[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. II. Aminoalkylamino-*s*-triazines[1]

BY HARRY S. MOSHER AND FRANK C. WHITMORE

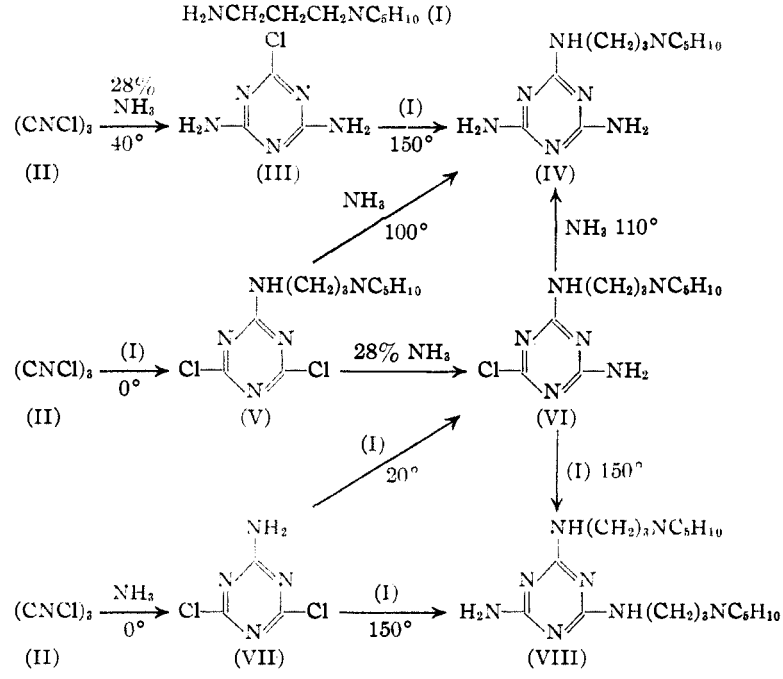
In line with the program in this Laboratory of investigating basically-substituted derivatives of simple ring systems such as pyridine[2] and pyrimidine,[3] we have now prepared the symmetrical triazine derivatives described in the experimental section of this paper. The recent announcement by Freidheim[4] of the therapeutic efficaciousness of certain *s*-triazine derivatives in trypanosomiasis was additional incentive for undertaking a study of the basically-substituted aliphatic amino derivatives of the *s*-triazine system. Other than the substituted anilino derivatives reported by Banks,[5] Freidheim[4] and von Meyer,[6] some heterocyclic quinoline derivatives described in a patent by Jensch,[7] and the original investigations on the simple amino and substituted amino derivatives by Liebig[8] and Diels,[9] there has been very little published work on related compounds of this type. In particular there has been no previous work on the basically-substituted aliphatic derivatives.

Ammonia reacts with cyanuric chloride to replace either one, two or all of the chlorine atoms. As each is replaced, the introduction of the next "amino" group becomes more difficult. Thus, in ether solution at 0° one chlorine atom is replaced, at 30–45° in aqueous ammonia two chlorine atoms are replaced, and with alcoholic ammonia at 110°, melamine is formed. It was found that this same sequence of reactions was possible with a substituted amine such as γ-piperidinopropylamine (I). That the substituted compounds have the structures assigned, is shown by the formation of several of the products by two or more different sequences of reactions. Thus 2,4-dichloro-6-γ-piperidinopropylamino-*s*-triazine (V) will react with alcoholic ammonia at 110° to give the same product IV that is obtained upon heating 2,4-diamino-6-chloro-*s*-triazine (III) with γ-piperidinopropylamine at 150°, or is obtained by heating 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI) with alcoholic ammonia at 110°. Likewise, 2-amino-4,6-dichloro-*s*-triazine (VII), upon reaction with γ-piperidinopropylamine at 120° produces the same compound as obtained by the reaction of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI) with γ-piperidinopropylamine (I).

