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Chemical and Biological Studies on 1,2-Dihydro-s-triazines. II. Three-Component Synthesis[1]

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The synthesis of a new class of 1,2-dihydro-s-triazines, with experimental anti-vitamin, anti-malarial, anti-tumor, and anti-coccidial activity, is described. The scope and limitations of this previously unreported synthesis, which involves the condensation in one step of an arylamine hydrochloride, dicyandiamide or N^1-methyldicyandiamide, and a ketone or an aldehyde, are outlined. Under the influence of alkali and heat, these compounds, to which the structure 4,6-diamino-1-aryl-1,2-dihydro-s-triazine has been assigned, undergo an irreversible, intramolecular rearrangement to a series of isomeric 4-amino-6-arylamino-1,2-dihydro-s-triazines with reduced biological activity. The mechanism of the rearrangement and evidence for the structure of these dihydrotriazines are discussed.

Previous communications from these laboratories have reported the results of preliminary studies concerning a new series of biologically active dihydrotriazines.[2] These compounds, to which structure I has been assigned, have been found to exhibit activity against experimental avian and rodent malaria,[3-5] anti-vitamin activity in microbiological systems,[4,6,7] and anti-tumor activity against a number of experimental tumors.[8,9] Two compounds of structure I have been found to be active against malaria in monkeys[10] and several against coccidiosis in chicks.[11]

As communicated to us privately by Dr. F. L. Rose, these dihydrotriazines (I) have also been prepared and investigated independently at the Imperial Chemical Industries, Ltd., in the course of studies on the isolation and synthesis of a metabolite of the antimalarial drug, paludrine, N^1-(*p*-chlorophenyl)-N^5-isopropylbiguanide (III: R_1 = Cl; R_2 = R_3 = R_4 = H; R_5 = isopropyl).[12-14] Several investigators have suspected the existence of this metabolite since the early evidence that such a derivative, with enhanced antimalarial activity, is formed from the parent drug *in vivo*.[15-18] There

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

(2) Synthesized as part of an over-all program of cancer chemotherapy directed by Dr. Sidney Farber.

(3) We are indebted to Dr. J. H. Williams and his colleagues of the Lederle Laboratories, Pearl River, New York, for these antimalarial assays.

(4) E. J. Modest, G. E. Foley, M. M. Pechet, and S. Farber, *J. Am. Chem. Soc.*, **74**, 855 (1952). This is paper I of this series.

(5) R. I. Hewitt, W. S. Wallace, A. Gumble, E. White, and J. H. Williams, *Am. J. Trop. Med. Hyg.*, **3**, 225 (1954).

(6) G. E. Foley and E. J. Modest, *Proc. 52nd General Meeting, Society of American Bacteriologists, Boston, Mass.*, May 1, 1952, p. 63.

(7) (a) G. E. Foley, *Proc. Soc. Exptl. Biol. Med.*, **83**, 733 (1953). (b) G. E. Foley, *ibid.*, **83**, 740 (1953). (c) G. E. Foley and P. L. Watson, *ibid.*, **83**, 742 (1953). (d) G. E. Foley, *Thesis, Universiteit van Amsterdam*, Nederland, June, 1954. (e) G. E. Foley, *et al.*, *Antonie van Leeuwenhoek*, in press (1955).

(8) S. Farber, I. Diamond, G. Foley, and E. J. Modest, *Am. J. Pathol.*, **28**, 559 (1952).

(9) S. Farber, G. Foley, V. Downing, R. Appleton, and J. King, *Proc. Am. Assoc. Cancer Research*, **1**, 15 (1953).

(10) L. H. Schmidt, T. L. Loo, R. Fradkin, and H. B. Hughes, *Proc. Soc. Exptl. Biol. Med.*, **80**, 367 (1952).

(11) R. E. Lux, *Antibiotics and Chemotherapy*, **4**, 971 (1954).

(12) H. C. Carrington, A. F. Crowther, D. G. Davey, A. A. Levi, and F. L. Rose, *Nature*, **168**, 1080 (1951).

(13) A. F. Crowther and A. A. Levi, *Brit. J. Pharmacol.*, **8**, 93 (1953).

(14) H. C. Carrington, A. F. Crowther, and G. J. Stacey, *J. Chem. Soc.*, 1017 (1954).

(15) L. H. Schmidt, H. B. Hughes, and C. C. Smith, *J. Pharmacol. Exptl. Therap.*, **90**, 233 (1947).

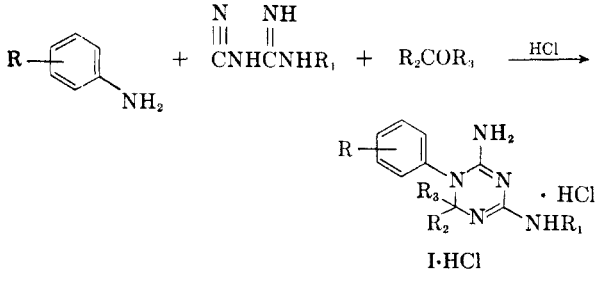
(16) F. Hawking, *Nature*, **159**, 409 (1947).

(17) F. Hawking and W. L. M. Perry, *Brit. J. Pharmacol.*, **3**, 320 (1948).

(18) N. N. Crounse, *J. Org. Chem.*, **16**, 492 (1951).

is no doubt that one of the dihydrotriazines reported herein, I-3, 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine, is identical with the "paludrine metabolite",[12-14] by virtue of the similarity of the physical, chemical, and antimalarial properties and the synthetic method, and the isomerization of both to IIb, 4-amino-6-(*p*-chloroanilino) - 1,2 - dihydro - 2,2 - dimethyl - *s* - triazine.[19] I-3, which is presumably responsible for the antimalarial action of paludrine, is undoubtedly formed from the biguanide *in vivo* by enzymatic dehydrogenation.

The forerunner of this new series of dihydrotriazines was produced by the condensation of ethyl *p*-aminobenzoate, dicyandiamide, and concentrated hydrochloric acid in acetone. The structure I-6·HCl (R = *p*-$CO_2C_2H_5$; R_1 = H; R_2 = R_3 = CH_3), 4,6-diamino-1-(*p*-carbethoxyphenyl)-1,2 - dihydro - 2,2 - dimethyl-*s*-triazine hydrochloride, has been proposed for this substance.[4] This compound was selected for further study after it had been found to be a potent inhibitor of microbiological systems, in particular, *Streptococcus faecalis* #8043[4,7,20]-pteroylglutamic acid and *Lactobacillus arabinosus* #17-5[4,7,20]-nicotinic acid bio-assay systems. The indicated method of synthesis, on examination, proved to be general for the preparation of a sereis of 4,6-diamino-1-aryl-1,2-dihydro-*s*-triazines. The reaction has been extended to include aldehydes as



I·HCl

well as ketones. In addition to this synthetic method, which has been termed the "three-component synthesis", another synthetic route, the "two-component synthesis", has been developed by the condensation of arylbiguanides (III) with ketones or aldehydes under strongly acidic conditions.[21]

The net result of the three-component synthesis is the condensation of molecular equivalents of the arylamine acid salt, dicyandiamide, and the ketone or aldehyde, with loss of one molecule of water. Either the arylamine plus one equivalent of acid, or the arylamine acid salt can be used. The reaction is carried out in an appropriate solvent, *e.g.*, the carbonyl reagent itself or an inert solvent such as an alcohol, preferably under anhydrous conditions. Usually, the reagents are heated at reflux for a number of hours, and the reaction mixture becomes a clear solution, from which the product crystallizes directly in quite pure form and good yield. The dihydrotriazine acid salts are stable and moderately soluble in water, crystallizing from this solvent in the form of colorless prisms.

Arylamines variously substituted in the nucleus can be employed successfully in the condensation. The amino group must be unsubstituted and the amine must be aromatic; the reaction fails with N-methylaniline or with aliphatic amines or ammonium chloride. The acid used may be any sufficiently strong inorganic or organic acid, such as hydrochloric acid, nitric acid, or picric acid. Hydrochloric acid is the acid of choice. When acetic acid is used, the condensation is not successful. Dicyandiamide or N^1-methyldicyandiamide, but not the N^1,N^1- or N^1,N^2-dimethyl derivatives, can be used in the condensation.

The reaction proceeds best with sterically unhindered ketones. The similarity of behavior of ketones in this condensation and in bisulfite addition is evident. It is noteworthy that only those ketones react which form bisulfite addition-products. Furthermore, the speed and completeness of the condensation vary approximately with the speed and extent of bisulfite addition-product formation of the ketone. The ketones that have undergone the condensation, approximately in decreasing order of rapidity and completeness of reaction, include acetone, cyclopentanone, cyclohexanone, methyl ethyl ketone, methyl *n*-propyl ketone, and diethyl ketone. The reaction has not yet been successful with aromatic ketones, such as acetophenone and benzophenone. Apparently an α-phenyl group renders the condensation unsuccessful, just as it inhibits bisulfite addition. The three-component synthesis proceeds well with aromatic aldehydes in place of ketones but fails with aliphatic aldehydes under the usual conditions of the reaction. It is likely that because of their high reactivity aliphatic aldehydes become unavailable to the reaction through the prior formation of a Schiff base with the amine. However the preparation of dihydrotriazines (I) from aliphatic aldehydes can be achieved by the two-component synthesis.[21]

Although the three-component synthesis is generally carried out at reflux temperature, it has been found that condensation can be effected at room temperature (I-3·HCl, I-4·HCl, I-5·HCl, I-19·HCl, I-20·HCl, I-21·HCl, I-22·HCl) and in some cases at ice-bath temperature (I-3·HCl, I-5·HCl). Readily formed compounds, such as I-3·HCl, can be synthesized efficiently at a wide range of temperatures. When the condensation proceeds successfully at room temperature, a slight exothermic effect is observed.

With the more hindered ketones, the use of elevated temperatures during the reaction tends to

(19) Furthermore, the 3′,4′-dichlorophenyl derivative, I-16·HCl, proved to be indistinguishable from a sample supplied through the courtesy of Imperial Chemical Industries, Ltd.

(20) American Type Culture Collection strains.

(21) E. J. Modest and P. Levine, *J. Org. Chem.*, **21**, 14 (1956).

