

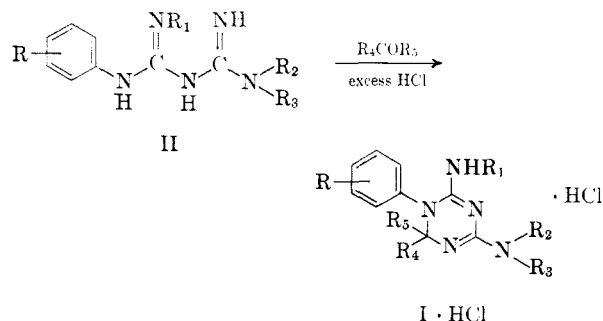
Chemical and Biological Studies on 1,2-Dihydro-*s*-triazines. III. Two-Component Synthesis^{1,2}

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An alternate synthesis of biologically active 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazines by the condensation of arylbiguanides and ketones or aldehydes under acid conditions is described.

In preceding communications^{1,4} the synthesis of a new class of 1,2-dihydro-*s*-triazines, with experimental anti-vitamin, anti-malarial, anti-tumor, and anti-coccidial activity, has been described. These compounds were prepared by the "three-component synthesis", which is the condensation of an arylamine hydrochloride, dicyandiamide or *N*¹-methylidicyandiamide, and a ketone or aldehyde. In the present communication an alternate synthetic route to the same series of compounds is reported. This reaction, which is called the "two-component synthesis" for purposes of identification, involves the condensation of an arylbiguanide (II) and a ketone or an aldehyde under



acid conditions, with formation of *I*·HCl, 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazine hydrochloride.⁵

The conditions of the two-component synthesis require the presence of more than one equivalent of a strong acid per equivalent of arylbiguanide. The solvent for the reaction is alcohol or the carbonyl reagent itself. The reaction time varies from about one hour to two weeks and depends on the temperature employed, the homogeneity of the reaction mixture, and the reactivity of the carbonyl reagent. The approximate speed of reactivity of the car-

bonyl reagents employed is aliphatic aldehydes > aromatic aldehydes > ketones. This synthesis is generally carried out under reflux with stirring for several hours, although a longer period of time is required if the reactants are not in solution. The condensation can also be effected at temperatures below the reflux point. The reaction is best effected under essentially anhydrous conditions, the presence of a large excess of water generally preventing the condensation from going to completion. One exception is the preparation of *I*-6·2HCl, in which it was found necessary to use water in the reaction, undoubtedly because of the extreme insolubility of *p*-biguanidophenylbiguanide dihydrochloride in acetone.

The progress of the reaction can be followed by observation of changes in the ultraviolet absorption spectrum⁶ of the reaction mixture or by measurement of the disappearance of the arylbiguanide, which is accomplished by means of the colored copper complex formed characteristically by arylbiguanides with cuprammonium ion but not formed under these conditions by arylidihydrotriazines.¹ After the reaction the product, which is partly or entirely in the form of the dihydrochloride, is usually collected directly. Alternative methods of isolation involve neutralization of the reaction mixture by the addition of base or by ion-exchange before isolation of the product. In any case additional material can be obtained from the mother liquor of the reaction. The product is purified by crystallization from water or aqueous alcohol, during which process any dihydrochloride present is converted to the monohydrochloride.

A variety of ring-substituted arylbiguanides can be employed successfully in the two-component synthesis. The reaction of *p*-nitrophenylbiguanide with acetone in this synthesis is exceptional in that it is unsatisfactory at reflux temperature. The product is formed in extremely low yield in the mother liquor of the reaction mixture when the two-component synthesis of *I*-3·HCl is carried out at room temperature for a week. Difficulty was also experienced with the three-component synthesis of this

(1) E. J. Modest, *J. Org. Chem.*, **21**, 1 (1956) is paper II in this series.

(2) E. J. Modest, *Abstracts of Papers, 122nd Meeting, American Chemical Society, Atlantic City, N. J.*, September 16, 1952, page 9-L.

(3) Pyrotex Leather Co., Leominster, Mass.

(4) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952).

(5) The two-component synthesis has been described independently by the group at Imperial Chemical Industries, Ltd.: H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **163**, 1080 (1951); H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(6) E. J. Modest and H. Kangur, *Abstracts of Papers, 124th Meeting, American Chemical Society, Chicago, Illinois*, September 7, 1953, page 26-O; the ultraviolet absorption spectral data will be published separately.

compound, that reaction being successful only at room temperature.¹ With respect to methyl-substitution in the biguanide group, the two-component synthesis with acetone is successful with N²- and N⁵-methyl and N⁵,N⁵-dimethyl arylbiguanides but fails to afford compounds of structure I with N¹-methyl and N⁴,N⁵-dimethyl arylbiguanides. On condensation with acetone under acid conditions, N¹-phenyl-N²-methylbiguanide afforded I-7 (isolated as the picrate), N¹-phenyl-N⁵-methylbiguanide afforded I-5·HCl, and N¹-phenyl-N⁵,N⁵-dimethylbiguanide provided I-8·2HCl; similar condensations attempted with N¹-phenyl-N¹-methylbiguanide and with N¹-(*p*-chlorophenyl)-N⁴,N⁵-dimethylbiguanide did not lead to compounds of type I.

