

course, in that electrophilic displacement occurs at but a single site.

Experiments are underway which definitely indicate a steric factor also operative in the reaction.

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

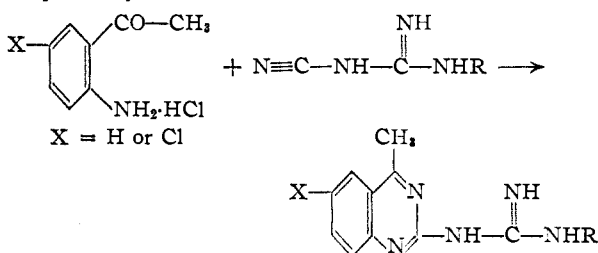
## 2-Guanidinoquinazolines

BY L. F. THEILING AND R. L. MCKEE

A series of 2-guanidinoquinazolines has been prepared for pharmacological evaluation. The compounds were formed by condensation of *o*-aminoacetophenones with appropriate cyanoguanidines.

A study of the preparation of numerous heterocyclic compounds carrying guanidine substituents has been initiated in this Laboratory. The 2-guanidinoquinazolines are felt to be of special interest since, when appropriately substituted, they embody the skeleton present in Paludrine.

Initial attempts at preparation from 2-aminoquinazolines were abandoned when these compounds were found to resist the action of cyanogen bromide, cyanamides, substituted cyanamides and alkyl isothiocyanates. A convenient synthesis was finally developed by interaction of *o*-aminoacetophenone hydrochloride and dicyandiamide or its alkyl or aryl derivatives



The nitration of acetophenone<sup>1</sup> produced about 85% of the theoretical of mixed nitroacetophenones which consisted of approximately 65% of the meta-isomer and 35% of the ortho. After separation, *o*-nitroacetophenone was hydrogenated to form *o*-aminoacetophenone.<sup>1</sup> The *m*-nitroacetophenone was converted in 72% yield by an adaptation of the procedure of reference 2 into *m*-chloroacetophenone which was nitrated<sup>3</sup> in 39% yield to give 2-nitro-5-chloroacetophenone. This was in turn reduced over platinum oxide (96% yield) or with iron and acetic acid (87% yield) to 2-amino-5-chloroacetophenone.<sup>3</sup>

1-Alkyl-3-cyanoguanidines, 1,1-dialkyl-3-cyanoguanidines, and 1-aryl-3-cyanoguanidines were prepared from sodium dicyandiamide and amine hydrochlorides.<sup>4</sup>

Interaction of the aminoacetophenone hydrochlorides with the cyanoguanidines was brought about by refluxing in rather concentrated aqueous

solution or by fusion in the absence of a solvent. Although the products from the former procedure were more easily purified, the yields from the latter procedure occasionally were higher. During the vigorous reaction accompanying the fusion method, hydrogen chloride and the amino ketone were evolved from the reaction mixture. After this was observed, it was found possible to minimize this loss by inclusion of pyridine hydrochloride in the fusion mixture with a significant increase in yield.

The 2-guanidinoquinazolines form monohydrochlorides of varying solubility in cold water, while their nitrates are quite sparingly soluble in cold water, especially in the presence of a slight excess of nitrate ion. They are quite stable to boiling aqueous mineral acids and are only slowly degraded to 2-aminoquinazolines by alkali. In contrast to the behavior of 2-guanidinobenzimidazole<sup>5</sup> the guanidinoquinazolines were found to be inert to nitrous acid both in the cold and at 55°. Finally, an attempt to alkylate 2-guanidino-4-methylquinazoline with butyl iodide in propanol-2 resulted in recovery of starting materials.

### Experimental

**2-Amino-4-methylquinazoline** was prepared by warming a mixture of *o*-aminoacetophenone hydrochloride (5.0 g.) and cyanamide (1.5 g.). At 50°, a vigorous reaction occurred as indicated by evolution of vapor and a rapid rise in temperature. After cooling, the reaction mixture was dissolved in 50 cc. of hot water containing 5 drops of hydrochloric acid, treated with Norite, and made alkaline with ammonia. The resulting oil was separated by decantation and crystallized from hot water. Further recrystallization from water or from benzene-petroleum ether mixtures did not alter the initial melting point, 159–159.8°, of the pale-yellow needles obtained in 65% yield.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>: C, 67.9; H, 5.7; N, 26.4. Found: C, 67.7; H, 5.8; N, 26.3.

The monohydrochloride was prepared in benzene solution with dry hydrogen chloride and, after crystallization from 95% alcohol, appeared as pale yellow needles melting at 239–240° (dec.). Calcd. for monohydrochloride, neut. equiv., 196. Found: neut. equiv. (by titration), 204.

