tions, esterifying with methanol–hydrochloric acid, and chromatographing on silicic acid. In each case a band corresponding to the methyl ester was obtained.

ALBANY 6, CALIFORNIA RECEIVED SEPTEMBER 7, 1951

[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

Some Substituted Biguanides and s-Triazines[1]

BY W. K. DETWEILER AND E. D. AMSTUTZ

This paper discusses the products arising from the fusion of dicyandiamide with pyrrolidine hydrochloride. The reactions of cycloaliphatic amines and primary heterocyclic amines of the amidine or guanidine type with 2-chloro-4,6-diamino-s-triazine are presented. The preparation of several 2,4,6-trisubstituted-amino-s-triazines by the use of cyanuric chloride are also given.

The purpose of this work was to synthesize a few selected compounds containing the amidine or guanidine structure for pharmacological testing.

The standard method of fusing an amine hydrochloride with dicyandiamide appeared to offer an attractive method for the preparation of a variety of substituted biguanide hydrochlorides. Thus, the fusion of pyrrolidine hydrochloride with dicyandiamide at approximately 130° for 24 hours permitted the isolation of 1,1-tetramethylenebiguanide hydrochloride in acceptable (44%) yield. Occasionally however, and under apparently the identical conditions, the same reactants have been found to evolve ammonia rapidly (6.5 hr.) and produce 1,1-tetramethyleneguanidine hydrochloride and 2-(1-pyrrolidyl)-4,6-diamino-s-triazine in addition to a very poor yield of 1,1-tetramethylenebiguanide hydrochloride.

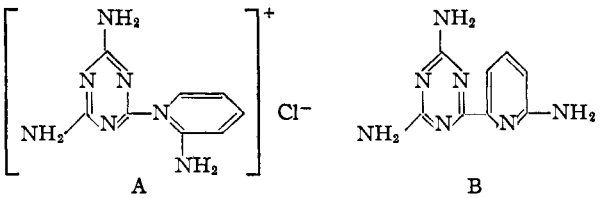
Although this method of preparation of substituted biguanides appears to be general and suitable for aliphatic, cycloaliphatic and aromatic amine hydrochlorides, it does not appear to be satisfactory for heterocyclic primary amine salts which contain a guanidine or amidine structure.[2]

Potassium dicyanoguanidine has been reported[3] to react with aliphatic, cycloaliphatic and aromatic secondary amine salts in aqueous solution to form N,N-disubstituted melamines. We have successfully treated pyrrolidine with potassium dicyanoguanidine in an acidic solution to produce a 14% yield of 2-(1-pyrrolidyl)-4,6-diamino-s-triazine. In contrast, the reaction of several heterocyclic primary amines such as 2-aminopyridine, 2-aminopyrimidine and 2-aminothiazole produced products which were infusible and insoluble in the common organic reagents and water. After considering the physical properties and the data obtained from complete analyses of the products obtained from this reaction, we have reached the conclusion that if the desired products were initially formed (which is doubtful) they hydrolyzed to produce a mixture of what may possibly be ammeline and ammelide.

The most satisfactory method of producing N,N-disubstituted melamines was found to be through the interaction of 2-chloro-4,6-diamino-s-triazine with an excess of the appropriate cycloaliphatic amine; 2-(1-pyrrolidyl)-, 2-(1-piperidyl)- and 2-(4-morpholinyl)-4,6-diamino-s-triazine were produced in yields ranging between 75 and 79%. After our work had been completed, the latter two s-triazines were reported[4] to have been prepared in yields of 22 and 48%, respectively. The present superior yields and the vigor with which our reactions took place seem to indicate that this type of reaction might best be run in such an excess of the amine that it can act as its own solvent.

An excess of piperazine reacted vigorously with 2-chloro-4,6-diamino-s-triazine to give a mixture of products from which 2-(1,4-piperazinyl)-bis-(4,6-diamino-s-triazine) was isolated in 48% yield.