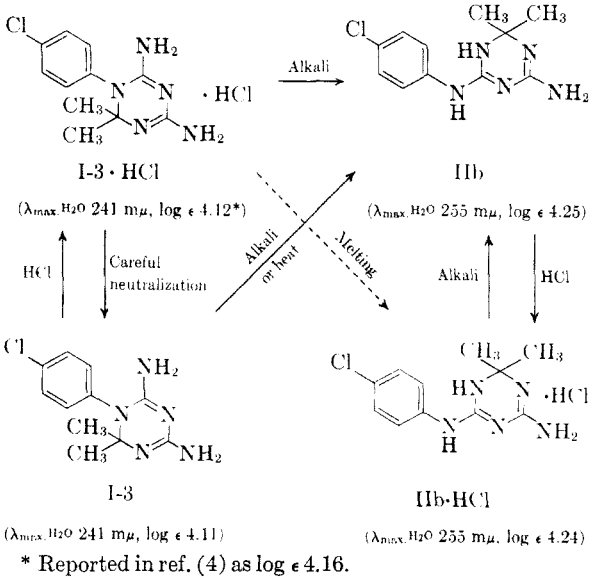
decrease the yield of dihydrotriazine, with corresponding formation of arylbiguanide. For example, when methyl ethyl ketone is used in the synthesis at reflux temperature in place of acetone, the arylbiguanide is the chief product. However, when this reaction is carried out at room temperature, with methyl ethyl ketone and absolute ethanol, the dihydrotriazine (I-19·HCl or I-20·HCl) is formed preferentially. Similar observations have been made in the synthesis of I-21·HCl and I-22·HCl, both of which compounds have been prepared by the three-component synthesis only at reduced temperatures. In general, where there exists a tendency to biguanide formation in this condensation, a lowering of the reaction temperature favors dihydrotriazine formation. However, even at room temperature, there is accompanying biguanide formed in the synthesis of I-21·HCl and I-22·HCl, and also in the room temperature synthesis of I-19·HCl and I-20·HCl, with methyl ethyl ketone only as solvent. The efficiency of the room temperature synthesis falls rapidly with increasing molecular weight of the homologs of acetone. With the pentanones, methyl *n*-propyl ketone and diethyl ketone, the biguanide is the principal product, and the yield of dihydrotriazine is quite low. In fact I-21·HCl and I-22·HCl have been isolated only by refrigeration of the filtered mother liquor of the reaction mixture.

In one case, the reaction is difficult even with acetone, under normally favorable conditions. I-5·HCl can be synthesized by reaction at room temperature or below, but even under these conditions some accompanying biguanide is formed. At the reflux point, *p*-nitrophenylbiguanide hydrochloride (IIIe·HCl) was the only detectable product. In fact, this method represents a simple route to the biguanide in excellent yield and purity, and avoids the purification steps necessary when IIIe is prepared by reaction in aqueous medium.[22] In contrast to the other compounds of structure I, I-5·HCl is light-sensitive and is not stable in aqueous or alcoholic solution at elevated temperatures. When an attempt is made to crystallize this compound from hot water or alcohol, the elements of acetone are lost and the arylbiguanide is formed. Purification of I-5·HCl was achieved on the basis of the difference in solubility between the dihydrotriazine and biguanide hydrochlorides, by aqueous extraction of the crude reaction product at room temperature and lyophilization of the extract. Both the difficulty of synthesis of this compound and the ready conversion to the biguanide are undoubtedly due to the fact that the electron-attracting nitro group reduces the basicity of the nitrogen atom, N^1, in I-5·HCl.

There are certain other conditions that make for biguanide formation in the three-component synthesis. When reagents are employed which are incapable of reaction in the three-component synthesis, there is exclusive formation of the corresponding biguanide. This is the case with N-methylaniline and with N^1,N^1- and N^1,N^2-dimethyl dicyandiamide, which have blocking methyl groups, and also with acetophenone or benzophenone.

The relatively unstable free bases of structure I can be prepared by careful neutralization of the hydrochlorides at moderate temperatures. In this manner I-1, I-3, I-6, and I-7 have been prepared. I-8, which has greater stability, can be made either by alkali treatment of I-8·HCl at room temperature or by crystallization of I-8·HCl from water.

When compounds of structure I are treated with an excess of alkali at elevated temperatures, they undergo readily an irreversible, intramolecular rearrangement to isomeric compounds of structure II, which are relatively inactive biologically.[4,7] The conversion is that of a phenyldihydrotriazine to an anilinodihydrotriazine. The interrelationships of I-3 and IIb provide a specific example of this general rearrangement. Treatment of I-3·HCl with alkali and heat affords IIb directly. The action of hydrochloric acid on IIb under a variety of conditions leads only to IIb·HCl, which reverts to IIb on neutralization. By very careful neutralization of I-3·HCl, I-3 can be isolated, which is relatively unstable and susceptible to rapid isomerization to IIb



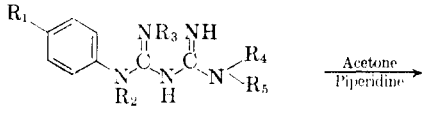
* Reported in ref. (4) as log ε 4.16.

under the influence of mild heat. Furthermore, basic conditions alone are sufficient to effect the isomerization: I-3 in strongly alkaline solution is converted quantitatively to IIb over a period of about three weeks at room temperature, as determined by measurement of the ultraviolet absorption spectrum of the solution.[23] I-3·HCl is regenerated by acid treatment of I-3.

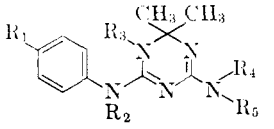
(22) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

(23) 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 in detail separately.

IIb has been synthesized previously (*a*) by condensation of *p*-chlorophenylbiguanide and acetone under basic conditions,[24,25] (*b*) by the same reaction in glacial acetic acid,[18,25,26] and (*c*) by the condensation of 2-amino-4-methylthio-6,6-dimethyldihydro-*s*-triazine with *p*-chloroaniline hydrochloride.[24] Samples of IIb made by alkali treatment of I-3·HCl and by method (*a*) have been shown to be identical by coincidence of the chemical and physical properties and also by comparison of the infrared absorption spectra.[27] Several compounds of structure II have been prepared from the corresponding hydrochlorides of I, and some have been made from the arylbiguanides (III) by a slight



III



II

modification of method (a) (Table II). Also, it has been demonstrated that the synthesis of II from III can be effected very slowly and in low yield without the use of a catalyst. IIa has been prepared in this way from phenylbiguanide and acetone in methanol. Thus in the presence of basic or weak acid catalysis or in the absence of a catalyst, arylbiguanides (III) condense with carbonyl reagents with formation of anilinodihydrotriazines (II) and under strong acid catalysis formation of aryldihydrotriazines (I) occurs.[21]

Although the aryldihydrotriazine hydrochlorides (I·HCl) are quite stable under ordinary conditions, being unaffected by storage for over four years in crystalline form and being resistant to boiling water for prolonged periods, these compounds rearrange instantly to the isomeric anilinodihydrotriazine hydrochlorides (II·HCl) on being melted. I-3·HCl is converted quantitatively to IIb·HCl at the melting point. As expected, the free bases (I) behave in similar fashion, I-3 being isomerized immediately to IIb at the melting point.

In summary, then, this investigation has revealed a number of new methods for the preparation of compounds of structure II: by treatment of I·HCl with heat and alkali; by the action of mild heat on I; by the prolonged action of alkali on I in aqueous solution at room temperature; by thermal rearrangement of I·HCl or I in the dry state; and by uncatalyzed condensation of III with acetone.

The free bases of structure I and II are relatively strong diacid bases forming monoacid salts preferentially. Diacid salts can be prepared in non-aqueous media. In base strength, I and II resemble arylbiguanides (III). Potentiometric titrations in 50 per cent ethanol (Fig. 1) show that IIb·H_2O has a

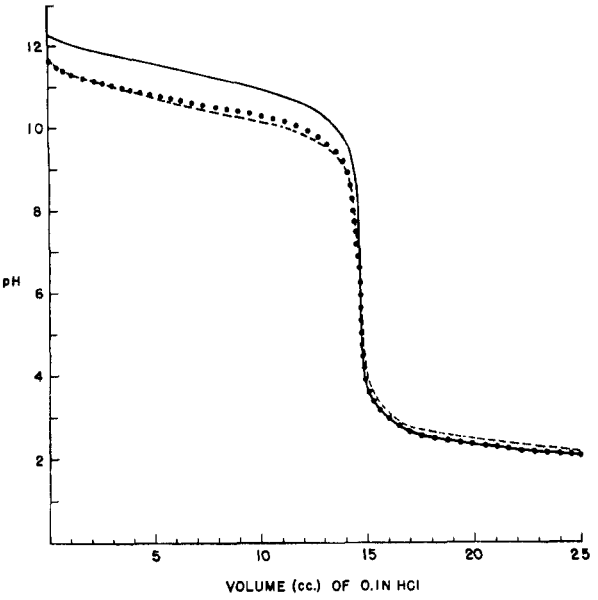


FIG. 1.—TITRATION CURVES IN 50% ETHANOL: ——, 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (I-3); ••••••, 4-amino-6-(*p*-chloroanilino)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrate (IIb·H_2O); – – – –, *p*-chlorophenylbiguanide hydrate. For these determinations, 1.5 × 10^{-3} mole of each compound was taken, and the solutions were 0.03 molar.

pK_a' value of 10.4, which is comparable to that of *p*-chlorophenylbiguanide hydrate[22] (pK_a' = 10.3) and is lower than that of the more strongly basic I-3 (pK_a' = 11.2).

The identification of compounds both of structure I and structure II is made possible by means of the characteristic ultraviolet absorption spectra of these substances.[23] In most cases a smooth curve with one minimum and one maximum is obtained (Fig. 2). In general, with 2,2-dimethyl substitution, structure I exhibits an absorption maximum at 241 mμ. The maximum of the corresponding isomer of structure II in each case appears at a longer wave length, and thus the isomerization of I to II can be followed readily. The dihydrotriazines may be easily distinguished from arylbiguanides by means of the ultraviolet absorption spectra or by the failure of the dihydrotriazines to form colored copper complexes with cuprammonium ion, in contrast to the arylbiguanides. Microbiological assay[28] has

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

(25) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951).

(26) S. Birtwell, *J. Chem. Soc.*, 1279 (1952).