An excess of any sufficiently strong inorganic or organic acid is necessary for the success of the condensation. I-1 has been prepared as the picrate by the condensation of phenylbiguanide and acetone in the presence of an excess of picric acid, and, similarly, I-2 has been synthesized as the nitrate. Ordinarily, hydrochloric acid is used in this reaction. When acetic acid was used, there was formed the isomeric anilindihydrotriazine (III, 4-amino-6-aryl-amino-1,2-dihydro-*s*-triazine), which is also produced by the base-catalyzed condensation of arylbiguanides with carbonyl reagents^{7,1} or by several other methods described in the preceding communication.¹ Crouse⁸ has reported that the condensation of *p*-chlorophenylbiguanide and acetone in the presence of excess glacial acetic acid leads to the formation of IIIc. The preparation of aryl-dihydrotriazines (I) from arylbiguanides (II) can be done only with strong acid catalysis.

The successful two-component synthesis requires more than one equivalent of a strong acid per equivalent of arylbiguanide free base. The ratio of equivalents of acid to arylbiguanide free base routinely employed is 1.5, or, if the arylbiguanide hydrochloride is used, the proportion is 0.5. The condensation is successful when an arylbiguanide dihydrochloride is substituted for the arylbiguanide plus acid or when there is as little as 1% excess acid present. Undoubtedly the two-component synthesis

can be effected with even less excess acid present. In our hands, however, the reaction has been unsuccessful when equivalent amounts of arylbiguanide and acid are used.⁹

As in the case of the three-component synthesis, the efficiency of the two-component synthesis with ketones varies directly with the efficiency of bisulfite addition-product formation of the ketone. The same ketones have been investigated in the two-component synthesis and their reactivity with respect to this condensation is in the same order as in the three-component synthesis. The two-component synthesis goes to completion when acetone, cyclopentanone, or cyclohexanone is used as the ketone. Only in these instances is there no unreacted arylbiguanide detectable in the final reaction mixture. In the case of higher aliphatic ketones, the reaction becomes progressively less efficient with increasing steric hindrance of the carbonyl group, the evidence being the presence of increasing amounts of unreacted arylbiguanide in the reaction mixture. As in the three-component synthesis, the striking efficiency of acetone in the two-component synthesis at reflux temperature in contrast to that of the homologous methyl ethyl ketone is evident. When the condensation of phenylbiguanide and methyl ethyl ketone is carried out under acid conditions, the product, I-12·HCl, must be separated from unreacted starting material. In the case of the two-component synthesis of I-13·HCl from *p*-chlorophenylbiguanide and methyl *n*-propyl ketone, it was not found practical to carry out the condensation at the reflux point. When this reaction was done at room temperature for two weeks, the product was obtained in very low yield from the mother liquor, which had been filtered free of unreacted arylbiguanide. Under similar conditions a low yield of I-14·HCl was obtained from *p*-chlorophenylbiguanide and diethyl ketone. It has not yet been possible to isolate any dihydrotriazine from the attempted condensations with acetophenone or benzophenone.

Aldehydes in general react successfully in the two-component synthesis, except for highly reactive aldehydes such as formaldehyde, which may undergo copolymerization with the arylbiguanide in preference to dihydrotriazine formation. Aromatic aldehydes do not react as rapidly as do aliphatic aldehydes. It will be noted that because aliphatic aldehydes cannot be employed in the three-component synthesis,¹ the two-component synthesis is the only route at present to the 2-monoalkyl substituted aryl-dihydrotriazines.

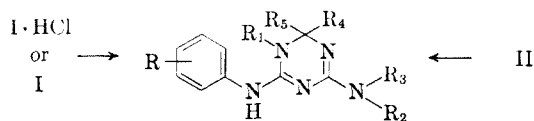
The relatively unstable free bases (I) are prepared by careful neutralization of I·HCl, and isomeric anilindihydrotriazines (III) are formed readily by the irreversible, intramolecular rearrangement of I·HCl or I under alkaline conditions.¹ In this connection representative compounds I-17 and I-27 have been prepared and rearranged to the isomeric

(7) S. Birtwell, F. H. S. Curd, J. A. Hendry, and F. L. Rose, *J. Chem. Soc.*, 1645 (1948).

(8) N. N. Crouse, *J. Org. Chem.*, 16, 492 (1951).

(9) Carrington, *et al.*, (ref. 5) report that the two-component synthesis succeeds with just one equivalent of a strong acid per equivalent of arylbiguanide. They describe the condensation of *p*-chlorophenylbiguanide monohydrochloride with acetone under aqueous conditions with formation of a minute amount of 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (I-2·HCl). T. L. Loo, *J. Am. Chem. Soc.*, 76, 5096 (1954) claims that recrystallization of the monohydrochloride of *p*-chlorophenylbiguanide from acetone affords I-2·HCl. With respect to both of these observations, the critical nature of the acid requirement in the two-component synthesis should be emphasized and it should be considered that a trace of acid inadvertently present in the reaction mixture might be sufficient to catalyze the dihydrotriazine condensation.

anilinodihydrotriazines IIIa and IIIb, respectively, under the influence of alkali and heat. IIIb has been prepared both by hot alkaline treatment of I-27·HCl and by crystallization of I-27 free base from hot



III

Ref. No.	III	R	R ₁	R ₂	R ₃	R ₄	R ₅
(DX60)	a:	4'-Cl	H	H	H	H	C ₂ H ₅
(DX34)	b:	H	H	H	H	H	C ₆ H ₅
(DX20)	c:	4'-Cl	H	H	H	CH ₃	CH ₃
(DX23)	d:	H	H	H	H	CH ₃	CH ₃
(DX29)	e:	H	H	CH ₃	CH ₃	CH ₃	CH ₃

ethanol. The hydrochlorides were formed by the action of hydrochloric acid on I-27 and IIIb free bases. Also I-8·2HCl was converted to IIIe¹ both in hot alkaline solution and at the melting point in the dry state. The synthesis of compounds of structure III from the appropriate arylbiguanides (II) by base or weak acid catalysis has been mentioned. IIIb has been prepared in this way by the condensation of phenylbiguanide and benzaldehyde in the presence of piperidine.