**2-(6-Methoxy-1,2,3,4-tetrahydroquinolyl-1)-4-methylquinazoline** was similarly prepared in 19% yield from 2 g. of 1-cyano-6-methoxy-1,2,3,4-tetrahydroquinoline<sup>6</sup> and 1.8 g. of *o*-aminoacetophenone hydrochloride at 200° in diphenyl ether. The acid-soluble material was recrystallized from benzene-petroleum ether to afford a yellow, crystalline material melting at 86.5–88°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O: N, 13.8; CH<sub>3</sub>O, 10.2. Found: N, 13.8; CH<sub>3</sub>O, 10.4.

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(3) J. C. E. Simpson, C. M. Schofield and O. Stephenson, *J. Chem. Soc.*, 646 (1945).

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**2-Amino-6-chloro-4-methylquinazoline** was prepared by fusing together 1.05 g. of cyanamide and 5.15 g. of 2-amino-5-chloroacetophenone hydrochloride. Final purification was achieved by sublimation *in vacuo*. The product was obtained in 55% yield and melted at 224–224.5°.

*Anal.* Calcd. for  $C_9H_8N_3Cl$ : N, 21.7; Cl, 18.3. Found: N, 21.9; Cl, 18.3.

**Attempted Reactions of 2-Aminoquinazolines.**—From the following reactions using 2-amino-4-methylquinazoline or 2-amino-6-chloro-4-methylquinazoline, the corresponding amines were recovered unchanged. (1) 2-Amino-4-methylquinazoline was treated with one molar proportion of cyanogen bromide in alcohol in the presence of potassium acetate both at room temperature and under reflux. (2) 2-Amino-6-chloro-4-methylquinazoline was refluxed in acetone with one equivalent of ethyl isothiocyanate. (3) Both the free base and the hydrochloride of 2-amino-4-methylquinazoline were fused with cyanamide, diethylcyanamide, and with 1-cyano-6-methoxy-1,2,3,4-tetrahydroquinoline at temperatures varying from 140 to 210°.

**2-Cyanamido-4-methylquinazoline.**—To an aqueous solution of sodium dicyanamide,<sup>7</sup> 4.29 g. of *o*-aminoacetophenone hydrochloride was added slowly with stirring. An oil separated which quickly solidified. The product, which was filtered and washed with dilute hydrochloric acid, weighed 3.8 g. and melted from 200–206° (dec.). Crystallization from aqueous alcohol gave 1.6 g. (35% yield) of pale-yellow needles melting at 237.5–238.5° (dec.). Surprisingly, it was later found that this compound could be sublimed unchanged *in vacuo*.

*Anal.* Calcd. for  $C_{10}H_8N_4$ : C, 65.2; H, 4.4; N, 30.4. Found: C, 64.9; H, 4.2; N, 30.5.

An attempt to convert this cyanamide into a guanidine by fusion with diethylamine hydrochloride at 150–160° and at 190–200° resulted in extensive decomposition.

**2-Guanidino-4-methylquinazoline. (Hydrochloride, Free Base and Nitrate) A.**—Nine grams of *o*-aminoacetophenone hydrochloride and 2 g. of dicyandiamide<sup>8</sup> were intimately mixed and placed in an oil-bath at 130°. The mixture melted immediately. The melt was maintained at 130–140° for four hours, dissolved in a minimum amount of boiling water containing 5 drops of hydrochloric acid, treated with Norite, made strongly acid with hydrochloric acid, and chilled. The tan solid which separated, after filtration and washing with cold 1:1 hydrochloric acid, was found to melt with decomposition over a wide range beginning at 255°; this behavior was not improved after recrystallization from 2:1 aqueous hydrochloric acid. However, on washing the solid with cold water until the washings were colorless<sup>9</sup> and then recrystallizing from 2:1 hydrochloric acid, 3.0 g. (53%) of a white crystalline powder melting at 319–320° (dec.) was obtained.

*Anal.* Calcd. for  $C_{10}H_{11}N_5 \cdot HCl$ : C, 50.5; H, 5.1; N, 29.5; Cl, 14.9. Found: C, 50.8; H, 5.0; N, 29.4; Cl, 14.9.

The free base was liberated from the hydrochloride and found to melt at 242–244°.

*Anal.* Calcd. for  $C_{10}H_{11}N_5$ : C, 59.7; H, 5.5; N, 34.8. Found: C, 59.5; H, 5.3; N, 34.6.

The nitrate was prepared from an aqueous solution of the hydrochloride by addition of nitric acid and, after recrystallization from water, was found to melt at 300–301° (dec.).

*Anal.* Calcd. for  $C_{10}H_{11}N_5 \cdot HNO_3$ : N, 31.8. Found: N, 31.7.