(27) The infrared spectra reported were done under the supervision of Dr. E. R. Blout.

(28) Microbiological studies have been carried out under the direction of Dr. G. E. Foley. For purposes of identification, inhibition of the *Streptococcus faecalis* #8043-pteroylglutamic acid bio-assay system has been employed (ref. 7a).

been a valuable guide in the identification of I and II. In general, compounds of structure I are active inhibitors of certain microbiological systems, whereas the isomers of structure II are relatively inactive. Information obtained in this manner has been used to advantage in conjunction with absorption spectral data, during the course of this investigation.

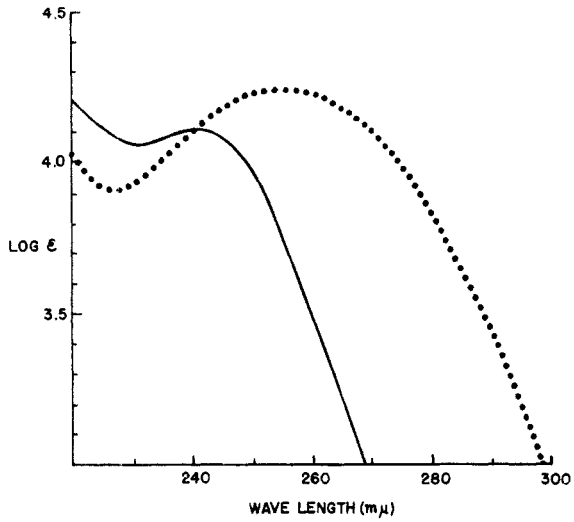
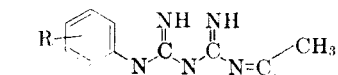
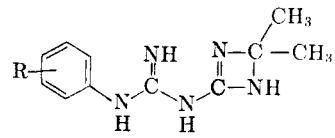


FIG. 2.—ULTRAVIOLET ABSORPTION SPECTRA IN WATER. ————, 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (I-3•HCl), [$\lambda_{max.}^{H_2O}$ 241 mμ, log ε 4.12; $\lambda_{min.}^{H_2O}$ 232 mμ, log ε 4.06]; ••••••, 4-amino-6-(*p*-chloroanilino)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrate (IIb•H_2O), [$\lambda_{max.}^{H_2O}$ 255 mμ, log ε 4.25; $\lambda_{min.}^{H_2O}$ 227 mμ, log ε 3.91].

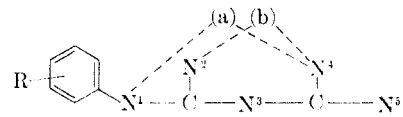
The evidence for the isomeric structures I and II rests largely on the basis of reactions involving methyl-substituted reactants. First, however, there are some general considerations regarding both structures. Since I[21] and II can be synthesized from the arylbiguanide directly, it may be assumed that in each case an intermediate exists with the arylbiguanide configuration. It is evident from the microanalytical data that each structure represents the sum of the elements of the arylbiguanide and acetone (taken as the typical carbonyl compound) less a molecule of water. In view of the presumedly common origin of I and II, the facile isomerization of I to II, and the similar appearance of the ultraviolet absorption spectral curves,[23] it is reasonable to conclude that the two structures are closely related. Structures of the arylbiguanide type with an open-chain configuration, such as IV, may be excluded on the grounds that neither I nor II forms a complex with cuprammonium sulfate, a test for the biguanide type grouping that involves chelation at N^2 and N^4, and also because the ultraviolet absorption spectra of I and II are not in keeping with the spectrum to be expected of IV. Arylbiguanide type structures with a four-membered ring, such as V, may also be excluded, by the failure of copper complexing, the incompatibility of the ultraviolet absorption spectra, and the relative stability of both I and II. Birtwell, *et al.*,[24] proposed the anilinodihydrotriazine structure for IIb on the basis of the microanalytical data and the failure of copper complexing. The obvious conclusion is that the acetone has condensed with formation of a cyclic structure, probably a six-membered ring, in each case. If one considers the skeletal arylbiguanide intermediate (VI) as a hypothetical precursor of both structures



IV



V



VI

I and II, it can be seen that two six-membered rings are possible by condensation of acetone: (a), between N^1 and N^4, and (b), between N^2 and N^4. (In this connection N^4 is taken to indicate the imino nitrogen of the amidine moiety.)

In the establishment of structure I, a critical experiment was the failure of N-methylaniline to undergo the three-component synthesis with dicyandiamide and acetone, with formation of the appropriate derivative of I. This indicated the necessity of both of the hydrogen atoms of the aniline amino group, or of the single hydrogen atom of N^1 of the hypothetical arylbiguanide intermediate (VI), for the synthesis of I. The failure of N^1,N^2-dimethyldicyandiamide to react in the three-component synthesis and the successful three-component reaction of N^1-methyldicyandiamide indicated that the hydrogen atom of the dicyandiamide imino group, or of N^4 of the intermediate (VI), must be available for condensation leading to I. The failure of N^1,N^1-dimethyldicyandiamide to undergo the three-component synthesis is anomalous, but the successful conversion of N^1-phenyl-N^5, N^5-dimethylbiguanide (IIId) to 6-amino-4-dimethylamino-1,2-dihydro-1-phenyl-*s*-triazine *via* the two-component synthesis[21] supports condensation at atom N^4 of VI, and also rules out possible four-membered ring structures for I involving N^5 as a ring atom, such as V. The conclusion is that in the formation of I the elements of water are lost between the oxygen atom of acetone and one hydrogen atom each of N^1 and N^4 of the hypothetical arylbiguanide intermediate, and, therefore, that N^1 and N^4 are involved as ring

atoms of a cyclic structure. Further evidence is provided by the failure of N^1-phenyl-N^1-methylbiguanide (IIIb) and of N^1-(*p*-chlorophenyl)-N^4,N^5-dimethylbiguanide (IIIc) and the success of N^1-phenyl-N^5-methylbiguanide (III: $R_4 = CH_3$; $R_1 = R_2 = R_3 = R_5 = H$) in giving rise to compounds of type I by the two-component synthesis.[21]

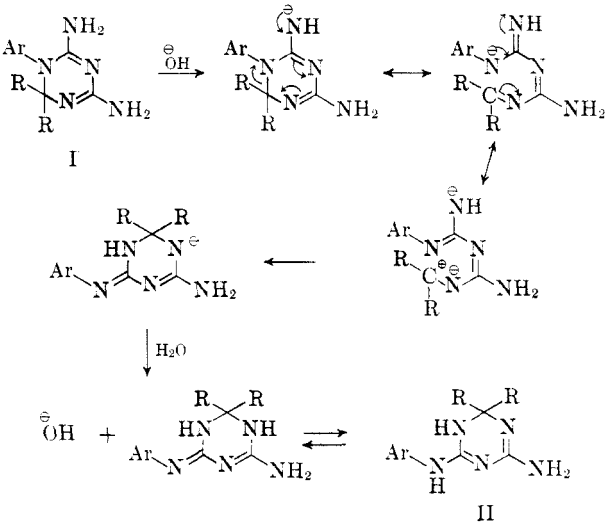
Thus a phenyldihydrotriazine structure has been assigned to I, by cyclization of VI at N^1 and N^4 according to possibility (a). Structure I has also been proposed for this type of compound by Carrington, *et al.*,[12,14] and has been confirmed by x-ray crystallographic studies of two acid salts of I-3.[29] Unsuccessful attempts have been made to synthesize I-3 by an alternate route, involving aminolysis of 6-alkylthio-4-amino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine.[26,30]

With respect to N-methylated derivatives of I, two 4-methylamino derivatives, I-13 and I-25, are reported and the synthesis of 6-methylamino and 4-dimethylamino derivatives by the two-component synthesis has also been accomplished.[21] N^3-Methyl derivatives of I are unavailable because of the failure of N^1,N^2-dimethyldicyandiamide to participate in the three-component synthesis.

In the case of structure II, the appropriate compounds have been made successfully by the basic condensation of acetone with N^1-phenyl-N^1-methylbiguanide (IIIb), N^1-(*p*-chlorophenyl)-N^5-methylbiguanide (IIIa), N^1-phenyl-N^5,N^5-dimethylbiguanide (IIId), and N^1-phenyl-N^2-methylbiguanide, with corresponding formation of IIe, IIf, IIg, and IIh, respectively, and the conversion in alkali of I-13 to the corresponding 4-methylamino derivative of II has been done.[23] Therefore, the evidence points to the involvement of N^2 and N^4 of VI in cyclization to a six-membered ring according to possibility (b), since none of the hydrogen atoms of N^1 or N^5 appears to be involved. Possible exocyclic double bonds in II involving N^1 or N^5 of the hypothetical biguanide intermediate, as well as open-chain and four-membered ring structures, such as IV and V, are eliminated by the synthesis of the N-methylanilino derivative, IIe, and the 4-dimethylamino compound, IIg. In view of the successful synthesis of the N^1-methyl derivative, IIh, double bonds involving positions 1 and 2 of the triazine ring are considered to be excluded and the 1,2-dihydrotriazine structure, II, is therefore the indicated tautomeric configuration. Thus the anilinodihydrotriazine structure originally proposed for II[24] is the correct one. Further evidence for both structures I and II has been presented by Carrington, *et al.*[14]

Structures I and II have been assigned principally on the presumption that blocking methyl groups prevent condensation and non-blocking methyl groups do not interfere. Evidence that the presence of methyl groups does not alter the path of the successful condensations or the structures of the products is provided by the close correlation of the ultraviolet absorption spectra of the methylated and non-methylated derivatives of I and II, with respect to the shape of the absorption curves and the positions of the maxima and minima.[23] I-3 and I-13 both absorb maximally at 241 mμ, and similarly, I-24 and I-25 both exhibit maxima at 251 mμ. The absorption maximum of the N-methylanilino derivative, IIe, is 247 mμ, which is 4 mμ shorter than that of the corresponding unmethylated compound, IIa. In the case of substitution at N^5 of structure II, there is a shift to longer wavelengths of 2–3 mμ per additional methyl group.