It has been observed in one instance that an attempted two-component synthesis with a methylated arylbiguanide which is incapable of reacting to form a compound of structure I yields instead an anilinodihydrotriazine (III). Thus, under acid conditions, N¹-phenyl-N¹-methylbiguanide hydrochloride and acetone condense with formation of 4-amino-1,2-dihydro-2,2-dimethyl-6-(N-methyl-anilino)-s-triazine hydrochloride.¹

Proof of the structure of I and II has been presented in the preceding paper of this series.¹ Further corroboration of the phenyldihydrotriazine structure assigned to I is furnished by the successful two-component synthesis with acetone of N⁵-methyl and N⁵,N⁵-dimethyl arylbiguanides, and the failure of N¹-methyl and N⁴,N⁵-dimethyl arylbiguanides to yield compounds of structure I by condensation with acetone under acid conditions. Thus the presence of one hydrogen atom at each of the terminal nitrogen atoms of the arylbiguanide is required for the success of the two-component synthesis. The over-all result of this reaction is a Mannich-like condensation between the hydrogen atoms at N¹ and N⁴ of the arylbiguanide and the oxygen function of the carbonyl reagent. The observations that the two-component synthesis fails with exactly one equivalent of a strong acid per equivalent of arylbiguanide and succeeds with as little as 1% excess acid present suggest that the excess acid functions as a true catalyst in this reaction. Further studies on the mechanism of the two-component synthesis are being carried out.

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EXPERIMENTAL¹⁰

Arylbiguanides. N¹-Phenyl-N¹-methylbiguanide hydrochloride, N¹-phenyl-N⁵,N⁵-dimethylbiguanide hydrochloride, N¹-(*p*-chlorophenyl)-N⁴,N⁵-dimethylbiguanide hydrochloride, N¹-phenyl-N²-methylbiguanide, and *p*-nitrophenylbiguanide hydrochloride have been described in the preceding paper of this series.¹ *p*-Chlorophenylbiguanide monohydrate,¹¹ *p*-chlorophenylbiguanide hydrochloride,¹¹ *p*-anisylbiguanide hydrochloride,¹² and *p*-biguanidophenylbiguanide dihydrochloride¹³ have been reported. Generous samples of phenylbiguanide, phenylbiguanide hydrochloride, and *o*-tolylbiguanide hydrochloride were supplied through the courtesy of the American Cyanamid Company.

N¹-Phenyl-N⁵-methylbiguanide hydrochloride. Aniline hydrochloride (9.02 g., 0.0696 mole) and N¹-methylidicyandiamide¹⁴ (6.85 g., 0.0698 mole) were dissolved in 28 cc. of water and the solution was refluxed for 18 hours. Because of the extreme solubility of the product in water, the final solution was evaporated to dryness *in vacuo*. The residue was transferred to a filter with the aid of absolute ethanol, washed with the same solvent, and dried; 10.4 g. (65%) of yellowish solid, m.p. 198–202° (uncorr.). This material crystallized from *n*-butanol in 70% recovery as colorless rods. A second crystallization from the same solvent yielded an analytically pure product, m.p. 201–203°.

Anal. Calc'd for C₈H₁₃N₅·HCl: C, 47.47; H, 6.18; N, 30.76. Found: C, 47.41; H, 6.21; N, 30.90.

3,4-Dichlorophenylbiguanide hydrochloride. The 3,4-dichloroaniline necessary for the synthesis of this arylbiguanide was prepared by the reduction of 3,4-dichloronitrobenzene in 95% ethanol over platinum oxide either at atmospheric pressure or at 50 p.s.i. in a Parr low-pressure hydrogenator. After the reduction, the catalyst was removed by filtration and the alcoholic filtrate was taken to dryness *in vacuo*. The residue was dissolved in ether and the ethereal solution was filtered and saturated with hydrogen chloride. The crude 3,4-dichloroaniline hydrochloride formed was obtained in 70–75% yield as a grayish solid, which was collected, washed thoroughly with ether, and used without further treatment.

A mixture of 198.5 g. (1 mole) of 3,4-dichloroaniline hydrochloride, 90 g. (1.07 moles) of dicyandiamide, and 600 cc. of *n*-propanol was refluxed with stirring for 17 hours. After the reaction mixture had been thoroughly refrigerated,

(10) Melting points, which are actually decomposition points, are corrected unless otherwise designated; the melting points given in the table are all corrected. Corrected melting points were taken under specified conditions at 2° per minute. For details of physical and chemical measurements, see experimental part, ref. (1). All compounds were dried for analysis *in vacuo* over phosphorus pentoxide at 70–100° for 17 hours, unless otherwise specified.

(11) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

(12) H. King and I. M. Tonkin, *J. Chem. Soc.*, 1063 (1946).

(13) B. R. Jacobs and Z. E. Jolles, British Patent 587,907, May 8, 1947 [*Chem. Abstr.*, 42, 214¹ (1948)].

(14) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray, and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).

the white crystals were collected and washed; yield, 190.5 g. (67%); m.p. 223–238° (uncorr.). Crystallization of this product from 10% ethanol afforded colorless prismatic rods in 83% recovery, and a second crystallization provided analytically pure material, melting at 228–230°.

Anal. Calc'd for $C_8H_9Cl_2N_5 \cdot HCl$: C, 34.00; H, 3.57. Found: C, 34.07; H, 3.15.

The free base was obtained by treatment of a solution of the hydrochloride in 10% ethanol with excess sodium hydroxide. Two crystallizations of this material from *n*-propanol yielded colorless, rectangular, prismatic plates of 3,4-dichlorophenylbiguanide, m.p. 156–157°.

