 3,4-Dimethoxyaniline with Cyanoguanidine and Acetone.

A. Modified Three-Component Synthesis.

A mixture of 3,4-dimethoxyaniline (5.0 g., 0.033 mole), cyanoguanidine (2.8 g., 0.033 mole), concentrated hydrochloric acid (0.3 ml., 0.0036 mole), and acetone (25 ml.) was stirred under reflux for 1 hour. Addition of a second portion of acid (2.7 ml., 0.032 mole) caused vigorous evolution of isobutylene and copious precipitation of a solid (crop A), which was filtered, washed with acetone and a small amount of 95% ethanol, and dried; yield 6.2 g. Upon standing overnight, the mother liquor yielded additional material (crop B), which was recrystallized from 95% ethanol-ether; yield 0.8 g. Crops A and B, which appeared to contain some unchanged 3,4-dimethoxyaniline hydrochloride, were dissolved in boiling water (200 ml.), the solution was basified to pH 10 with ammonia, and the 3,4-dimethoxyaniline was removed by ether extraction. The remaining ether-insoluble material was dissolved in 95% ethanol (1500 ml., Darco), concentrated hydrochloric acid (20 ml.) and ether (1500 ml.) were added, and the solid was filtered, washed with ether, and dried; yield 3.4 g. (35%). Three recrystallizations, once from 95% ethanol-ether (Darco) and twice from 95% ethanol, afforded analytically pure 2-guanidino-6,7-dimethoxy-4-methylquinazoline hydrochloride, m.p. 258-259° dec.

Anal. Calcd. for $C_{12}H_{15}N_5O_2 \cdot HCl \cdot 0.5H_2O$: C, 46.98; H, 5.59; Cl, 11.56; N, 22.83. Found: C, 47.10; H, 5.59; Cl, 11.29; N, 22.78.

B. Standard Three-Component Synthesis.

A mixture of 3,4-dimethoxyaniline (5.7 g., 0.037 mole), cyanoguanidine (3.2 g., 0.038 mole), concentrated hydrochloric acid (3.3 ml., 0.040 mole), and acetone (75 ml.) was stirred under reflux for 18 hours. Cooling and filtration gave a pink solid (9.4 g.), from which the color was extremely difficult to remove. One crystallization from 95% ethanol-ether (Darco) and three additional crystallizations from water (Darco) were required to prepare colorless material. A final recrystallization from 95% ethanol-ether afforded analytically pure 4,6-diamino-1,2-dihydro-1-(3',4'-dimethoxyphenyl)-2,2-dimethyl-s-triazine hydrochloride m.p. 240-242° (softening at 230°).

Anal. Calcd. for $C_{13}H_{19}N_5O_2 \cdot HCl$: C, 49.76; H, 6.42; Cl, 11.30; N, 22.32. Found: C, 49.72; H, 6.48; Cl, 11.37; N, 22.43.

Reaction of 3,5-Dimethoxyaniline with Cyanoguanidine and Acetone.

A mixture of 3,5-dimethoxyaniline (5.0 g., 0.033 mole), cyanoguanidine (2.8 g., 0.033 mole), concentrated hydrochloric acid (0.3 ml., 0.0036 mole), and acetone (75 ml.) was stirred under reflux for 1 hour. Addition of another portion of concentrated hydrochloric acid (2.7 ml., 0.032 mole) caused immediate evolution of isobutylene and deposition of a crystalline product. After 10 minutes of refluxing, the solid (crop A) was filtered, washed with acetone, rinsed with ether, and dried; yield 5.0 g. The mother liquor was returned to the reaction flask, refluxing was continued for another 15 minutes, and the precipitate (crop B) was isolated as described above; yield 0.3 g. After three crystallizations from 95% ethanol (Darco), crops A and B (combined yield 5.3 g., 54%) afforded analytically pure 2-guanidino-5,7-

dimethoxy-4-methylquinazoline hydrochloride, m.p. 234-235°.

Anal. Calcd. for $C_{12}H_{15}N_5O_2 \cdot HCl$: C, 48.40; H, 5.42; Cl, 11.91; N, 23.52. Found: C, 48.11; H, 5.45; Cl, 11.70; N, 23.39.

The mother liquor remaining after isolation of crop B was heated under reflux for another 18 hours, and the solid (crop C) collected as described above; yield 3.5 g. (34%). One recrystallization from 95% ethanol (Darco) gave analytically pure 4,6-diamino-1,2-dihydro-1-(3',5'-dimethoxyphenyl)-2,2-dimethyl-s-triazine hydrochloride, m.p. 192-195° (softening at 190°).

Anal. Calcd. for $C_{13}H_{19}N_5O_2 \cdot HCl \cdot 0.4H_2O$: C, 48.64; H, 6.53; Cl, 11.05; N, 21.82. Found: C, 48.40; H, 6.63; Cl, 11.06; N, 22.22.

Reaction of 2-Naphthylamine with Cyanoguanidine and Acetone.

A mixture of 2-naphthylamine (5.0 g., 0.035 mole), cyanoguanidine (2.9 g., 0.035 mole), concentrated hydrochloric acid (0.3 ml., 0.0035 mole), acetone (87 ml.), and 95% ethanol (15 ml.) was stirred at room temperature for 15 hours, and then heated under reflux for 4 hours. A second portion of acid (2.6 ml., 0.031 mole) was added, and refluxing was continued for another 10 minutes. The dense precipitate (crop A) was filtered, washed with acetone, and dried; yield 6.1 g. Upon being stirred under reflux for another hour, the combined mother liquor and wash solution gave additional solid (crop B), which was isolated as described above; yield 0.8 g. The mother liquor and washings were heated under reflux for another 11 hours (total refluxing time 16 hours) and cooled in the freezer; another 0.2 g. of product (crop C) was thereby obtained. The total yield of 3-guanidino-1-methylbenzo[f]quinazoline hydrochloride (crops A-C) was 7.1 g. (71%). When the solution remaining after isolation of crop C was evaporated to dryness, a gum was obtained. Trituration of this gum with acetone, followed by alternate warming and cooling, afforded 0.65 g. (6%) of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-(2-naphthyl)-s-triazine hydrochloride. The identity and purity of the two products was established by melting point and ir and nmr spectral comparison with previously obtained specimens (4a).

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