The proposed structures are compatible with the irreversible isomerization of I to II, which involves rupture of the N^1-C^2 bond in I and recyclization of C^2 to the exocyclic nitrogen atom of the 6-amino group. A possible mechanism for the base-catalyzed isomerization of I to II is indicated below:



The thermal rearrangement of the ordinarily stable I·HCl to II·HCl must proceed by a different mechanism, because it occurs under neutral conditions and requires a relatively high temperature. In view of the strain and hindrance in a Fischer-Hirschfelder molecular model of I and the lack of such strain in II, it is reasonable to suppose that the driving force of both the base-catalyzed and thermal rearrangements is the conversion of an internally strained structure to a strain-free molecule in a lower energy state. The thermal rearrangement of I to II appears to be analogous to that of 1-aryl-5-aminotetrazoles (or triazoles) to the isomeric 5-arylaminotetrazoles (or triazoles).[30,31]

With regard to possible reaction mechanisms of the three-component synthesis, it is considered

(29) M. Bailey, *Acta Cryst.*, **7**, 366 (1954).
(30) T. L. Loo, *J. Am. Chem. Soc.*, **76**, 5096 (1954).
(31) (a) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 88 (1954). (b) W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1269 (1953). (c) O. Dimroth, *Ann.*, **364**, 183 (1909).

likely that the first step is addition of the aromatic amine to the cyano group of dicyandiamide, followed by a Mannich-like condensation between the hydrogen atoms at N^1 and N^4 of the arylbiguanide intermediate and the carbonyl group of the ketone or aldehyde. There is close similarity of this synthesis to the arylbiguanide synthesis with respect to the reaction conditions and requirements. However, the possibility of prior formation of an aminocarbinol by addition of the amino group of either the arylamine or dicyandiamide to the carbonyl group cannot be absolutely excluded at present. Further work is in process on the mechanism of this reaction. Also, studies on the biologically active form of the phenyldihydrotriazines (I), which is thought to be a singly charged cation with the phenyl and the triazine rings essentially coaxial and close to coplanarity, will be reported in detail shortly.[32]

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EXPERIMENTAL[33]

Physical and chemical measurements. Melting points. The reproducibility of the melting points of the compounds described in this manuscript has been found to be dependent on four conditions: (*a*) rate of heating, (*b*) state of crystal subdivision, (*c*) amount of sample taken, and (*d*) temperature at which sample is immersed in the heating bath. These melting points, which are actually decomposition points, are not reproducible unless all these factors are rigidly controlled. All melting points reported herein are corrected, unless otherwise indicated; the melting points given in the tables are all corrected. Corrected melting points were taken in a modified Hershberg apparatus at 2° per minute. The Pyrex melting point tubes were filled to a height of 2 mm. with finely divided material and immersed 10–15° below the lower limit of the melting point range expected.

Absorption spectra. The ultraviolet absorption spectra reported[23] were measured with a Cary recording spectrophotometer, model 11. Aqueous solutions at 5×10^{-5} molar were prepared for this purpose. The infrared spectra reported[27] were measured in mineral oil mulls on a Perkin-Elmer double-beam recording infra-red spectrophotometer, model 21, with a sodium chloride prism.

Titrations. Several of the free bases of structure I and II were titrated against 0.1 *N* hydrochloric acid either potentiometrically with a Beckman *p*H meter, model H-2, or with Bromcresol Purple as an indicator. In most cases 200 to 400 mg. of the base was dissolved in 50% ethanol (by volume) at a concentration of 0.01 to 0.03 *molar*. Apparent pK_a values (pK_a') were calculated by determination of the *p*H at half neutralization from the titration curves (Fig. 1).

Substituted anilines. p-Aminobenzamide was prepared by the reduction of *p*-nitrobenzamide in 95% ethanol over platinum oxide at atmospheric pressure. After filtration, the reaction solution was taken to dryness under reduced pressure and the residue was crystallized from water with the aid of charcoal. The product was obtained in 75–78% yield as light tan prisms, melting at 178–181° (uncorr.) and was used directly for the synthesis of 4,6-diamino-1-(*p*-carboxamidophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (I-7·HCl). 3,4-Dichloroaniline hydrochloride was prepared as outlined in the following communication.[21]

Methylated dicyandiamides. N^1-Methyldicyandiamide,[34] N^1,N^1-dimethyldicyandiamide,[34] and N^1,N^2-dimethyldicyandiamide[24] were prepared according to published procedures.

GENERAL THREE-COMPONENT SYNTHESIS OF PHENYLDIHYDROTRIAZINE HYDROCHLORIDES (I·HCl)

(*A*). *With ketones.* The general procedure with acetone, the most frequently used ketone, is given first. A mixture of 0.1 mole of the substituted aniline hydrochloride (or 0.1 mole of the aniline and an equivalent of concentrated hydrochloric acid), 0.107 mole of dicyandiamide or N^1-methyldicyandiamide, and 50 cc. of acetone is refluxed with stirring for one to 24 hours, preferably for 17 hours. Generally the reaction mixture becomes a clear amber solution from which prismatic crystals begin to separate in ten minutes to one hour. In those few instances in which crystals are not deposited during the run, the product is obtained when the reaction mixture is cooled. On completion of the reaction the product (I·HCl) is collected, washed with acetone, and dried. The yield is between 30% and 95%, averaging 70%, and can be augmented by the separation of further material when the mother liquor is refrigerated or concentrated. At this stage the compound is quite pure. Further purification may be achieved by crystallization from water or an alcohol, with an average recovery of 70%. With the less soluble compound I-16·HCl, three times the volume of acetone was used in the reaction. The acid employed, in general, may be one of several strong inorganic or organic acids, including nitric and picric acids.

When other ketones are used, the reaction is done with 0.15–0.2 mole of the ketone and 50 cc. of 95% or absolute ethanol as solvent. The yields in this event are lower, ranging from 20% to 65% and averaging 50%. This procedure is useful with acetone when a clear solution is not otherwise obtained during the reaction; this was the case with I-7·HCl.

The ketones, acetone, cyclopentanone, and cyclohexanone, have been used successfully to date in the three-component synthesis at reflux temperature. When the condensation is effected at room temperature, the conditions and behavior of the reaction are essentially unchanged and the yield and purity of the product are about the same. In general condensations that proceed at the reflux point can be carried out at room temperature. However, with methyl ethyl ketone and the pentanones, or with *p*-nitroaniline, the room temperature synthesis is the most successful method (I-5·HCl, I-19·HCl, I-20·HCl, I-21·HCl, I-22·HCl) (*vide infra*). The three-component synthesis can also be effected at 0–5° (I-3·HCl, I-5·HCl).

Details of a number of syntheses in which there is some departure from the general procedure are given below.

4,6-Diamino-1,2-dihydro-2,2-dimethyl-1-(p-nitrophenyl)-s-triazine hydrochloride (I-5·HCl). A mixture of 6.91 g. (0.05 mole) of *p*-nitroaniline, 4.2 cc. (0.05 mole) of concentrated

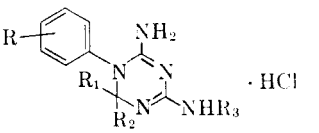
(32) A preliminary report on this subject, based on structure-microbiological activity correlations, has appeared: E. J. Modest, S. Farber, and G. E. Foley, *Proc. Am. Assoc. Cancer Research*, 1, 33 (1954).

(33) All compounds were dried for analysis *in vacuo* over phosphorus pentoxide at 70–100° for 17 hours, unless otherwise specified.

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

TABLE I

PHENYLDIHYDROTRIAZINE HYDROCHLORIDES



Cpd.	Ref. No.	Substitution[a] R	R_1	R_2	M.P.,[b] °C.	Formula	Analyses Calc'd C	H	N	Found C	H	N
					KETONE PRODUCTS							
I-1	D23	H	CH_3	CH_3	200–203	$C_{11}H_{15}N_5$·HCl	52.07	6.36	27.60	51.88	6.60	27.34
I-2	D83	4′-CH_3	CH_3	CH_3	206–208	$C_{12}H_{17}N_5$·HCl	53.82	6.78		53.93	6.96	
I-3	D20	4′-Cl	CH_3	CH_3	210–215	$C_{11}H_{14}ClN_5$·HCl	45.84	5.25	24.31	45.98	5.17	24.48
I-4	D65	4′-Br	CH_3	CH_3	203–208	$C_{11}H_{14}BrN_5$·HCl	39.71	4.55		39.31	4.89	
I-5[c]	D73	4′-NO_2	CH_3	CH_3	202–205[d]	$C_{11}H_{14}N_6O_2$·HCl	44.22	5.06		43.86	5.22	
I-6	D19	4′-$CO_2C_2H_5$	CH_3	CH_3	189–191	$C_{14}H_{19}N_5O_2$·HCl	51.61	6.19	21.50	51.97	6.12	21.22
I-7	D27	4′-$CONH_2$	CH_3	CH_3	210–212[e]	$C_{12}H_{16}N_6O$·HCl	48.56	5.78	28.32	48.59	5.61	28.47
I-8	D22	4′-CO_2H	CH_3	CH_3	200–210[f]	$C_{12}H_{15}N_5O_2$·HCl	48.40	5.42	23.52	48.67	5.47	23.68
I-9	D38	2′-CH_3	CH_3	CH_3	224–226	$C_{12}H_{17}N_5$·HCl	53.82	6.78		53.89	6.72	
I-10	D68	2′-Cl	CH_3	CH_3	217–221	$C_{11}H_{14}ClN_5$·HCl	45.84	5.25		46.13	5.42	
I-11	D82	2′-Br	CH_3	CH_3	217–222	$C_{11}H_{14}BrN_5$·HCl	39.71	4.55		40.04	4.69	
I-12	D69	3′-Cl	CH_3	CH_3	195–200	$C_{11}H_{14}ClN_5$·HCl	45.84	5.25		45.69	5.33	
I-13[a]	D32	H	CH_3	CH_3	170–172[g]	$C_{12}H_{17}N_5$·HCl	53.82	6.78	26.16	53.59	6.91	26.24
I-14	D53	2′,4′-Cl_2	CH_3	CH_3	204–208	$C_{11}H_{13}Cl_2N_5$·HCl	40.95	4.37		40.80	4.56	
I-15	D56	2′,5′-Cl_2	CH_3	CH_3	186–196	$C_{11}H_{13}Cl_2N_5$·HCl	40.95	4.37		40.55	4.78	
I-16	D54	3′,4′-Cl_2	CH_3	CH_3	207–212	$C_{11}H_{13}Cl_2N_5$·HCl[h]	40.95	4.37		41.23	4.28	
I-17	D64	4′-Cl	—$(CH_2)_4$—		212–216	$C_{13}H_{16}ClN_5$·HCl	49.69	5.46		50.00	5.60	
I-18	D40	4′-Cl	—$(CH_2)_5$—		224–226	$C_{14}H_{18}ClN_5$·HCl	51.23	5.83		51.61	6.19	
I-19[c]	D43	4′-Cl	CH_3	C_2H_5	196–201	$C_{12}H_{16}ClN_5$·HCl	47.69	5.67		47.77	5.70	
I-20[c]	D75	3′,4′-Cl_2	CH_3	C_2H_5	202–208	$C_{12}H_{15}Cl_2N_5$·HCl	42.81	4.79		42.38	4.95	
I-21[c]	D87	4′-Cl	CH_3	n-C_3H_7	188–192	$C_{13}H_{18}ClN_5$·HCl	49.37	6.06	22.15	49.37	6.17	21.96
I-22[c]	D42	4′-Cl	C_2H_5	C_2H_5	172–180	$C_{13}H_{18}ClN_5$·HCl	49.37	6.06		49.39	6.37	
					ALDEHYDE PRODUCTS							
I-23	D34	H	H	C_6H_5	215–220	$C_{15}H_{15}N_5$·HCl	59.70	5.35		59.87	5.68	
I-24	D37	4′-Cl	H	C_6H_5	217–221	$C_{15}H_{14}ClN_5$·HCl	53.58	4.50		53.59	4.52	
I-25[a,c]	D86	4′-Cl	H	C_6H_5	186–194	$C_{16}H_{16}ClN_5$·HCl	54.86	4.89		55.30	5.18	
I-26	D47	4′-Cl	H	2′-ClC_6H_4	221–224	$C_{15}H_{13}Cl_2N_5$·HCl	48.60	3.81		48.77	4.19	
I-27	D57	2′,4′-Cl_2	H	C_6H_5	217–221	$C_{15}H_{13}Cl_2N_5$·HCl	48.60	3.81		48.46	4.09	
I-28	D58	2′,5′-Cl_2	H	C_6H_5	211–216	$C_{15}H_{13}Cl_2N_5$·HCl	48.60	3.81		48.58	4.27	
I-29	D55	3′,4′-Cl_2	H	C_6H_5	213–217	$C_{15}H_{13}Cl_2N_5$·HCl	48.60	3.81		48.66	4.00	