Anal. Calc'd for $C_8H_9Cl_2N_5$: C, 39.04; H, 3.69. Found: C, 38.97; H, 3.78.

GENERAL TWO-COMPONENT SYNTHESIS OF PHENYLDIHYDRO-TRIAZINE HYDROCHLORIDES (I·HCl)

Preferred method. A mixture of 0.1 mole of the substituted arylbiguanide, 0.15 (or 0.2) mole of concentrated hydrochloric acid, 0.105–0.2 mole of the ketone or aldehyde, and 50–100 cc. of absolute ethanol is refluxed with stirring. Reaction times of about three hours for aliphatic aldehydes, eight hours for aromatic aldehydes, and 17 hours for ketones have been found to be optimal. If the arylbiguanide monohydrochloride is used, only 0.05 (or 0.1) mole of concentrated hydrochloric acid is necessary, and with the arylbiguanide dihydrochloride, no acid is required. The progress of the reaction may be followed by examination of the ultraviolet absorption spectrum of the reaction mixture or by measurement of the disappearance of the arylbiguanide. The condensation is considered to be complete when a sample of the reaction mixture no longer gives a colored complex (usually a pink precipitate) with cuprammonium sulfate (negative biguanide test). On completion of the reaction the mixture is cooled on ice and the product is usually obtained in crystalline form, entirely or partly as the dihydrochloride. At this point one of several procedures can be used to obtain the monohydrochloride in pure form: (a) After thorough cooling (several days may be necessary), the product may be collected without further treatment, washed with solvent, and dried. The yield is between 40% and 100%, averaging 75%. In most cases additional material can be isolated by manipulation of the mother liquor after collection of the first crop of the product. One crystallization from water or aqueous alcohol affords I·HCl, with an average recovery of 60%. During crystallization from an aqueous solvent any dihydrochloride present is converted to monohydrochloride. This is the isolation procedure commonly employed. (b) The product can be converted to the monohydrochloride directly by adjustment of the cooled reaction mixture to about pH 6 with concentrated ammonia before collection of the compound. (c) The reaction mixture is taken to dryness *in vacuo* and the residue is taken up in water. This aqueous solution is clarified with charcoal, filtered, and stirred with Amberlite IR-4B resin in the amount of about one gram of resin per milliequivalent of excess acid used in the synthesis, until the solution is brought to pH 6–7. The resin is removed by filtration and the filtrate brought to dryness by vacuum distillation or lyophilization. The product is now crystallized from water.

An excess of the ketone or aldehyde itself can be used as solvent, although in this event the reaction mixture generally does not become a clear solution at any point. In place of absolute alcohol, 95% ethanol can be used. When the reaction mixture does not become homogeneous, or when the carbonyl reagent is particularly unreactive, reaction times up to one week may be necessary. The two-component synthesis can be carried out at room temperature with an increased time of reaction. In certain cases reaction at room temperature is preferable, particularly with less reactive ketones, such as the pentanones.

Details of several synthetic procedures differing from the general method in some respects are given below.

Variation of the acid in the two-component synthesis. Although hydrochloric acid is the acid of choice in this condensation, the acid used may be one of several strong inorganic or organic acids. Also the reaction can be effected with as little as 1% excess acid and will undoubtedly proceed with still less excess acid present.

(a) *Nitric acid.* A mixture of 1.94 g. (0.01 mole) of *p*-chlorophenylbiguanide monohydrate, 0.79 cc. (0.0125 mole) of concentrated nitric acid, 2.9 cc. of acetone, and 6 cc. of absolute ethanol was refluxed with stirring for five hours, after which period the biguanide test with cuprammonium sulfate was negative (no further pink coloration or precipitate). The reaction mixture was cooled and the white product, 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (I-2) nitrate, collected; yield, 1.4 g. (44%); m.p. 190–193° (uncorr.). Crystallization from water afforded colorless prisms, identical with an authentic sample of I-2-nitrate¹ with respect to melting point and mixture melting point (198–199°) and ultraviolet absorption spectrum ($\lambda_{\max}^{H_2O}$ 241 m μ).

(b) *Picric acid.* A mixture of 0.89 g. (0.005 mole) of phenylbiguanide, 1.2 g. (0.00524 mole) of picric acid, and 20 cc. of acetone was refluxed for 17 hours. The product, 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-*s*-triazine (I-1) picrate, was collected from the cooled reaction mixture and thoroughly washed and dried; 1.87 g. (84%) of yellow prismatic rods, m.p. 208–209°. This material was submitted directly for analysis after being dried *in vacuo*.

Anal. Calc'd for $C_{11}H_{15}N_5 \cdot C_6H_3N_3O_7$: C, 45.74; H, 4.06. Found: C, 45.74; H, 4.22.

(c) *Acetic acid.* A solution of 8.86 g. (0.05 mole) of phenylbiguanide and 28.8 cc. (0.5 mole) of glacial acetic acid in 30 cc. of acetone was refluxed for six days, at the end of which period the reaction gave a negative biguanide test with cuprammonium sulfate and showed the characteristic ultraviolet absorption spectrum of 4-amino-6-anilino-1,2-dihydro-2,2-dimethyl-*s*-triazine (III_d) ($\lambda_{\max}^{H_2O}$ 250 m μ). The reaction solution was treated with 12.06 g. (0.0525 mole) of picric acid dissolved in 30 cc. of acetone and the product was isolated as III_d-picrate; 15.15 g. (68%); m.p. 219–222° (uncorr.). Recrystallization from 85% ethanol afforded analytically pure yellow prismatic rods, melting at 219–221°.