**B.**—Three grams of dicyandiamide, 4.1 g. of *o*-aminoacetophenone hydrochloride and 2.7 g. of pyridine hydrochloride were fused at 130°. After leaching with hot water, 4.0 g. of the hydrochloride melting at 319–320° (dec.) were,

(7) Prepared by adding 0.025 mole of cyanogen bromide to 20 cc. of water containing 0.025 mole of cyanamide and 0.50 mole of sodium hydroxide.

(8) Additional experiments in which the mole ratios of the two reactants were varied from 2:1, 1:1 and 1:2 showed no significant effect on yields.

(9) Acidification of the filtrate (hydrochloric acid) caused separation after thorough chilling of 2.6 g. of yellow crystals melting from 270–275°. Liberation of the free base (sodium hydroxide) produced a yellow compound which melted at 78–79° alone and when mixed with 2-(2-aminophenyl)-4-methylquinoline.<sup>10</sup>

(10) R. Camps, *Ber.*, **32**, 3231 (1899).

obtained. By addition of ammonium nitrate to the filtrates, an additional 0.8 g. of the nitrate melting at 300–301° (dec.) was obtained, corresponding to a total yield of 83%.

**C.**—Dicyandiamide (2.1 g.) and *o*-aminoacetophenone hydrochloride (4.46 g.) were refluxed in 10 cc. of water. The mixture, initially homogeneous, began to deposit crystals after ten minutes. An additional 10 cc. of water was added and refluxing continued for 70 minutes. On chilling, 4.05 g. of the hydrochloride was obtained melting at 319–320° (dec.), and from the initial filtrate and those from recrystallizations, 0.37 g. of the nitrate melting at 300–301° (dec.) was obtained as in B. The total yield amounted to 74%.

**2-Guanidino-6-chloro-4-methylquinazoline (Hydrochloride and Nitrate).**—When prepared from 4.93 g. of 2-amino-5-chloroacetophenone hydrochloride and 3.00 g. of dicyandiamide according to method A above, the hydrochloride was obtained in 65% yield as long silky needles melting at 299–300° (dec.).

*Anal.* Calcd. for  $C_{10}H_{10}N_5Cl \cdot HCl$ : C, 44.1; H, 4.1; N, 25.7. Found: C, 44.2; H, 4.1; N, 25.7.

The nitrate appeared as fine yellow needles (from water) melting at 301–302° (dec.).

*Anal.* Calcd. for  $C_{10}H_{10}N_5Cl \cdot HNO_3$ : N, 28.1. Found: N, 28.1.

When prepared according to method C, a total yield of 42% based on hydrochloride and nitrate was obtained.

A small portion of the hydrochloride was refluxed for 16 hours with 40% sodium hydroxide without effect. On fusion at 200° with moist sodium hydroxide, the compound was degraded, and about 31% of 2-amino-6-chloro-4-methylquinazoline was isolated.

**2-(1-Methyl-3-guanidino)-6-chloro-4-methylquinazoline nitrate** was prepared by method A, using 1-methyl-3-cyanoguanidine.<sup>4</sup> The product was unusually difficult to purify and was obtained in a yield of only 6.7% of purified material melting at 225° (dec.).

*Anal.* Calcd. for  $C_{11}H_{12}N_6Cl \cdot HNO_3$ : C, 42.3; H, 4.2; N, 26.9. Found: C, 42.1; H, 4.1; N, 26.8.

**2-(1-Ethyl-3-guanidino)-6-chloro-4-methylquinazoline hydrochloride hydrate** was obtained in 49% yield according to method A using 1-ethyl-3-cyanoguanidine.<sup>4</sup> In determining the melting point, it was observed that at about 130°, the material softened and appeared wet. On continued heating the semi-solid dried and melted at 258–259° (dec.); when placed in a bath at 200°, the material melted, resolidified, and re-melted at 258–259° (dec.).

*Anal.* Calcd. for  $C_{12}H_{14}N_6Cl \cdot HCl \cdot H_2O$ : N, 22.0; Cl, 22.3. Found: N, 21.9; Cl, 22.2.

That this compound is truly a hydrate rather than an intermediate ketobiguanide is shown by the fact that it can be obtained from fusion reactions carried out well above the temperature at which it was observed to undergo dehydration.

**2-(1-Isopropyl-3-guanidino)-6-chloro-4-methylquinazoline nitrate.**—Method A and method C afforded yields of 45 and 42% of yellow needles melting at 239° with decomposition.

*Anal.* Calcd. for  $C_{13}H_{16}N_6Cl \cdot HNO_3$ : C, 45.8; H, 5.0; N, 24.7; Cl, 10.4. Found: C, 45.7; H, 5.0; N, 24.4; Cl, 10.4.

**2-(1,1-Dimethyl-3-guanidino)-6-chloro-4-methylquinazoline nitrate** (and hydrate) was obtained in yields of 58 and 51% by methods A and C, appearing as long fibrous yellow needles melting at 260.5–261°.