The fusion of a large excess of 2-aminopyridine with 2-chloro-4,6-diamino-s-triazine produced what appeared to be a quantitative yield of 2-(2-pyridylamino)-4,6-diamino-s-triazine hydrochloride. It seemed to us unlikely that this apparent hydrochloride would be capable of isolation from the reaction mixture which contained a large excess of 2-aminopyridine.[5] A dry pyridine extraction of this substance removed 11% of the total weight; from this pyridine extract a water-insoluble free base was isolated. This substance upon analysis compared rather closely to 2-(2-pyridylamino)-4,6-diamino-s-triazine or an isomer of it. The pyridine-insoluble portion of the reaction product gave, after further purification, a precipitate with acidified silver nitrate solution. This water-soluble halogen containing compound upon analysis yielded results rather close to the theoretical values required for 2-(2-pyridylamino)-4,6-diamino-s-triazine hydrochloride or an isomer of it. These data make it appear as though the initial product of this reaction was possibly the pyridinium salt (A) which partially rearranged under the influence of heat to produce 2-



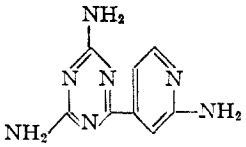
(1) Taken from a thesis presented by W. K. Detweiler to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the Ph.D. degree, June, 1951.

(2) The fusion of 2-aminopyrimidine hydrochloride with dicyandiamide at 178° produced a pitch which could not be purified; the same reaction in refluxing butanol did not yield any product which could be identified. The fusion of 2-aminothiazole hydrochloride with dicyandiamide resulted in the evolution of ammonia and hydrogen sulfide.

(3) D. E. Nagy, U. S. Patent 2,392,608 (1946); *C. A.*, **40**, 3480 (1946).

(4) D. F. Walker, Y. J. L'Italien, W. M. Pearlman and C. K. Banks, *J. Am. Pharm. Assoc.*, **39**, 393 (1950).

(5) It was suggested by the referee that the pyridylmelamine may actually be a stronger base than melamine. While this is true it would not explain the difficulty experience in removing the hydrochloric acid from the salt.



C

(2-pyridylamino)-4,6-diamino-*s*-triazine or one of its ring substituted isomers (B) and (C). The structures (B) and (C) appear to be consistent with the experimental findings of Saure[6] who has investigated the reactions of cyanuric chloride with pyridine in aqueous solution.

Cyanuric chloride reacted with an excess of pyrrolidine, piperidine and morpholine to produce the respective 2,4,6-trisubstituted-amino-*s*-triazines in yields which varied between 93 and 97%.

Experimental[7]

1,1-Tetramethylenebiguanide Hydrochloride.—Dicyandiamide (I) (51.4 g., 0.61 mole) and dry pyrrolidine hydrochloride (II) (65.6 g., 0.61 mole) were intimately mixed and fused in an oil-bath at 125–135° for 24 hours. The product of the fusion was treated with 325 ml. of boiling absolute ethanol, filtered from a trace of insoluble material, concentrated to approximately 250 ml. and allowed to crystallize. The colorless granular crystals obtained were filtered, washed with a 1:1 mixture of absolute ethanol and dry ether followed by several portions of dry ether. After drying under vacuum over phosphorus pentoxide, the yield was 42.5 g. (36.3%). m.p. 220.2–224.2°. Concentration of the ethanolic mother liquor yielded an additional 9 g. (7.7%) which had a slightly lower melting point. The melting point of these crystals can be raised to 225.9–226.6° by recrystallization from absolute ethanol. *Anal.* Calcd. for $C_6H_{14}N_5Cl$: C, 37.60; H, 7.36; N, 36.54; Cl, 18.50. Found: C, 37.44; H, 7.34; N, 36.58; Cl, 18.34. Trituration of this hydrochloride with 48% sodium hydroxide followed by filtration, drying and a dry ether extraction in a Soxhlet extractor yielded the free base, m.p. 153.5–154.4°. *Anal.* Calcd. for $C_6H_{13}N_5$: C, 46.43; H, 8.44; N, 45.13. Found: C, 46.21; H, 8.23; N, 45.12.

On several occasions, the fusion of I and II under conditions apparently identical with those already described led to the evolution of ammonia after only 6.5 hours to produce 2-(1-pyrrolidyl)-4,6-diamino-*s*-triazine (III) and 1,1-tetramethyleneguanidine hydrochloride (IV) in addition to 1,1-tetramethylenebiguanide hydrochloride (V). The products III, IV and V were separated by fractional crystallization. The major portion of III was separated from the remainder of the reaction mixture by its insolubility in boiling absolute ethanol. The colorless plates, III, melted 294.9–296.5° (from water). *Anal.* Calcd. for $C_7H_{12}N_6$: C, 46.65; H, 6.71; N, 46.64. Found: C, 46.49; H, 6.77; N, 46.77.