Anal. Calc'd for $C_{11}H_{15}N_5 \cdot C_6H_3N_3O_7$: C, 45.74; H, 4.06. Found: C, 46.12; H, 4.09.

The reaction was observed to proceed much more slowly with only a two-fold molar proportion of acetic acid and more rapidly with a 20-fold ratio. This sample of III_d-picrate was proved to be identical with material prepared from III_d¹ and picric acid, by comparison of the melting point, mixture melting point, and ultraviolet absorption spectrum.

(d) *Use of 1% excess acid.* A mixture of 21.37 g. (0.1 mole) of phenylbiguanide hydrochloride, 0.083 cc. (0.001 mole) of concentrated hydrochloric acid, 14.4 cc. (0.2 mole) of *n*-butyraldehyde, and 50 cc. of absolute ethanol was refluxed with stirring for six hours, during which time only a portion of the arylbiguanide dissolved. The hot reaction mixture was filtered and 13.73 g. of starting material was recovered. On refrigeration of the filtrate, 3.26 g. (12%, or 34% based on biguanide consumed) of colorless prismatic rods, 4,6-diamino-1,2-dihydro-1-phenyl-2-(*n*-propyl)-*s*-triazine hydrochloride (I-19·HCl), was obtained, m.p. 224–226° (uncorr.); negative biguanide test with cuprammonium sulfate. One crystallization from water provided colorless rectangular plates, which proved to be identical with an authentic sample of I-19·HCl (Table I) with respect to melting point and mixture melting point (226–227°) and ultraviolet absorption spectrum ($\lambda_{\max}^{H_2O}$ 245 m μ).

(e) *Use of no excess acid.* Phenylbiguanide hydrochloride (21.4 g., 0.1 mole) and acetone (100 cc.) was stirred at reflux for a period of one week. A white solid (21.2 g.) was recovered from the reaction mixture and this proved to be unchanged phenylbiguanide hydrochloride, having the same melting point and mixture melting point (243–244°) and

ultraviolet absorption spectrum ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 244 μ) and giving the same pink precipitate with cuprammonium sulfate (positive biguanide test).

A number of similar unsuccessful attempts were made to effect the condensation of phenylbiguanide hydrochloride, phenylbiguanide acetate, and *p*-chlorophenylbiguanide hydrochloride with acetone, cyclohexanone, *n*-butyraldehyde, and benzaldehyde under a variety of reaction conditions. In each case starting material was recovered and no condensation product was detected.⁹

4,6-Diamino-2-ethyl-1,2-dihydro-2-methyl-1-phenyl-s-triazine hydrochloride (I-12·HCl). A mixture of 21.35 g. (0.1 mole) of phenylbiguanide hydrochloride, 4.2 cc. (0.05 mole) of concentrated hydrochloric acid, 18 cc. (0.2 mole) of methyl ethyl ketone, and 50 cc. of absolute ethanol was refluxed with stirring for four hours. Although the reaction had not gone to completion, giving a pink precipitate with cuprammonium sulfate (positive biguanide test), the reaction mixture was taken nearly to dryness *in vacuo*. The semi-solid residue was crystallized directly from 25 cc. of water and 8.72 g. (33%) of a colorless crystalline product (I-12·HCl) resulted; m.p. 215–220° (uncorr.); no precipitate with cuprammonium sulfate. Analytically pure material was obtained after recrystallization from water (Table I).

p-Phenylene-bis-(4,6-diamino-1,2-dihydro-2,2-dimethyl-1-s-triazine) dihydrochloride (I-6·2HCl). In this synthesis it was found necessary to employ water because of the extreme insolubility of the starting material in acetone. A mixture of 2.44 g. (0.007 mole) of *p*-biguanidophenylbiguanide dihydrochloride, 0.59 cc. (0.007 mole) of concentrated hydrochloric acid, 100 cc. of acetone, and 65 cc. of water was refluxed with stirring for 18 hours. A complete solution was not observed at any time. The product (I-6·2HCl) was collected and washed with acetone; yield, 1.8 g. (60%) of white, microcrystalline material, m.p. 284–285° (uncorr.), with effervescence to a dark brown melt. For analysis a sample was crystallized twice from water (Table I).

4-Amino-1,2-dihydro-2,2-dimethyl-6-methylamino-1-phenyl-s-triazine picrate (I-7·Picrate). A mixture of 1.14 g. (0.005 mole) of *N*¹-phenyl-*N*²-methylbiguanide hydrochloride (prepared from the corresponding free base¹), 0.21 cc. (0.0025 mole) of concentrated hydrochloric acid, 2 cc. of acetone, and 6 cc. of absolute ethanol was refluxed with stirring for 16 hours. The clear yellowish solution that resulted was taken to dryness *in vacuo* and the residue was dissolved in 10 cc. of water and clarified with charcoal. The clarified filtrate was brought to pH 7.0 by reaction for 30 minutes with 2 g. of Amberlite IR-4B resin (hydroxyl form). The aqueous filtrate, on being lyophilized, afforded 1.1 g. (82%) of a glassy, non-crystallizable material, presumably I-7·HCl. This material was dissolved in water, filtered free of some insoluble matter, and treated with saturated aqueous picric acid. The yellow precipitate (I-7·picrate) was collected, washed, and crystallized for analysis from 95% ethanol (Table I).