[a] R_3 = H except for I-13 and I-25, in which R_3 = CH_3. [b] All compounds crystallized from water as colorless prisms and were dried for analysis *in vacuo* at 70–100°C for 17 hours, unless otherwise indicated. [c] Details of synthesis reported in the experimental part. [d] Analytical sample obtained as a pale yellow microcrystalline powder by lyophilization. Crystallization from water results in conversion to the biguanide, IIIe·HCl. [e] Crystallized from 70% ethanol. [f] Submitted for analysis directly from the reaction mixture after being washed and dried. Crystallization from water affords the free base I-8. [g] Crystallized from *n*-butanol. [h] Calc'd: Cl, 32.97. Found: Cl, 32.81.

hydrochloric acid, 4.2 g. (0.05 mole) of dicyandiamide, and 100 cc. of acetone was stirred at room temperature. The reaction mixture became a clear, brownish solution within a few minutes, and crystalline material began to be deposited shortly thereafter. After six hours, the reaction was stopped and the product (I-5·HCl) was collected and washed with acetone. It was a very pale yellow, light-sensitive solid; yield, 11.1 g. (74%); m.p. 227–233° (uncorr.); $\lambda_{max}^{H_2O}$ 238mμ; turbidity with cuprammonium sulfate (slightly positive biguanide test).[35] The same material was obtained when this reaction was repeated at 5°. It was apparent that this crude preparation of I-5·HCl was contaminated with some *p*-nitrophenylbiguanide hydrochloride (IIIe·HCl). Since I-5·HCl tends to lose the elements of acetone with formation of the biguanide on being heated, crystallization could not be employed for purification. Therefore, a purification technique, based on the fact that I-5·HCl is more soluble in water than is IIIe·HCl, was developed which involved aqueous extraction and lyophilization. One gram of the crude product was shaken with 25 cc. of water for 15 minutes and the suspension was filtered free of a dark yellow solid, m.p. 259–260° (uncorr.); orange-brown precipitate with cuprammonium sulfate (positive biguanide test). On lyophilization of the clear, yellow filtrate, a pale yellow solid was obtained; 0.82 g.; m.p. 211–218° (uncorr.); faint turbidity with cuprammonium sulfate. When this partially purified material was treated by the same procedure of extraction with insufficient water and lyophilization, a very pale yellow microcrystalline product resulted; m.p. 206–207° (uncorr.); no precipitate or turbidity with cuprammonium sulfate (negative biguanide test); $\lambda_{max.}^{H_2O}$ 240 mμ. This substance (I-5·HCl) was submitted directly for analysis, after being dried (Table I).

When an attempt was made to purify I-5·HCl by crystallization from water or dilute ethanol, long yellow needles were obtained; m.p. 278–280° (uncorr.); $\lambda_{max.}^{H_2O}$ 230 mμ, 324 mμ; orange precipitate with cuprammonium sulfate (positive biguanide test). This compound was demonstrated to be IIIe·HCl (Table III) by a mixture melting point determination with an authentic sample and a comparison of the ultraviolet absorption spectra.

Attempts to synthesize I-5·HCl by the three-component

(35) The coloration or precipitate (usually pink) formed by treatment of an aqueous solution of the sample with a drop of *ca.* 5% copper sulfate in excess ammonium hydroxide indicates a positive biguanide test.

synthesis at elevated temperatures led to the formation of IIIe·HCl in excellent yield (80%) and relatively pure form. This represents an improved synthesis of this biguanide over the method involving condensation of *p*-nitroaniline hydrochloride and dicyandiamide in aqueous medium.[22] The improvement resides in the facts that the weakly basic *p*-nitroaniline reacts as a stronger base in non-aqueous medium and that unreacted free amine remains in solution in the acetone employed as solvent.

4,6-Diamino-1-(p-chlorophenyl)-2-ethyl-1,2-dihydro-2-methyl-s-triazine hydrochloride (I-19·HCl). A mixture of 6.38 g. (0.05 mole) of *p*-chloroaniline, 4.2 cc. (0.05 mole) of concentrated hydrochloric acid, 4.5 g. (0.0535 mole) of dicyandiamide, 40 cc. of methyl ethyl ketone, and 10 cc. of absolute ethanol was stirred at room temperature and became a clear, greenish-yellow solution in three hours. The reaction was stopped after 24 hours, at which time a white crystalline product had formed. The reaction mixture was refrigerated overnight and the product (I-19·HCl) was collected and washed with methyl ethyl ketone; 8.38 g. (50%); m.p. 211–213° (uncorr.). For analysis a sample was crystallized from water (Table I). Numerous attempts to prepare this compound under similar conditions at elevated temperatures led predominantly to biguanide formation.

4,6-Diamino-1-(3',4'-dichlorophenyl)-2-ethyl-1,2-dihydro-2-methyl-s-triazine hydrochloride (I-20·HCl). This compound was prepared by a procedure similar to that used for I-19·HCl from 59.55 g. (0.3 mole) of 3,4-dichloroaniline hydrochloride, 27 g. (0.321 mole) of dicyandiamide, 375 cc. of methyl ethyl ketone, and 375 cc. of absolute ethanol; yield, 67.8 g. (67%); m.p. 210–216° (uncorr.). Analytically pure material was obtained on crystallization from water (Table I). Attempts to prepare I-20·HCl at elevated temperatures led to biguanide formation.

4,6-Diamino-1-(p-chlorophenyl)-1,2-dihydro-2-methyl-2-(n-propyl)-s-triazine hydrochloride (I-21·HCl). A mixture of 3.26 g. (0.02 mole) of *p*-chloroaniline hydrochloride and 1.8 g. (0.0214 mole) of dicyandiamide in 15 cc. of methyl *n*-propyl ketone and 4 cc. of absolute ethanol was stirred at room temperature for 24 hours; at no time was a complete solution observed. Filtration of the reaction mixture afforded 1.12 g. of a white solid, m.p. 223–228° (uncorr.); pink precipitate with cuprammonium sulfate (positive biguanide test). This product, which is essentially biguanide, was discarded. The clear brown filtrate, on being refrigerated for three months, afforded 1.05 g. (17%) of colorless prisms (I-21·HCl), melting at 200–205° (uncorr.); negative reaction with cuprammonium sulfate. Crystallization from water afforded an analytical sample (Table I).

4,6-Diamino-1-(p-chlorophenyl)-2,2-diethyl-1,2-dihydro-s-triazine hydrochloride (I-22·HCl). A mixture of 32.81 g. (0.2 mole) of *p*-chloroaniline hydrochloride, 18 g. (0.214 mole) of dicyandiamide, 150 cc. of diethyl ketone, and 50 cc. of absolute ethanol was stirred for three days at room temperature, during which period the reaction mixture did not become a complete solution. The insoluble white material was filtered off, washed with ethanol, and found to be essentially *p*-chlorophenylbiguanide hydrochloride; yield, 32.2 g.; m.p. 190–230° (uncorr.); positive biguanide test with cuprammonium sulfate. The amber filtrate deposited 1.4 g. of colorless prisms upon refrigeration; m.p. 198–214° (uncorr.); very slightly positive biguanide test. By fractional crystallization from water, I-22·HCl, which was more soluble than the small amount of contaminating arylbiguanide hydrochloride, was obtained pure, and gave a negative reaction with cuprammonium sulfate. This compound crystallized in transparent, colorless prisms, which became opaque and chalky on being dried at 70° in the drying pistol (Table I). Additional product could be obtained by further refrigeration of the original filtrate.

Other salts of 4,6-diamino-1-(p-chlorophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine (I-3). I-3·Nitrate. When nitric acid was used in place of hydrochloric acid in the usual manner, I-3·HNO_3 was formed in 72% yield. Crystallization from water afforded colorless prisms, m.p. 198–199°.

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot HNO_3$: C, 41.98; H, 4.80. Found: C, 42.03; H, 4.81.