The 2-amino-4,6-dichloro-*s*-triazine (VII) was made according to the method of Otto Diels[9] and was found to melt sharply at 237° when pure. This is in contrast to the statement in the original work that it does not melt.

In general it proved very difficult to obtain all of the nitrogen from the burned sample in the routine Dumas analysis of the compounds described here.

The compounds reported in the experimental section were made according to the following scheme and the products with properties and analyses are reported in Table I.



All of the products are non-hygroscopic, white, well-defined crystalline solids. With the exception of (III), (VI) and (VII) all dissolved in water readily to give basic solutions.

We are greatly indebted to Parke, Davis and Company for their help.

(1) Presented before the Organic Division of the American Chemical Society at the Pittsburgh Meeting, September 6, 1943.

(2) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(3) Whitmore and Adams, presented before the Organic Division of the American Chemical Society in Pittsburgh, September 6, 1943.

(4) (a) Freidheim, U. S. Patent 2,295,574 (1942); (b) Freidheim, THIS JOURNAL, **66**, 1775 (1944).

(5) Banks, Gruhzit, Tillitson and Controulis, *ibid.*, **66**, 1771 (1944).

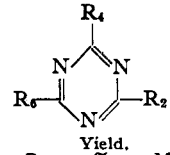
(6) von Meyer, *J. prakt. Chem.*, **82**, 521 (1910).

(7) Jensch, U. S. Patent 2,092,352 (1937).

(8) Liebig, *Ann.*, **10**, 43 (1834).

(9) Diels, *Ber.*, **32**, 695 (1899).

TABLE I



	R_2	R_4	R_6	Yield, %	M. p., °C.	Picrate M. p., °C.	Formula	N Analyses, % Calcd.	Found
1	—Cl[7]	—NH_2	—NH_2	90	370	210[a] dec.		...	...
2	—NH_2	—NH_2	—NH_2	..		318		...	...
3	—$NH(CH_2)_3NC_5H_{10}$	—Cl	—Cl	90	90[b] dec.	...	$C_{11}H_{18}N_5Cl_3$	21.12	20.95
4	—$NH(CH_2)_3NC_5H_{10}$	—NH_2	—Cl	75	178–179	165.5–166	$C_{11}H_{19}N_6Cl$	31.02	30.89
5	—$NH(CH_2)_3NC_5H_{10}$	—OC_2H_5	—NH_2	86	130.0–130.5	...	$C_{13}H_{24}N_6O$	29.95	29.81
6	—$NH(CH_2)_3NC_5H_{10}$	—NH_2	—NH_2	83	152.5–153.5	226–227	$C_{11}H_{21}N_7$	39.00	38.88
7	—$NH(CH_2)_3NC_4H_8O$	—NH_2	NH_2	65	163–164	140	$C_{10}H_{19}N_7O$	38.71	38.60
8	—$NH(CH_2)_3N(C_2H_5)_2$	—NH_2	—NH_2	71	132.8	197–199	$C_{10}H_{21}N_7$	40.95	40.12
9	—$NH(CH_2)_4N(C_2H_5)_2$	—NH_2	—NH_2	74	241	158–159	$C_{11}H_{23}N_7$	33.90	34.51
10	—$NH(CH_2)_6NH_2$	—NH_2	—NH_2	78	154	204 dec.	$C_9H_{19}N_7$	43.50	42.57
11	—$NH(CH_2)_3NC_5H_{10}$	—$NH(CH_2)_3NC_5H_{10}$	—NH_2	43	78–80	182–183	$C_{19}H_{36}N_8$	29.75	29.50

[a] Does not melt below 300° when heated slowly but when immersed in a bath at 210° it melts with bubbling. [b] This material liquefied with bubbling at about 90°, depending upon the rate of heating.