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(p-nitrophenyl)-s-triazine hydrochloride (I-3·HCl). Because the biguanide was recovered unchanged in the attempted two-component synthesis of I-3·HCl under the usual conditions, the following procedure was necessary. A mixture of 2.59 g. (0.01 mole) of *p*-nitrophenylbiguanide hydrochloride, 0.042 cc. (0.0005 mole) of concentrated hydrochloric acid, 10 cc. of acetone, and 10 cc. of absolute ethanol was stirred for one week at room temperature. The yellow crystalline solid present in the reaction mixture was collected and washed, and proved to be unreacted starting material; 2.45 g. ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 231, 323 μ); positive biguanide test (orange precipitate) with cuprammonium sulfate. The filtered, undiluted mother liquor, which was pale yellow in color, was refrigerated for several days. There were deposited ten milligrams of nearly colorless prisms, which proved to be identical with a previous sample of I-3·HCl,¹ having the same melting point and mixture melting point (202–205°) and ultra-

violet absorption spectrum ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 240 μ) and giving no precipitate with cuprammonium sulfate.

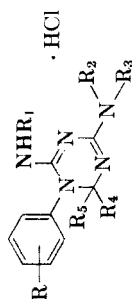
4,6-Diamino-1-(p-chlorophenyl)-1,2-dihydro-2-methyl-2-(n-propyl)-s-triazine hydrochloride (I-13·HCl). *p*-Chlorophenylbiguanide hydrochloride (12.41 g., 0.05 mole), concentrated hydrochloric acid (2.08 cc., 0.025 mole), methyl *n*-propyl ketone (10.6 cc., 0.1 mole), and absolute ethanol (30 cc.) were stirred at room temperature for two weeks. The reaction mixture was filtered and 0.65 g. of starting material was recovered. The filtered, undiluted mother liquor, which showed the proper ultraviolet absorption spectrum for I-13 ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 244 μ), was refrigerated. After one month, 30 mg. of high-melting crystals (m.p. above 350°) was removed by filtration and not further investigated. After another two weeks 160 mg. of colorless prisms was collected from the mother liquor. Crystallization of this product from water afforded I-13·HCl, identical with an authentic sample prepared by another method:¹ melting point and mixture melting point, 192–199° (uncorr.); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ 244 μ . On further standing the mother liquor yielded more I-13·HCl.

4,6-Diamino-1-(p-chlorophenyl)-2,2-diethyl-1,2-dihydro-s-triazine hydrochloride (I-14·HCl). A mixture of 24.81 g. (0.1 mole) of *p*-chlorophenylbiguanide hydrochloride, 8.33 cc. (0.1 mole) of concentrated hydrochloric acid, 21.1 cc. (0.2 mole) of diethyl ketone, and 100 cc. of 95% ethanol was stirred at about 35°. The reaction mixture, which was a very thick slurry at first, began to become thin within one day and in three days became a clear yellow solution, from which crystals soon began to separate. After seven days the reaction was stopped and the crystalline product (I-14·HCl) was collected, washed with ethanol, and dried; yield, 2.15 g. (6.8%); m.p. 205–245° (uncorr.); negative biguanide test with cuprammonium sulfate. Two crystallizations from water afforded analytically pure, colorless, transparent prisms, which became opaque and chalky on being dried at 70° *in vacuo*¹ (Table I). Additional material could be isolated by refrigeration of the reaction mother liquor.

6-Amino-4-dimethylamino-1,2-dihydro-2,2-dimethyl-1-phenyl-s-triazine dihydrochloride (I-8·2HCl). A mixture of 2.42 g. (0.01 mole) of *N*¹-phenyl-*N*²,*N*⁶-dimethylbiguanide hydrochloride, 0.83 cc. (0.01 mole) of concentrated hydrochloric acid, 6 cc. of acetone, and 20 cc. of 95% ethanol was refluxed with stirring for 24 hours, the reaction mixture becoming a crystal-clear, colorless solution after a few hours of reflux. This solution, which gave a negative biguanide test with cuprammonium sulfate, was reduced *in vacuo* to a small volume (ca. 2 cc.), at which point colorless prisms began to separate. After overnight refrigeration of the mixture, the product (I-8·2HCl) was collected, washed with acetone, and dried; yield, 1.0 g. (31%); m.p. 196–200° (uncorr.). Two crystallizations from *n*-propanol-ether afforded analytically pure material of the same crystal form (Table I). On being heated for an hour in strong alkali, this compound was converted to the isomeric 4-dimethylamino-6-anilino-1,2-dihydro-2,2-dimethyl-*s*-triazine.¹ This isomerization was effected also when crystals of I-8·2HCl were melted.

Acidic condensation of N¹-phenyl-N¹-methylbiguanide hydrochloride and acetone. A mixture of 4.56 g. (0.02 mole) of *N*¹-phenyl-*N*¹-methylbiguanide hydrochloride, 1.67 cc. (0.02 mole) of concentrated hydrochloric acid, 12 cc. of acetone, and 40 cc. of 95% ethanol was refluxed with stirring, a clear, colorless solution being obtained within 17 hours. After a total reaction time of four days, the reaction solution, which now gave a negative biguanide test with cuprammonium sulfate, was neutralized to pH 6 with sodium hydroxide and evaporated to dryness *in vacuo*. The evaporated residue was triturated with acetone, collected, and dried, 2.96 g. of a white powder being obtained. This material was leached with 15 cc. of boiling *n*-butanol and the hot suspension was filtered. After the filtrate had cooled, an equal volume of ether was added and 0.69 g. of colorless prisms was deposited, m.p. 236–239° (uncorr.). This sample of 4-amino-1,2-dihydro-2,2-dimethyl-6-(*N*-methylanilino)-*s*-triazine hydro-