I-3·Picrate. Hydrochloric acid was replaced by picric acid in the synthesis of I-3·picrate in 98% yield. This product crystallized from 95% ethanol in yellow rods, melting at 202–203°.

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot C_6H_3N_3O_7$: C, 42.46; H, 3.57. Found: C, 42.29; H, 3.54.

The *picrate* of I-3 was also prepared by the mixing of equal volumes of saturated aqueous solutions of I-3·HCl and picric acid. The yellow precipitate was identical with the product described above.

I-3·Nitrite. To a solution of 4.32 g. (0.015 mole) of I-3·HCl in 96 cc. of water was added 1.04 g. (0.015 mole) of sodium nitrite in 3 cc. of water. Shortly after the addition, small, cubic crystals of I-3·HNO_2 began to separate from the solution. After five hours, the product was collected and washed with water; yield, 2.14 g. (48%); m.p. 163–166° with effervescence to a brown melt. One crystallization from water afforded analytically pure material, crystal form and melting point unchanged.

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot HNO_2$: C, 44.22; H, 5.06; N, 28.13; Cl, 11.87. Found: C, 44.45; H, 5.32; N, 28.32; Cl, 12.02.

I-3·Bicarbonate. Two hundred cc. of a saturated, aqueous solution of I-3·HCl (containing *ca.* 9 g. of the compound) was mixed with 100 cc. of a saturated, aqueous solution of sodium bicarbonate, and the clear solution was refrigerated overnight. The crop of colorless prisms (I-3·H_2CO_3) was collected and washed with water; 3.1 g.; m.p. 194–197°.

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot H_2CO_3$: C, 45.93; H, 5.14. Found: C, 45.64; H, 5.39.

The molecular weight of this compound was determined by metathetical titration of bicarbonate with hydrochloric acid, both potentiometrically and to a Bromophenol Blue end-point. In aqueous solution 468 mg. required 14.95 cc. of 0.1 *N* HCl. Calc'd: M.W., 314. Found: M.W., 313.

I-3·Dihydrochloride. Gaseous HCl was bubbled into a suspension of 2 g. of I-3·HCl in 40 cc. of acetone until a clear solution was observed. After filtration this solution was mixed with 40 cc. of ether and refrigerated overnight. The crop of white, microcrystalline material that had formed was collected and washed with acetone; yield, 1.9 g. (85%). This product (I-3·2HCl) started to melt at 190° to a semi-solid at 193°, becoming clear at 196°. A sample was dried and submitted directly for analysis.[36]

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot 2HCl$: C, 40.69; H, 4.97; N, 21.57. Found: C, 40.98; H, 4.87; N, 21.70.

Unsuccessful reactions. A number of attempted condensations, under varied conditions, of aniline hydrochloride, N^1, N^1-dimethyldicyandiamide, and acetone, and of *p*-chloroaniline hydrochloride, N^1,N^2-dimethyldicyandiamide, and acetone led only to N^1-phenyl-N^5,N^5-dimethylbiguanide hydrochloride (IIId·HCl) and N^1-(*p*-chlorophenyl)-N^4,N^5-dimethylbiguanide hydrochloride (IIIe·HCl), respectively (Table III). When the reaction of N-methylaniline hydrochloride, dicyandiamide, and acetone was attempted under various conditions, N^1-phenyl-N^1-methylbiguanide hydrochloride (IIIb·HCl) was the exclusive product (Table III). Numerous attempts to effect the three-component condensation with acetophenone and benzophenone under a variety of reaction conditions proved to be unsuccessful; and when acetic acid was used in place of hydrochloric acid, no dihydrotriazine formation was observed.

(*B*). *With aldehydes.* A solution of 0.1 mole of the substi-

(36) In ref. (10) the synthesis of I-3·2HCl·$2H_2O$ is reported, m.p. 216–221° (uncorr.). This formula was assigned on the basis of a nitrogen analysis only and is suspect in view of the high m.p. reported and the fact that these dihydrotriazine dihydrochlorides tend to revert to monohydrochlorides in the presence of water.

tuted aniline hydrochloride (or 0.1 mole of the aniline and an equivalent of concentrated hydrochloric acid), 0.107 mole of dicyandiamide or N^1-methyldicyandiamide, 0.105 to 0.15 mole of the aromatic aldehyde, and 50 cc. of 95% or absolute ethanol is refluxed for six hours. Crystals of the product are deposited either during the run or when the reaction mixture is cooled. After thorough cooling the product is collected, washed with absolute ethanol or acetone, and dried. The yield is from 10% to 80%, averaging 50%. Further material can be isolated from the mother liquor. The compound may be crystallized from water or an alcohol, in an average recovery of 65%.

6-Amino-1-(p-chlorophenyl)-1,2-dihydro-4-methylamino-2-phenyl-s-triazine hydrochloride (I-25·HCl). A mixture of 12.76 g. (0.1 mole) of *p*-chloroaniline, 8.33 cc. (0.1 mole) of concentrated hydrochloric acid, 10.5 g. (0.1 mole) of N^1-methyldicyandiamide, and 15.3 cc. (0.15 mole) of benzaldehyde in 50 cc. of 95% ethanol was refluxed for six hours, and the clear yellow solution was refrigerated. Since all efforts to induce crystallization failed, the reaction mixture was allowed to evaporate slowly in air at room temperature. After one month, manipulation of the glassy residue afforded colorless crystals (I-25·HCl), which were triturated with absolute ethanol and collected; yield, 6.9 g. (19%); m.p. 195–198° (uncorr.). On crystallization from water analytically pure material was obtained (Table I).

Unsuccessful reactions. A number of attempts to condense *p*-chloroaniline hydrochloride and dicyandiamide with formaldehyde, acetaldehyde, and *n*-butyraldehyde under a variety of reaction conditions led only to the formation of deeply colored, viscous resins.

Conversion of I·HCl *to* I. This conversion is done usually with sodium hydroxide or ammonia at moderate temperatures because isomerization to II occurs readily at elevated temperatures under alkaline conditions.

(*A*). *Preparation of* I-3. Upon addition of an excess of sodium hydroxide to a solution of 10 g. of I-3·HCl in water at room temperature, a copious precipitate (I-3) formed immediately. It was collected, washed thoroughly with water, and dried; quantitative yield; m.p. 143–156° (uncorr.); $\lambda_{max.}^{H_2O}$ 241 mμ. This procedure can also be done with ammonium hydroxide and is general for the preparation of bases of this type. Often it is desirable to cool the solution in an ice-bath before the addition of alkali. An analytical sample of this material was obtained by the following procedure. To 1 g. of I-3·HCl in 25 cc. of water was added 8 cc. of a saturated aqueous solution of barium hydroxide, and the clear solution resulting was left overnight on ice. A crop of colorless, well-formed, elongated, rectangular plates (I-3) formed and was collected and washed with water; yield, 0.2 g. The crystals are efflorescent, becoming chalky and opaque in air. The melting point is 136–144°; $\lambda_{max.}^{H_2O}$ 241 mμ, log ε 4.11. For analysis this compound was dried *in vacuo* at room temperature and was not purified further.

Anal. Calc'd for $C_{11}H_{14}ClN_5$: C, 52.48; H, 5.61; N, 27.82; N.E., 252. Found: C, 52.40; H, 5.55; N, 28.01; N.E., 253.

When I-3 was treated with an equivalent of dilute hydrochloric acid and the evaporated residue was crystallized from water, a compound resulted that was shown to be identical with I-3·HCl by a mixture melting point determination and the identity of the infrared absorption spectra.

Preparation of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-phenyl-s-triazine (I-1). Treatment of a solution of 2 g. of I-1·HCl in 15 cc. of water with 15 cc. of saturated aqueous barium hydroxide afforded 1.21 g. (71%) of long, colorless, prismatic needles (I-1), which were submitted for analysis directly after being washed and dried *in vacuo* at room temperature; m.p. 142–151°.

Anal. Calc'd for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96. Found: C, 60.6; H, 6.9.

(*B*). *Formation of 4,6-diamino-1-(p-carbethoxyphenyl)-1,2-dihydro-2,2-dimethyl-s-triazine* (I-6) *and 4,6-diamino-1-(p-carboxamidophenyl)-1,2-dihydro-2,2-dimethyl-s-triazine* (I-7). A solution of 500 mg. of I-6·HCl in 4 cc. of water was warmed to 40° and brought to *p*H 9 with concentrated ammonium hydroxide, at which point incipient crystallization was observed. After one hour the product (I-6) was collected and washed with water; 300 mg. (68%) of small, colorless prisms, which started to melt to a semi-solid at 132° and became a clear melt with effervescence at 155–160°. This analytical sample was dried *in vacuo* at room temperature.

Anal. Calc'd for $C_{14}H_{19}N_5O_2$: C, 58.11; H, 6.62; N, 24.21. Found: C, 57.51; H, 7.03; N, 23.92.

Similar treatment of an aqueous solution of I-7·HCl with ammonium hydroxide afforded the free base (I-7), colorless prisms which started to melt at 178° to a semi-solid by 182°, becoming clear with effervescence at 212–214°. This product was dried at room temperature *in vacuo* for analysis.

Anal. Calc'd for $C_{12}H_{17}N_5O$: C, 55.15; H, 6.57; N, 32.17. Found: C, 55.08; H, 6.42; N, 32.03.

Both I-6 and I-7 can be prepared with sodium hydroxide in place of ammonium hydroxide.

(*C*). *Preparation of 4,6-diamino-1-(p-carboxyphenyl)-1,2-dihydro-2,2-dimethyl-s-triazine* (I-8). I-8·HCl (5 g.) was crystallized from 53 cc. of water and 1.28 g. (29%) of crystalline material (I-8) was obtained, melting at 342–344° (uncorr.) to a dark brown melt. This substance was crystallized again from water, colorless plates, m.p. 346–348° (uncorr.).

Anal. Calc'd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.81. Found: C, 55.25; H, 5.71; N, 26.57.

The same product was obtained by another method. Agitation of a mixture of 1.49 g. (0.005 mole) of I-8·HCl in 85 cc. of 0.1 *N* sodium hydroxide at room temperature afforded a clear, colorless solution, *p*H 12.9. The solution was adjusted to *p*H 11 with 1 *N* hydrochloric acid, at which point a white solid separated. This precipitate (I-8) was filtered off, washed with water, and dried; tiny, colorless rods; yield, 1.09 g. (83%); m.p. 330–340° (uncorr.).