Experimental

2-Amino-4,6-dichloro-*s*-triazine (VII).—The monoaminodichlorotriazine (VII) was prepared according to the method of Diels[9] and the crude yield of 90% was confirmed. The product, after two crystallizations from ether and one from benzene, melted sharply at 237° without bubbling. *Anal.* Calcd. for $C_3H_4N_4Cl_2$: N, 33.94. Found: N, 33.70. Samples which were crystallized only once from ether melted at approximately 235–237° with the evolution of hydrogen chloride gas and then resolidified. Typical nitrogen analyses of such samples were low. Found: N, 31.82, 31.74, 32.18. The product does not form a picrate.

2-Amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI).—A cold (−5°) solution, prepared from 7.1 g. of γ-piperidinopropylamine (I)[10] and 5 ml. of water, was added to a suspension of 5.3 g. of purified 2-amino-4,6-dichloro-*s*-triazine (VII) in 15 ml. of water. The reaction mixture was shaken and allowed to slowly reach room temperature. The white precipitate was filtered, washed with two 5-ml. portions of water, warmed with 20 ml. of water, filtered and dried; yield 7.5 g., m. p. 178–179°. *Anal.* Calcd. for $C_{11}H_{19}N_6Cl$: N, 31.02. Found: N, 30.85, 30.89. A picrate, after successive crystallizations from ethanol and methanol, melted at 165.5–166.0°. *Anal.* Calcd. for $C_{11}H_{19}N_6Cl \cdot 2C_6H_3O_7N_3$: N, 23.12. Found: N, 22.97.

If the reaction is carried out in anhydrous ether at 0°, a fine white precipitate of a mixture of VI and the hydrochloride of I is obtained. By washing this mixture with water and crystallizing the residue from ethanol, VI can be obtained pure. It is interesting to note that it is safe to crystallize VI from ethanol but V or VII reacts with ethanol to give ethyl chloride, an ammelide, or the substituted ammelide, respectively, while II gives cyanuric acid.

2,4-Diamino-6-γ-piperidinopropylamino-*s*-triazine (IV)

Method A.—A mixture of 440 mg. of dry 2,4-diamino-6-chloro-*s*-triazine (III)[5] and 5 ml. of γ-piperidinopropylamine was heated on the steam-bath for two hours. The excess γ-piperidinopropylamine was removed at 100° under 1 mm. pressure until only a sirup remained. This was dissolved in water and decolorized with Norit. The solution was made basic with a 10% solution of potassium hydroxide and extracted with chloroform. The chloroform extracts were dried over potassium carbonate and the solvent removed by distillation. On triturating the residue with ether, a white precipitate formed which was recrystallized from acetone to give 453 mg. of product melting at 152.5–153.5°; yield 83%. *Anal.* Calcd. for $C_{11}H_{21}N_7$: N, 39.00. Found: N, 38.88. A picrate derivative, after recrystallization from ethanol, melted at 226–227°.

Method B.—A mixture of 200 ml. of saturated alcoholic ammonia and 800 mg. of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI) was heated in a sealed tube at 120° for eight hours and the reaction mixture evaporated on a steam-bath to a volume of 10 ml. The crystals that separated on cooling were filtered; 660 mg., m. p. 267.5–8°, yield 89%. Recrystallization from methanol did not change the melting point. This compound gives an excellent ionic halogen test and apparently is the monohydrochloride of the desired 2,4-diamino-6-γ-piperidinopropylamino-*s*-triazine. A picrate was prepared from this which melted at 225.5–226.0°, and gave a mixed melting point with the picrate from Method A of 226–227°. A sample of the hydrochloride was converted to the base with potassium hydroxide solution and purified by extraction with chloroform and working up as in Method A. The white crystals of the base from acetone melted at 153–153.5° and gave no lowering of the melting point when mixed with the crystals obtained in Method A.

Method C.—By treating the crude 2,4-dichloro-6-γ-piperidinopropylamino-*s*-triazine (V) (obtained as indicated later) with an excess of alcoholic ammonia as in Method B above and working up the reaction by concentrating to a sirup, dissolving this in water, and purifying as indicated in Method A above, a product was obtained which was identical in melting point to that found in Methods A and B. A mixed melting point of the three samples from Methods A, B and C was 151–153°.