Fractional concentration of the alcoholic solution from which III had been separated ultimately yielded colorless crystals of V. Additional concentration yielded a viscous mass of crystals which were extracted with boiling acetone. Concentration of this acetone extract yielded colorless square platelets IV which melted at 88.8–89.8°. *Anal.* Calcd. for $C_5H_{12}N_3Cl$: C, 40.13; H, 8.09; N, 28.08; Cl, 23.70. Found: C, 40.25; H, 8.00; N, 27.98; Cl, 24.04.

2-Substituted-amino-4,6-diamino-*s*-triazines were prepared by methods (A) and (B). **2-(1-Pyrrolidyl)-4,6-diamino-*s*-triazine (Method A).**—Concentrated hydrochloric acid was added to a mixture of pyrrolidine (10 g., 0.141 mole), potassium dicyanoguanidine (VI) (20.8 g., 0.141 mole), and 100 ml. of water to produce a solution having a *p*H of 7.5. This aqueous solution was heated at just below reflux for 20 hours. The light tan colored reaction product was filtered from the chilled solution, washed with water, and dried at 100°; yield 3.42 g. (13.5%), m.p. 295.8–297.5°. A mixed melting point of this sample with the sample obtained from the dicyandiamide reaction showed no depression. This method yielded mixtures of infusible and insoluble substances when 2-aminopyridine, 2-aminopyrimidine and 2-aminothiazole were treated with (VI).

2-(1-Piperidyl)-4,6-diamino-*s*-triazine (Method B).—Piperidine (66.5 g., 0.78 mole) and 2-chloro-4,6-diamino-*s*-triazine[8] (37.9 g., 0.26 mole) were maintained below 40° during the first half hour by occasionally cooling the stirred mixture in an ice-bath; after this time the temperature rose to 106° over a 5-minute period. The reaction mixture was extracted with 70 ml. of boiling water after standing 3 hours at room temperature. The colorless powder remaining from the extraction was treated with approximately 650 ml. of a 1:1 mixture of ethanol and water, filtered through a heated funnel, and allowed to crystallize. The yield of fine colorless needles was 37.7 g. (74.8%) after drying under vacuum, m.p. 218.7–221.4°. After further recrystallization and vacuum sublimation at 2 mm. the melting point[9] was 222.2–223.6°. *Anal.* Calcd. for $C_8H_{14}N_6$: C, 49.46; H, 7.27; N, 43.27. Found: C, 49.43; H, 7.24; N, 43.28.

The following compounds were also prepared by (Method B):

2-(1-Pyrrolidyl)-4,6-diamino-*s*-triazine, yield approximately 75%, m.p. 295.2–297.2°.

2-(4-Morpholinyl)-4,6-diamino-*s*-triazine, yield 79%, m.p.[10] 250–252.4°. *Anal.* Calcd. for $C_7H_{12}N_6O$: C, 42.85; H, 6.16; N, 42.84. Found: C, 43.08; H, 6.32; N, 42.81.

2-(1-Piperazinyl)-bis-(4,6-diamino-*s*-triazine) (m.p. 398–400° uncor.) and a compound which may be **2-(1-piperazinyl)-4,6-diamino-*s*-triazine** (m.p. 263.4–270.9°) were isolated from the same reaction mixture in yields of 48 and 20%, respectively; the yield of the latter compound is approximate based upon its hydrochloride which was isolated from the reaction mixture: *Anal.* Calcd. for $C_{10}H_{16}N_{12}$: C, 39.46; H, 5.30; N, 55.24. Found: C, 39.61; H, 5.51; N, 55.36. *Anal.* Calcd. for $C_7H_{13}N_7$: N, 50.23. Found: N, 49.50.

The fusion of 2-aminopyridine with 2-chloro-4,6-diamino-*s*-triazine (VII) followed by a pyridine extraction gave two compounds VIII and IX which yielded correct analytical values for the empirical formulas $C_8H_9N_7$ and $C_8H_{10}N_7Cl$, respectively. Since the structure of these compounds is open to doubt, the experimental procedure is given: 2-aminopyridine (4.71 g., 0.05 mole) and VII (2.91 g., 0.02 mole) were fused in an oil-bath at 91° for one hour followed by an additional hour at 140–145°. The yellow paste was suspended in cold absolute ethanol, filtered, washed with cold absolute ethanol and dried at 100°; the yield of fine granular yellow crystals (X) was 4.25 g.; 296–316° (uncor.) with gaseous decomposition. This substance gave a flocculent precipitate with an acidified $AgNO_3$ soln., was soluble in water and practically insoluble in boiling absolute ethanol.