Synthesis of anilinodihydrotriazines (II) (*Table II*). These compounds were prepared by one or more of methods *A*, *B*, *C*, and *D*, described below. The yields of II from the phenyldihydrotriazines (I·HCl) are better than from the arylbiguanides (III). Where applicable, procedure *A* is preferred.

(*A*). *From* I·HCl *with alkali and heat.* A solution of I·HCl in water or aqueous ethanol is treated with excess alkali, heated for about one hour at steam-bath temperature, and cooled. The product (II), which crystallizes out, is collected and washed thoroughly with water.

Preparation of 4-amino-6-(p-chloroanilino)-1,2-dihydro-2,2-dimethyl-s-triazine (IIb). Sodium hydroxide (5*N*) was added to a solution of 1 g. of I-3·HCl in 40 cc. of 50% aqueous ethanol to *p*H 11. The solution was refluxed for one hour and then was refrigerated overnight. The product (IIb·H_2O), which had crystallized in large, colorless, thick plates, was collected and washed with water; yield, 0.85 g. (90%); m.p. 135–137° (uncorr.). For analysis a sample was crystallized from 95% ethanol; $\lambda_{max}^{H_2O}$ 255 mμ, log ε 4.25 (Table II). This compound proved to be identical with a sample of IIb·H_2O prepared according to Birtwell, *et al.*;[24] the crystal form, melting point, and ultraviolet and infrared absorption spectra are the same, and a mixture melting point is undepressed.

Treatment of IIb *with hydrochloric acid.* (*1*). *With dilute HCl.* A mixture of 9.93 g. (0.0433 mole) of IIb·H_2O in 43.3 cc. (0.0442 mole, 2% excess) of 1.018 *N* hydrochloric acid was heated and the resulting solution was filtered immediately. The product crystallized slowly, as the solution cooled, in well-formed, colorless prisms (IIb·HCl). The crystals were collected, washed with water, and dried; yield, 7.38 g. (70%); m.p. 129–136°. For analysis a sample was crystallized from water as colorless prisms, melting at 128–131°; $\lambda_{max.}^{H_2O}$ 255 mμ, log ε 4.24.

Anal. Calc'd for $C_{11}H_{14}ClN_5$·HCl: C, 45.84; H, 5.25; N,

24.31; Cl, 24.61. Found: C, 45.67; H, 5.21; N, 24.53; Cl, 24.70.

The physical properties of IIb·H_2O and IIb·HCl are quite similar: both have the same crystal form and ultraviolet absorption spectrum, and a mixture melting point of the two compounds is undepressed.

(*2*). *With hydrogen chloride.* One gram of IIb·H_2O was refluxed briefly in 20 cc. of acetone and a slightly cloudy solution resulted. The solution was saturated with hydrogen chloride. When the gas was first admitted, a crystal crop appeared which redissolved nearly completely on further admission of hydrogen chloride. The solution was filtered, treated with an equal volume of ether, and allowed to stand overnight. A quantitative yield of white, crystalline material was obtained (IIb·2HCl), which shrinks at 190°, starts melting at 200° to a semi-solid at 210°, and becomes clear at 213°; $\lambda_{max.}^{H_2O}$ 255 mμ, log ε 4.27. A sample was dried and submitted directly for analysis.

Anal. Calc'd for $C_{11}H_{14}ClN_5$·2HCl: C, 40.69; H, 4.97; N, 21.57. Found: C, 40.95; H, 4.88; N, 21.66.

A sample of IIb·2HCl was crystallized twice from extremely little water; compact prisms (IIb·HCl), melting at 128–132°.

Anal. Calc'd for $C_{11}H_{14}ClN_5$·HCl: C, 45.84; H, 5.25; N, 24.31. Found: C, 45.69; H, 5.20; N, 24.18.

This compound was shown to be identical with the sample of IIb·HCl prepared by the action of dilute HCl on IIb·H_2O in that it did not depress the melting point of that sample and had the same ultraviolet and infrared absorption spectra.

(*3*). *With concentrated HCl.* One gram of IIb·H_2O was spread evenly over the bottom of a small Petri dish and was covered with 3 cc. of concentrated HCl. A clear solution soon resulted, which was permitted to evaporate slowly at room temperature. After nearly a week, a hard, dry, crystalline crust was obtained (IIb·2HCl), which shrinks at 185°, starts to melt at 195° to a semi-solid at 210°, and becomes clear with effervescence at 214°. A sample of this material, crystallized from the minimum amount of water, afforded IIb·HCl.

Neutralization of IIb·HCl. One gram (0.00347 mole) of IIb·HCl was dissolved in 15 cc. of water, and 33.9 cc. of 0.1045 *N* sodium hydroxide (0.00354 mole, 2% excess) was added with swirling. Crystals soon began to deposit from the clear solution. After a day the crystal crop was collected and washed with water; yield, 0.35 g. (38%) of colorless rectangular plates melting at 137–142° (uncorr.). A sample of this compound (IIb·H_2O) was recrystallized from aqueous ethanol for analysis, m.p. unchanged.

Anal. Calc'd for $C_{11}H_{14}ClN_5$·H_2O: C, 48.98; H, 5.98; Cl, 13.14. Found: C, 49.11; H, 6.01; Cl, 13.32.

Formation of IIb·HNO_2. A solution of 345 mg. (0.005 mole) of sodium nitrite in 1 cc. of water was added to 1.44 g. (0.005 mole) of IIb·HCl in 32 cc. of water. Crystallization of the product (IIb·HNO_2) began shortly and the material was collected after three hours; 0.69 g. (46%); m.p. 120–125° (uncorr., eff.) to a pale yellow melt that decomposed and turned dark brown at 180° (uncorr.). One crystallization from absolute ethanol provided colorless prisms, m.p. 177–179° to a dark brown melt.

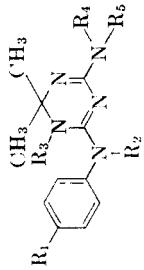
Anal. Calc'd for $C_{11}H_{14}ClN_5$·HNO_2: C, 44.22; H, 5.06; Cl, 11.87. Found: C, 44.50; H, 5.40; Cl, 12.10.

Preparation of 4-amino-6-(p-carboxyanilino)-1,2-dihydro-2,2-dimethyl-s-triazine (IId) *from* I-8·HCl. A suspension of 1.49 g. (0.005 mole) of I-8·HCl in 85 cc. of 0.1 *N* sodium hydroxide was heated for one hour at steam-bath temperature, during which time a clear, colorless solution resulted, *p*H 12.5. The solution was cooled and a white precipitate was obtained when the solution was adjusted to *p*H 8 with 0.5 *N* hydrochloric acid. The solid (IId) was collected, washed with water, dried, and submitted directly for analysis; yield, 0.98 g. (75%) (Table II).

(*B*). *From the free bases,* I. Simple crystallization of I by

TABLE III

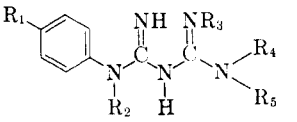
ANILINODIHYDROTRIAZINES



Cpd.	Ref. No.	Substitution					Method[a]	M.P., °C.	Crystal[b] Form	Solvent for Cryst.	N.E.		Formula	Analyses				
		R_1	R_2	R_3	R_4	R_5					Calc'd	Found		C	Calc'd H	N	C	Found H	N
IIa	DX23	H	H	H	H	H	1,2	187–189	prisms	H_2O	217	220	$C_{11}H_{15}N_5$	60.81	6.96	32.24	60.66	6.83	32.38
IIb·H_2O	DX20	Cl	H	H	H	H	1,2	130–133	prisms	95% EtOH	270	270	$C_{11}H_{14}ClN_5 \cdot H_2O$	48.98	5.98	25.97	49.03	6.12	25.78
IIe·C_2H_5OH	DX19	$CO_2C_2H_5$	H	H	H	H	2	123–128	prism. rods[c]	95% EtOH	335	338	$C_{14}H_{19}N_5O_2 \cdot C_2H_5OH$	57.29	7.51		57.19	7.57	
IId	DX22	CO_2H	H	H	H	H	2	340–346[d]	prism. rods	[e]			$C_{12}H_{15}N_5O_2$	55.16	5.79		55.09	6.03	
IIe·HCl	DX30	H	CH_3	H	H	H	1	240–241	prisms	*n*-BuOH			$C_{12}H_{17}N_5 \cdot HCl$	53.82	6.78		53.74	6.80	
IIf·HCl·H_2O	DX35	Cl	H	H	CH_3	H	1	122–127[f]	rods[g]	H_2O			$C_{12}H_{16}ClN_5 \cdot HCl \cdot H_2O$	45.01	5.98		45.08	6.24	
IIg	DX29	H	H	H	CH_3	CH_3	1	155–158	prisms	H_2O			$C_{13}H_{19}N_5$	63.64	7.81	28.55	63.64	7.67	28.69
IIh	DX89	H	H	CH_3	H	H	1	204–206	prisms	[d]			$C_{12}H_{17}N_5$	62.31	7.41	30.28	61.84	7.81	29.76

[a] 1: From the arylbiguanide; 2: from the appropriate I·HCl or I. [b] All compounds dried for analysis *in vacuo* at 70–100°C for 17 hours, unless otherwise indicated. [c] Analytical sample air-dried at room temperature for 17 hours. [d] With effervescence to a dark brown melt. [e] Submitted for analysis directly from the reaction mixture after being washed and dried. [f] With prior shrinking to a semi-solid at 82–87°. [g] Analytical sample dried *in vacuo* at 45° for 17 hours.