TABLE I
PHENYLDIHYDROTRIAZINE HYDROCHLORIDES



Cpd.	Ref. No.	Substitution ^a			M.P., °C.	Crystal ^b Form	Solvent for Cryst.	Formula	Analyses						
		R	R ₄	R ₅					Calc'd	Found	C	H	N		
KETONE PRODUCTS															
I-1 ^c	D23	H	CH ₃	CH ₃	200-203										
I-2 ^c	D20	4'-Cl	CH ₃	CH ₃	210-215										
I-3 ^{c,d}	D73	4'-NO ₂	CH ₃	CH ₃	202-205										
I-4 ^c	D38	2'-CH ₃	CH ₃	CH ₃	224-226										
I-5 ^{a,c}	D32	H	CH ₃	CH ₃	170-172										
I-6 ^{a,e}	D81	f	CH ₃	CH ₃	299-300	prisms	H ₂ O	C ₁₀ H ₁₄ N ₆ ·2HCl	44.76	6.10	24.34	44.62	6.29		
I-7 ^{a,d,e}	D89	H	CH ₃	CH ₃	209-210	yellow prism. rods	95% EtOH	C ₁₂ H ₁₇ N ₆ ·C ₆ H ₅ N ₃ O ₇	46.95	4.38		47.08	4.39	24.86	
I-8 ^{a,d,e}	D29	H	CH ₃	CH ₃	220-221 ^h	prism. rods	n-PrOH/Et ₂ O	C ₁₃ H ₁₉ N ₆ ·2HCl	49.06	6.65		49.60	7.01		
I-9 ^c	D64	4'-Cl	-(CH ₂) ₄ -		212-216										
I-10	D72	2'-CH ₃	-(CH ₂) ₄ -		218-223	prism. plates	H ₂ O	C ₁₄ H ₁₉ N ₆ ·HCl	57.23	6.86		57.42	7.02		
I-11 ^c	D40	4'-Cl	-(CH ₂) ₅ -		224-226										
I-12 ^d	D66	H	CH ₃	C ₂ H ₅	204-206	prisms	H ₂ O	C ₁₂ H ₁₇ N ₆ ·HCl	53.82	6.78		54.14	7.18		
I-13 ^{c,d}	D87	4'-Cl	CH ₃	n-C ₃ H ₇	188-192										
I-14 ^{c,d}	D42	4'-Cl	C ₂ H ₅	C ₃ H ₅	172-180										
ALDEHYDE PRODUCTS															
I-15	D45	4'-Cl	H	CH ₃	236-238	prisms	H ₂ O	C ₁₀ H ₁₅ ClN ₅ ·HCl	43.81	4.78	25.55	43.40	5.14	25.89	
I-16	D67	3',4'-Cl ₂	H	CH ₃	228-230	prisms	10% EtOH	C ₁₀ H ₁₁ Cl ₂ N ₅ ·HCl	38.92	3.92		38.79	4.25		
I-17	D60	4'-Cl	H	C ₃ H ₅	236-237	prisms	10% EtOH	C ₁₁ H ₁₄ ClN ₅ ·HCl	45.84	5.25		45.53	5.51		
I-18	D63	3',4'-Cl ₂	H	C ₃ H ₅	229-231	prisms	10% EtOH	C ₁₁ H ₁₅ Cl ₂ N ₅ ·HCl	40.95	4.37		41.08	4.43		
I-19	D31	H	H	n-C ₃ H ₇	226-227	prism. rods	H ₂ O	C ₁₃ H ₁₇ N ₆ ·HCl	53.82	6.78		53.66	6.91		
I-20	D49	4'-OCH ₃	H	n-C ₃ H ₇	227-228	prism. rods	n-PrOH	C ₁₃ H ₁₉ N ₆ O·HCl	52.43	6.77		52.71	6.63		
I-21	D48	4'-Cl	H	n-C ₃ H ₇	225-226	prism. rods	H ₂ O	C ₁₂ H ₁₆ ClN ₅ ·HCl	47.69	5.67		47.89	5.72		
I-22	D88	2'-CH ₃	H	n-C ₃ H ₇	241-243	prisms	H ₂ O	C ₁₃ H ₁₉ N ₆ ·HCl	55.41	7.15		55.62	7.34		
I-23	D76	3',4'-Cl ₂	H	n-C ₃ H ₇	224-227	prism. plates	15% EtOH	C ₁₂ H ₁₆ Cl ₂ N ₅ ·HCl	42.81	4.79		43.14	4.83		
I-24	D59	4'-Cl	H	i-C ₃ H ₇	226-227	prisms	10% EtOH	C ₁₃ H ₁₉ ClN ₅ ·HCl	47.69	5.67		47.66	5.54		
I-25	D62	3',4'-Cl ₂	H	i-C ₃ H ₇	228-230	prisms	10% EtOH	C ₁₂ H ₁₆ Cl ₂ N ₅ ·HCl	42.81	4.79		42.87	5.01		
I-26	D84	4'-Cl	H	n-C ₆ H ₁₃	220-222	prism. rods	H ₂ O	C ₁₅ H ₂₃ ClN ₅ ·HCl	52.33	6.73		52.49	7.05		
I-27 ^c	D34	H	H	C ₆ H ₅	215-220										
I-28 ^c	D37	4'-Cl	H	C ₆ H ₅	217-221										

^a R₁ = H except for I-7 in which R₁ = CH₃; R₂ = H except for I-5, in which R₂ = CH₃, and I-8, in which R₂ = R₃ = ClH₂. ^b All compounds were dried for analysis *in vacuo* at 70-100°C. ^c Prepared also by the three-component synthesis [ref. (1)]. ^d Details of synthesis reported in the experimental part. ^e As the dihydrochloride. ^f R = 4'- (4,6-diamino-1,2-dihydro-2,2-dimethyl-1-s-triazinyl)-. ^g As the picrate. ^h With prior shrinking at 185°C.

chloride did not depress the melting point of an authentic sample of this compound¹ and had the same ultraviolet absorption spectrum ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$, 247 m μ).