Addition of absolute alcohol to a dry pyridine extract of X yielded 0.35 g. of VIII, m.p. 270.6–279.2°. Solution of VIII in dry pyridine and precipitation with absolute alcohol followed by an alcoholic wash raised the melting point to 277–281.8° (dec.). *Anal.* Calcd. for $C_8H_9N_7$: C, 47.28; H, 4.46; N, 48.26. Found: C, 46.96; H, 5.24; N, 48.35, 48.03.

A 2.76-g. yield of IX remained from the pyridine extraction of X, m.p. 298–301° (dec.). IX was extracted with boiling dry pyridine, filtered, washed with absolute ethanol and dried at 100° over phosphorus pentoxide, m.p. 295.2–301.8°. IX was found to be soluble in water and to give a precipitate with acidified $AgNO_3$ soln.; it could be recovered unchanged upon treatment with 0.05 *N* sodium hydroxide solution; hydrochloric acid could be distilled from a solution of it acidified with H_2SO_4. *Anal.* Calcd. for $C_8H_{10}N_7Cl$: C, 40.09; H, 4.21; N, 40.91; Cl, 14.79. Found: C, 40.56; H, 4.51; N, 40.65, 41.04; Cl, 14.67.

2,4,6-Tri-1-pyrrolidyl-*s*-triazine.—Cyanuric chloride (25.83 g., 0.14 mole) was added over a 25-minute period with stirring to pyrrolidine (99.56 g., 1.4 mole) which had been cooled to 10°; the temperature of the reaction mixture was maintained below 55° during this process. This slurry was stirred an additional half-hour, diluted with 100 ml. of cold water, filtered, washed with cold water and dried under vacuum at 95°, yield 37.91 g. (94.6%), m.p. 185–188°. After several recrystallizations from 95% ethanol the m.p.

(6) S. Saure, *Ber.*, **83**, 225 (1950).

(7) All melting points are corrected for thermometer stem-emergence unless otherwise noted.

(8) C. K. Banks, O. M. Gruhzit, E. W. Tillitson and J. Controulis, THIS JOURNAL, **66**, 1771 (1944).

(9) D. F. Walker, *et al.*,[4] report m.p. 216–217°, yield 22%.

(10) Walker, *et al.*,[4] report m.p. 236–240°, yield 48%.

was 186.6–189.8°. *Anal.* Calcd. for $C_{16}H_{24}N_6$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.71; H, 8.48; N, 29.14.

The following 2,4,6-trisubstituted-amino-*s*-triazines were also prepared by treating an excess of the amine with cyanuric chloride: 2,4,6-tri-1-piperidyl-*s*-triazine[11]—yield 93%, m.p. 219–221.1° (from a toluene–ethanol mixture and then acetone). *Anal.* Calcd. for $C_{18}H_{30}N_6$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.65; H, 9.28; N, 25.41.

2,4,6-Tri-4-morpholinyl-*s*-triazine.—Yield 97%, m.p. 284–289° (dec.) (from ethanol). *Anal.* Calcd. for $C_{15}H_{24}N_6O_3$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.63; H, 7.13; N, 24.96.

(11) A. W. Hofmann, *Ber.*, **18**, 2779 (1885), obtained this compound by the reaction of the trimethyl ester of trithiocyanuric acid with piperidine, m.p. 213°.

Acknowledgments.—We are grateful to The Wm. S. Merrell Company for funds that made it possible for us to carry on this work and for many helpful discussions and suggestions. Our thanks are also due to the American Cyanamid Co. for generous supplies of cyanuric chloride, dicyandiamide and potassium dicyanoguanidine; to the Carbide and Carbon Chemicals Corp. for piperazine; to the Monsanto Chemical Company for piperidine and E. I. du Pont de Nemours and Co. for pyrrolidine.

BETHLEHEM, PENNSYLVANIA RECEIVED JUNE 20, 1951

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF LAKESIDE LABORATORIES, INC.]