TABLE III
PHENYLBIGUANIDES



Cpd.	Substitution R1	R2	R3	R4	R5	M.P., °C.	Crystal Form	Solvent for Cryst.	Formula	Analyses Calc'd C	H	N	Found C	H	N
IIIa·H_2O[a]	Cl	H	H	CH_3	H	110–115	rods[b]	H_2O	$C_9H_{12}ClN_5 \cdot H_2O$	44.35	5.79	28.74	44.38	5.70	28.64
IIIb·HCl	H	CH_3	H	H	H	200–203	prisms[c]	*n*-PrOH	$C_9H_{13}N_5 \cdot HCl$	47.47	6.20	30.76	47.63	6.01	30.91
IIIb·H_2O[d]	H	CH_3	H	H	H	94–96	rods[b]	H_2O	$C_9H_{13}N_5 \cdot H_2O$	51.66	7.23	33.47	51.83	7.14	33.35
IIIc·HCl[e]	Cl	H	CH_3	CH_3	H	251–253	prism.[c] plates	H_2O	$C_{10}H_{14}ClN_5 \cdot HCl$	43.49	5.47		43.57	5.58	
IIId·HCl[f]	H	H	H	CH_3	CH_3	251–253	prism.[c] rods	H_2O	$C_{10}H_{15}N_5 \cdot HCl$	49.68	6.67	28.97	49.44	6.25	28.92
IIId	H	H	H	CH_3	CH_3	125–126	plates[g]	H_2O	$C_{10}H_{15}N_5$	58.51	7.37	34.12	58.40	7.37	34.22
IIIe·HCl	NO_2	H	H	H	H	268–270	yellow[c] needles	70% EtOH	$C_8H_{10}N_6O_2 \cdot HCl$	37.14	4.29		37.25	4.48	

[a] F.H.S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946) (analysis not given). [b] Analytical sample dried *in vacuo* at room temperature for 17 hours. [c] Analytical sample dried *in vacuo* at 70–100° for 17 hours. [d] G. Cohn, *J. prakt. Chem.*, **84**, 394 (1911) (not characterized). [e] S. Birtwell, F. H. S. Curd, J. A. Hendry, and F. L. Rose, *J. Chem. Soc.*, 1645 (1948). [f] A. F. Crowther, F. H. S. Curd, D. N. Richardson, and F. L. Rose, *J. Chem. Soc.*, 1636 (1948). [g] Analytical sample dried *in vacuo* at 50° for 17 hours.

dissolution with gentle heat in a suitable solvent, such as aqueous ethanol or water, effects the isomerization to II. This rearrangement occurs at temperatures well below the boiling point of the solvent.

Crystallization of I-3 from 95% ethanol resulted in the isomerization to IIb·H_2O, isolated in the form of large, colorless prisms; $\lambda_{max.}^{H_2O}$ 255 mμ (Table II). A mixture melting point of this product and IIb·H_2O prepared from *p*-chlorophenylbiguanide showed no depression, and the infrared absorption spectra of the two samples of IIb·H_2O were identical.

4-Amino-6-(*p*-carbethoxyanilino)-1,2-dihydro-2,2-dimethyl-*s*-triazine (IIc), as the ethanolate, was prepared similarly by crystallization of I-6 from 95% ethanol (Table II).

An excess of 5 *N* sodium hydroxide was added to a concentrated solution of I-1·HCl in water and caused precipitation of a white solid, which was collected, washed with water, and dried. On crystallization of this product (I-1) from water, colorless prisms of 4-amino-6-anilino-1,2-dihydro-2,2-dimethyl-*s*-triazine (IIa) were obtained (Table II).

(*C*). *By thermal isomerization of* I·HCl *or* I. I·HCl is converted instantly to II·HCl at the melting point in excellent yield.

Thermal rearrangement of I-3·HCl *to* IIb·HCl. A test tube containing one gram of I-3·HCl was immersed in a metal bath at 245° until the solid was completely melted (about one minute). After the melt had cooled and hardened, it was crystallized from water; colorless prisms of IIb·HCl (0.5 g., 50%); $\lambda_{max.}^{H_2O}$ 256 mμ; m.p. and mixture m.p. with an authentic sample of IIb·HCl, 132–140° (uncorr.). The infrared spectrum was identical with that of IIb·HCl.

Anal. Calc'd for $C_{11}H_{14}ClN_5 \cdot HCl$: C, 45.84; H, 5.25. Found: C, 45.54; H, 5.30.

A similar experiment was conducted in which I-3 was isomerized immediately at the melting point to IIb, at a bath temperature of 155°.

(*D*). *From the arylbiguanides*, III. Many of the compounds of structure II were prepared from the appropriate arylbiguanides by modification of the procedure used by Birtwell, *et al.*, for the synthesis of 4-amino-6-(*p*-chloroanilino)-1,2-dihydro-2,2-dimethyl-*s*-triazine (IIb).[24] In general a longer period of reflux was used, and the course of the condensation was followed either by the disappearance of the biguanide test with cuprammonium sulfate or by the appearance of the characteristic ultraviolet absorption spectrum of II as measured in a sample of the reaction mixture.

Preparation of arylbiguanides (Table III). With the exception of N^1-phenyl-N^2-methylbiguanide, the necessary arylbiguanides (IIIa, IIIb, IIId) were synthesized in 34–85% yields as the hydrochlorides by reaction of the appropriate dicyandiamide with an arylamine hydrochloride (or arylamine and concentrated hydrochloric acid) in aqueous solution.[22,37] The free bases, including *p*-chlorophenylbiguanide hydrate,[22] were obtained in 65–80% yields by treatment of the hydrochlorides with alkali. The syntheses of IIIc·HCl, IIId·HCl, and IIIe·HCl in acetone have been discussed already. A generous amount of phenylbiguanide was supplied through the courtesy of the American Cyanamid Company.

4-Amino-6-anilino-1,2-dihydro-2,2-dimethyl-s-triazine (IIa). A mixture of 50.26 g. (0.284 mole) of phenylbiguanide, 260 cc. of acetone, and 4 cc. of piperidine was refluxed for 17 hours. The clear, pinkish solution was refluxed an additional 30 minutes with 5 g. of charcoal, filtered, and evaporated to dryness *in vacuo*. The viscous oil obtained was dissolved in 45 cc. of hot water and allowed to stand for several days without filtration. A crop of colorless prisms (IIa) crystallized and was collected and washed with water; yield, 39.52 g. (64%); m.p. 175–185° (uncorr.). Recrystallization from water afforded analytically pure material (Table II).

4-Amino-1,2-dihydro-2,2-dimethyl-6-(N-methylanilino)-s-triazine hydrochloride (IIe·HCl). A mixture of 3.05 g. (0.0146 mole) of N^1-phenyl-N^1-methylbiguanide (IIIb·H_2O), 14 cc. of acetone, and 0.27 cc. of piperidine was refluxed for three days. The reaction mixture was filtered free of a small amount of high-melting solid and after the solution had been adjusted to *p*H 4.5 with 1 *N* hydrochloric acid, the filtrate was taken to dryness *in vacuo* to a glassy material. Trituration with a small amount of acetone afforded 2.11 g. (54%) of a white, granular solid (IIe·HCl), m.p. 213–235° (uncorr.). Two crystallizations from *n*-butanol gave an analytical sample (Table II).

6-(p-Chloroanilino)-1,2-dihydro-2,2-dimethyl-4-methylamino-s-triazine hydrochloride (IIf·HCl). A clear, pale yellow solution resulted when 5 g. (0.0206 mole) of N^1-(*p*-chlorophenyl)-N^5-methylbiguanide (IIIa·H_2O), 30 cc. of acetone, and 0.3 cc. of piperidine was brought to reflux. After seven days of reflux, the solution was neutralized with concentrated hydrochloric acid and then was taken to dryness *in vacuo*. The sticky solid obtained crystallized from the minimum of water in the form of colorless prisms (IIf·HCl·H_2O); yield, 3.09 g. (47%); m.p. 120–123° (uncorr.) with prior shrinking. Analytically pure material was obtained by another crystallization from water (Table II).

6-Anilino-1,2-dihydro-2,2-dimethyl-4-dimethylamino-s-triazine (IIg). N^1-Phenyl-N^5,N^5-dimethylbiguanide (IIId)

(37) (a) A. Smolka and A. Friedreich, *Monatsh.*, **9**, 227 (1888); (b) G. Cohn, *J. prakt. Chem.*, **84**, 394 (1911).

(5 g., 0.0204 mole), 28 cc. of acetone, and 0.28 cc. of piperidine were refluxed for seven days. The clear, yellowish solution was distilled *in vacuo* to a viscous oil, which was crystallized without filtration from the minimum amount of hot water. The crop of colorless prisms that formed (IIg) was collected and washed with water; yield, 2.07 g. (35%); m.p. 155–160° (uncorr.). A small amount was crystallized further for analysis (Table II).

4-Amino-6-anilino-1,2-dihydro-1,2,2-trimethyl-s-triazine (IIh). N^1-Phenyl-N^2-methylbiguanide was prepared from phenylguanylthiourea[38] by the procedure used by Crowther, *et al.*,[39] for the synthesis of N^1-(*p*-chlorophenyl)-N^2-methyl-N^5-isopropylbiguanide. This biguanide was not isolated in pure form but was used as the glassy residue obtained on vacuum evaporation of the clarified filtrate of the reaction mixture. A mixture of 0.39 g. (0.002 mole) of the crude biguanide, 0.03 cc. of piperidine, and 10 cc. of acetone was heated at reflux for five days, during which time a nearly clear solution resulted. The hot reaction mixture was filtered and the filtrate was refrigerated for three days. The crop of small, well-formed prisms, which had been deposited, was collected and washed with acetone; 0.09 g. (19%); m.p. 210–215° (uncorr.). This material (IIh) was submitted directly for analysis after being dried (Table II).

Condensation of phenylbiguanide and acetone without catalyst. A solution of 8.86 g. (0.05 mole) of phenylbiguanide free base in 80 cc. of acetone and 40 cc. of methanol was refluxed for ten days, during which time the solution became orange in color. After prolonged standing at room temperature, there accumulated 70 mg. of colorless prismatic crystals, melting at 190–193° (uncorr.); negative biguanide test with cuprammonium sulfate. Crystallization from water afforded a pure sample of 4-amino-6-anilino-1,2-dihydro-2,2-dimethyl-*s*-triazine (IIa), m.p. 187–192° (uncorr.). This product did not depress the melting point of an authentic specimen of IIa and had the same ultraviolet absorption spectrum ($\lambda_{max.}^{H_2O}$ 251 mμ).

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(38) W. Cramer, *Ber.*, **34**, 2602 (1901).

(39) A. F. Crowther, F. H. S. Curd, D. N. Richardson, and F. L. Rose, *J. Chem. Soc.*, 1636 (1948).