2-Amino-4,6-di-(γ-piperidinopropyl)-amino-*s*-triazine (VIII)

Method A.—To 15 g. of γ-piperidinopropylamine was added 4 g. of powdered 2-amino-4,6-dichloro-*s*-triazine (VII) over a twenty-minute period. Reaction took place immediately and was completed by heating on the steam-bath for one and one-half hours. The solution was diluted with 50 ml. of water, decolorized with Norit, filtered, diluted further with water and extracted with chloroform three times. The chloroform extracts were washed once with water, dried, concentrated to 10 ml., and the residue taken up in acetone and precipitated as the hydrochloride by bubbling dry hydrogen chloride into the solution. The hydrochloride was crystallized from absolute alcohol–ether mixture to give 4.7 g. (43%), m. p. 241–242°. *Anal.* Calcd. for $C_{19}H_{36}N_8 \cdot 3HCl$: N, 23.07. Found: N, 22.92. A sample of the hydrochloride was converted to the free

(10) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

base with aqueous potassium hydroxide. The solution was extracted with chloroform, the chloroform extracts dried with potassium carbonate, filtered and evaporated. The residue was triturated with ether and crystallized twice from an acetone–ether mixture; m. p. 78–80°.

Method B.—A mixture of 5 g. of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI) and 20 g. of γ-piperidinopropylamine was heated at 100° on the steam-bath for two and a half hours and at 135° for five minutes. Solid potassium hydroxide was added and the solution, after warming on the steam-bath for five minutes, was filtered and the filtrate was freed of γ-piperidinopropylamine by heating to 120° at 3 mm. pressure for twenty minutes. The residue was triturated with ether to give 5.7 g. of material melting at 78–82°. Recrystallization from a ligroin–alcohol mixture gave a product melting at 78–80°. A mixed melting point with this and the compound prepared in Method A was 78–80°. This product formed a picrate with melting point of 183–184° which, when mixed with the picrate from the sample in Method A, melted at 182–3°.

2-Amino-4-ethoxy-6-γ-piperidinopropylamino-*s*-triazine.—Into a sodium ethylate solution, obtained from 0.175 g. of sodium and 50 ml. of absolute ethanol, was dropped 1.00 g. of 2-amino-4-chloro-6-γ-piperidinopropylamino-*s*-triazine (VI). This was refluxed for twenty-four hours, cooled and the precipitated sodium chloride filtered. The alcoholic filtrate was concentrated to a sirup which crystallized upon stirring with ether; crude yield, 0.875 g., m. p. 125–128°. This was recrystallized from absolute ethanol and again from methanol to give the pure ethoxy derivative melting at 130.0–130.5°. *Anal.* Calcd. for $C_{13}H_{24}N_6O$: C, 55.70; H, 8.63. Found: C, 55.31, H, 8.68.

2,4-Dichloro-6-γ-piperidinopropylamino-*s*-triazine (V).—Freshly distilled cyanuric chloride, 18.35 g., was dissolved in 500 ml. of anhydrous ether and cooled to 0°. To this solution was added with stirring a solution of 14.2 g. of γ-piperidinopropylamine in 50 ml. of anhydrous ether. After fifteen minutes of stirring, the precipitate was filtered, washed with three 200-ml. portions of ether, stirred with a fourth portion of boiling ether, filtered and dried in a vacuum; weight 30.0 g. This material melted with bubbling at approximately 90°. All attempts to purify this material further led to products with a low nitrogen content. On standing, this material evolves hydrogen chloride and slowly decomposes.