Antispasmodics. I. Substituted Acetic Acid Esters of 1-Alkyl-3-hydroxypiperidine[1]

BY JOHN H. BIEL, HARRIS L. FRIEDMAN, HELEN A. LEISER AND EDWIN P. SPRENGELER

The method of Paul and Tchelitcheff for the preparation of 1-alkyl-3-hydroxypiperidines from furfural or tetrahydrofurfuryl chloride has been modified and consistently high yields of the aminoalcohols were obtained. A more rigorous proof of structure of the piperidinol derivatives *via* the catalytic hydrogenation of 3-hydroxypyridine has been accomplished. Partial cleavage was observed during the reduction of 3-hydroxypyridine and some of its esters. The cleavage products were identified. A series of substituted acetic acid esters of N-alkyl-3-piperidinol has been prepared. In the guinea pig ileum test these esters proved to be potent acetylcholine antagonists. The diphenylacetate of 3-hydroxypyridine was devoid of any spasmolytic properties.

In 1945, Paul and Tchelitcheff[2] published a two-step synthesis for the preparation of 1-alkyl-3-piperidinols from either furfural or tetrahydrofurfuryl chloride.

N-Ethyl and N-methyl-3-hydroxypiperidine are closely related in structure to diethylaminoethanol and tropine, respectively, the distance between the amino nitrogen and the alcoholic hydroxyl group being the same or nearly the same in the two pairs of aminoalcohols.[3] From these structural analogies it was tempting, therefore, to speculate on possible similarities in spasmolytic properties of some of the esters of the two aminoalcohols.

With the exception of the benzoate[2] no esters of N-alkyl-3-hydroxypiperidine have as yet been reported. However, esters of N-methyl-4-hydroxypiperidine have been synthesized and notably the diphenylacetate and 9-fluorene carboxylate[4] of this aminoalcohol were shown to possess potent spasmolytic properties.

We felt that a more rigorous proof of structure of the aminoalcohol was desirable than the one offered by the French workers. This was readily accomplished by the catalytic reduction of 3-hydroxypyridine hydrochloride,[5] N-alkylation of 3-hydroxypiperidine and conversion to the corresponding benzoate ester hydrochloride. The respective N-alkyl-3-piperidyl benzoate hydrochlorides were found to be identical with those obtained from the "furan" procedure of Paul and Tchelitcheff.[2]

While this work was in progress, Reitsema[6] published an alternate structure proof which involved the reduction of N-ethyl-3-piperidone to the alcohol and conversion of the latter to its benzoate hydrochloride.

The procedure for the synthesis of N-ethyl-3-piperidinol as described by Paul and Tchelitcheff[2] resulted in low yields when applied in this, as well as in other laboratories.[7] Through modification of their method (see Experimental) we succeeded in nearly doubling the yield of the desired aminoalcohol.

The esters were obtained by the condensation of the aminoalcohols with the appropriate acid chloride (procedure A), the action of the free acid on N-ethyl-3-chloropiperidine in refluxing isopropyl alcohol[8] (procedure B) or by the ester interchange in boiling xylene[9] (procedure C). Inasmuch as Reitsema[6] had reported a "ring contraction" to N-ethyl-2-benzylaminomethylpyrrolidine during the interaction of N-ethyl-3-chloropiperidine with benzylamine, it became necessary to verify the structure of the esters obtained from procedure B. This was accomplished in two ways: (1) The interaction of diphenylacetyl chloride with N-ethyl-3-hydroxypiperidine, as well as the action of diphenylacetic acid on N-ethyl-3-chloropiperidine yielded one product, N-ethyl-3-piperidyl diphenylacetate hydrochloride. (2) Hydrolysis of a product obtained by procedure B, presumably N-ethyl-3-piperidyl benzilate hydrochloride, followed by conversion of the resulting aminoalcohol to its benzoate hydrochloride yielded a compound which was identical with an authentic sample of N-ethyl-3-piperidyl benzoate hydrochloride.

An alternate route of arriving at N-alkyl-3-

(1) Presented in part before the Division of Medicinal Chemistry at the Cleveland Meeting of the American Chemical Society, April, 1951.

(2) R. Paul and S. Tchelitcheff, *Compt. rend.*, **221**, 560 (1945).

(3) C. Pfeiffer, *Science*, **107**, 94 (1948).

(4) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(5) Chen-Heng Kao, *J. Chem. Eng. China*, **15**, 80 (1949); *C.A.*, **44**, 3993e (1950).

(6) R. R. Reitsema, THIS JOURNAL, **71**, 2041 (1949).

(7) R. C. Fuson and C. L. Zirkle, *ibid.*, **70**, 2760 (1948).

(8) H. Horenstein and H. Pählicke, *Ber.*, **71B**, 1644 (1938).

(9) C. H. Tilford, M. G. van Campen and R. S. Shelton, THIS JOURNAL, **69**, 2902 (1947).