Unsuccessful reactions. The attempted condensation of acetone with N¹-(*p*-chlorophenyl)-N⁴,N⁵-dimethylbiguanide hydrochloride under acid conditions with acetone as solvent resulted in recovery of starting material. Also, the attempted reactions in acid media of several arylbiguanides, principally *p*-chlorophenylbiguanide, with formaldehyde and acrolein led only to viscous resins, and with acetophenone and benzophenone afforded unchanged starting material, under the experimental conditions employed. It is conceivable, however, that both highly reactive and extremely unreactive carbonyl reagents may participate in dihydrotriazine formation to a very low extent under precisely the right experimental conditions.

4,6-Diamino-1,2-dihydro-1,2-diphenyl-s-triazine (I-27). To a clear solution of 500 mg. of I-27·HCl in 20 cc. of water at 45° was added 1 cc. of concentrated ammonium hydroxide. A crystalline product (I-27) began to form within several minutes and was collected in three hours and washed thoroughly with water; colorless plates, 370 mg. (84%), melting at 158–162°. A sample of this material was submitted directly for analysis after being dried.

Anal. Calc'd for C₁₅H₁₅N₅: C, 67.90; H, 5.70; N.E., 265. Found: C, 67.61; H, 5.74; N.E., 266.

A solution of I-27 in water containing an equivalent of hydrochloric acid was taken to dryness *in vacuo* and the residue was crystallized from water. The resulting product was shown to be identical with an authentic sample of I-27·HCl, having the same melting point and mixture melting point (215–220°) and ultraviolet absorption spectrum ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$, 251 m μ).

I-27 is readily converted into IIIb. A hot saturated solution of 250 mg. of I-27 in 95% ethanol was filtered into an equal volume of water. The product which crystallized from the cooled solution proved to be IIIb·C₂H₅OH, the melting point and mixture melting point (174–178°) and ultraviolet absorption spectrum ($\lambda_{\text{max}}^{\text{H}_2\text{O}}$, 253 m μ) being identical with those of another sample of IIIb·C₂H₅OH.

4-Amino-6-anilino-1,2-dihydro-2-phenyl-s-triazine (IIIb). A solution of 8.85 g. (0.05 mole) of phenylbiguanide, 7.6 cc. (0.075 mole) of benzaldehyde, 50 cc. of absolute ethanol, and 0.5 cc. of piperidine was refluxed for 18 hours and allowed to cool overnight. The crop of colorless rods which had crystallized was collected and washed; 11.82 g. (76%), melting at 120–125° (uncorr.), with effervescence, to a

white solid remelting at 187–188° (uncorr.). For analysis a sample was crystallized from 95% ethanol as colorless rods, m.p. 174–178° with prior effervescence. This product (IIIb·C₂H₅OH) was submitted for analysis after being dried in air at room temperature (drying *in vacuo* with heat resulted in partial loss of the molecule of ethanol).

Anal. Calc'd for C₁₅H₁₅N₅·C₂H₅OH: C, 65.57; H, 6.80; N.E., 311. Found: C, 65.52; H, 6.84; N.E., 311.

This compound was also prepared by reflux for one hour of a solution of I-27·HCl in 50% ethanol, containing an excess of 5 *N* sodium hydroxide. The crystalline product was IIIb·C₂H₅OH.

IIIb·HCl. A hot solution of 1.56 g. (0.005 mole) of IIIb·C₂H₅OH in 10 cc. of water containing 0.44 cc. (0.00525 mole) of concentrated hydrochloric acid was prepared and almost immediately deposited a heavy crop of white crystals (IIIb·HCl) that was collected and washed; 1.1 g. (73%), m.p. 213–215° (uncorr.). Two crystallizations from 10% ethanol afforded colorless prismatic needles, melting at 213–221°.

Anal. Calc'd for C₁₅H₁₅N₅·HCl: C, 59.70; H, 5.34. Found: C, 60.06; H, 5.45.

4,6-Diamino-1-(p-chlorophenyl)-2-ethyl-1,2-dihydro-s-triazine (I-17). A saturated aqueous solution was prepared from 3 g. of I-17·HCl in 90 cc. of water at room temperature. To this filtered solution was added 20 cc. of a saturated aqueous solution of barium hydroxide, and the mixture was refrigerated overnight. A crop of colorless prisms (I-17) had been deposited and was collected and thoroughly washed with water; 1.86 g. (71%), m.p. 164–167°; $\lambda_{\text{max}}^{\text{H}_2\text{O}}$, 245 m μ . A sample was dried *in vacuo* at room temperature.

Anal. Calc'd for C₁₁H₁₄ClN₅: C, 52.48; H, 5.61; N.E., 252. Found: C, 52.69; H, 5.88; N.E., 247.

4-Amino-6-(p-chloroanilino)-2-ethyl-1,2-dihydro-s-triazine (IIIa). A solution of one gram of I-17·HCl in 30 cc. of 50% ethanol was brought to pH 11 with 5 *N* sodium hydroxide and then was refluxed for 1½ hours. On refrigeration the solution afforded 0.53 g. (61%) of small prismatic crystals (IIIa), m.p. 170–175° (uncorr.) with prior effervescence at 128° (uncorr.); $\lambda_{\text{max}}^{\text{H}_2\text{O}}$, 256 m μ . A sample was crystallized from water in low yield as prismatic plates; m.p.: begins to melt at 101°, with effervescence, to a cloudy melt by 115°, becoming clear yellow by 170°.

Anal. Calc'd for C₁₁H₁₄ClN₅: C, 52.48; H, 5.61; N.E., 252. Found: C, 52.20; H, 6.06; N.E., 250.

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