2,4-Diamino-6-γ-morpholinopropylamino-*s*-triazine.—The following description is more or less typical of the method by which the remaining compounds in Table I were prepared. A mixture of 7.3 g. of γ-morpholinopropylamine[10] (0.05 mole), 12 g. of the damp filter cake of 2-chloro-4,6-diamino-*s*-triazine (III)[4] (0.05 mole) and 8 g. of pyridine was heated in a sealed tube at 160° for three hours. After cooling, the contents of the bomb tube were stirred with solid sodium hydroxide and a little pyridine until the mass solidified. About 20 ml. of water was cautiously added to dissolve the excess sodium hydroxide and sodium chloride and the mixture was filtered. The crystalline precipitate was washed with saturated sodium carbonate solution, acetone, and finally four times with ether. On drying at 90° for one hour, the resultant white product weighed 8.3 g. and melted at 160–164°. This was crystallized from acetone–water mixture after treating with Norit to give a total yield of 65% of product melting at 163–164°. Further crystallization did not raise this melting point. *Anal.* Calcd. for $C_{10}H_{19}ON_7$: C, 47.44; H, 7.56. Found: C, 47.14; H, 7.31.

The Reaction of Cyanuric Chloride with Excess γ-piperidinopropylamine.—In an attempt to replace each of the three chlorine atoms in cyanuric chloride with an aliphatic, basically-substituted side chain, several reactions under various conditions were performed. We did not, however, isolate an analytically pure sample from the reactions. The following was a typical experiment.

An ether solution of 28 g. of γ-piperidinopropylamine was added to a solution of 6.2 g. of freshly distilled cyanuric chloride in 200 ml. of anhydrous ether over a fifteen-minute period. The mixture was heated in an open flask on the steam-bath for one hour and finally in an oil-bath at 140° for one hour. The resultant viscous liquid was extracted with ether and the ether discarded. It was then thoroughly washed with three portions of saturated potassium carbonate solution. The chloroform was replaced with acetone and dry hydrogen chloride gas bubbled through the solution, which was cooled by the addition of Dry Ice. The precipitated hydrochloride weighed 17.5 g. This was recrystallized four times from absolute ethanol–ether mixtures and once from *n*-propanol to give a product melting at 177–180°. *Anal.* Calcd. for $C_{27}H_{51}N_9 \cdot 3HCl$: C, 53.1; H, 8.4; N, 20.6. Found: C, 49.8; H, 8.7; N, 19.2. A picrate prepared from this material melted at 148–150°. *Anal.* Calcd. for $C_{27}H_{51}N_9 \cdot 6C_6H_3O_7N_3$: C 40.0; H, 3.7. Found: C, 38.4; H, 3.3.

Summary

The reaction of cyanuric chloride with ammonia and various basically-substituted aliphatic amines, in particular γ-piperidinopropylamine, has been studied and nine new basically-substituted 1,3,5-triazine derivatives have been described.

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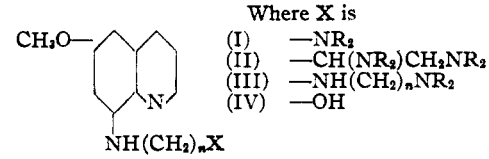
Heterocyclic Basic Compounds. III. Basically-substituted Quinoline Derivatives[1]

BY WILLIAM H. YANKO,[2] HARRY S. MOSHER AND FRANK C. WHITMORE

In extending the research on the type of compound represented by 8-γ-diethylaminopropylamino-6-methoxyquinoline,[3] we have prepared a series of related quinoline compounds represented by the general formulas.



In the above formulas, —NR_2 may represent either a dialkylamino group, such as the diethylamino radical, or a heterocyclic amino group, such as the piperidino or morpholino radicals.

(1) Presented before the Medicinal Section of the American Chemical Society in Cleveland, April 6, 1944.

(2) Parke, Davis Research Fellow, 1942. The following work is taken in part from a thesis submitted by William H. Yanko to The Pennsylvania State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Present address: Central Research, Monsanto Chemical Co., Dayton, Ohio.

(3) (a) Magidson and Strukov, *Arch. Pharm.*, **271**, 359–369 (1933); (b) Kritchevskii and Sternberg, *Z. Immunitäts.*, **80**, 438–459 (1933); (c) Fourneau, Trefouel, Bovet and Benoit, *Ann. inst., Past.*, **46**, 514–541 (1931); **50**, 731–744 (1933).