*Anal.* Calcd. for  $C_{12}H_{14}N_6Cl \cdot HNO_3 \cdot H_2O$ : N, 24.4; Cl, 10.3. Found: N, 24.4; Cl, 10.2.

After drying in a pistol, the appearance and melting point were unchanged, but analysis indicated that dehydration had occurred.

*Anal.* Calcd. for  $C_{12}H_{14}N_6Cl \cdot HNO_3$ : N, 25.7; Cl, 10.9. Found: N, 25.6; Cl, 10.7.

**2-(1,1-Diethyl-3-guanidino)-6-chloro-4-methylquinazoline Nitrate.**—Method A gave 81% and method C 39% of pale yellow crystals melting with decomposition at 205°.

*Anal.* Calcd. for  $C_{14}H_{18}N_6Cl \cdot HNO_3$ : N, 23.7; Cl, 10.0. Found: N, 23.8; Cl, 9.8.

**2-(1-Phenyl-3-guanidino)-6-chloro-4-methylquinazoline hydrochloride** was formed in 63% by method A. It was obtained as a light tan micro-crystalline powder (from aqueous alcohol) melting at 288° (dec.).

*Anal.* Calcd. for  $C_{16}H_{14}N_6Cl \cdot HCl$ : C, 55.2; H, 4.3; N, 20.1. Found: C, 55.1; H, 4.5; N, 20.3.

2-(1-*p*-Chlorophenyl-3-guanidino)-6-chloro-4-methylquinazoline hydrochloride was obtained by method A as cream-colored micro-crystalline needles melting at 261–262.5° with decomposition in 40% yield.

*Anal.* Calcd. for  $C_{16}H_{13}N_5Cl_2 \cdot HCl$ : C, 50.2; H, 3.7; N, 18.3. Found: C, 49.9; H, 3.9; N, 18.4.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MIAMI]

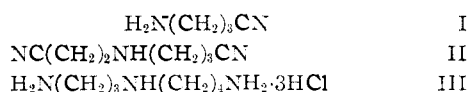
## The Preparation of Spermidine Trihydrochloride (1,8-Diamino-4-azaoctane Trihydrochloride)

BY MORRIS DANZIG<sup>1</sup> AND HARRY P. SCHULTZ

Spermidine trihydrochloride has been prepared in 11% over-all yield through the formation of  $\gamma$ -aminobutyronitrile, N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile and spermidine trihydrochloride.

Recent work<sup>2–6</sup> has redirected attention to spermidine. Although two syntheses<sup>7,8</sup> have already been reported, the processes are long, arduous and give low yields. The purpose of this investigation was to develop a shorter synthesis of spermidine trihydrochloride with a better over-all yield.

This three-step synthesis consists of ammonolysis of  $\gamma$ -bromobutyronitrile to  $\gamma$ -aminobutyronitrile (I), the cyanoethylation of  $\gamma$ -aminobutyronitrile to N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile (II), followed by reduction of N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile hydrochloride to spermidine trihydrochloride (III).



Most of the  $\gamma$ -aminobutyronitrile used was prepared by mixing a 30 to 1 molar ratio of liquid ammonia and  $\gamma$ -bromobutyronitrile in a steel bomb; the reaction was completed in 48 hours at room temperature. Ammonolysis of  $\gamma$ -chlorobutyronitrile gave no  $\gamma$ -aminobutyronitrile. A small amount of  $\gamma$ -aminobutyronitrile was also prepared by the hydrolysis of  $\gamma$ -phthalimidobutyronitrile according to the procedure of Goldberg and Kelly.<sup>9</sup>

The cyanoethylation of  $\gamma$ -aminobutyronitrile proceeded readily in ether solution at room temperature. Since the hydrochloride salt of N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile was to be reduced this salt was prepared by adding alcoholic hydrogen chloride to the ether solution of N-(2-

cyanoethyl)- $\gamma$ -aminobutyronitrile, and was reduced in ethanolic hydrogen chloride over platinum oxide catalyst. Reduction was initiated at room temperature at approximately 4 atmospheres after which it was brought to completion at 70°. Deviations from this procedure yielded no spermidine trihydrochloride, only high melting solids, although in all cases the theoretical amount of hydrogen was always absorbed by the reaction mixture.

### Experimental Procedures

**$\gamma$ -Aminobutyronitrile.**—Into a glass cylinder were placed 26.1 g. (0.18 mole) of  $\gamma$ -bromobutyronitrile<sup>10</sup> and about 90 g. (5.3 moles) of liquid ammonia. The glass container was sealed into a stainless steel bomb<sup>11</sup> and kept at room temperature for 48 hours occasionally rocked by hand. At the end of the reaction time the residue in the bomb was placed in 50% sodium hydroxide solution then extracted with three 75-ml. portions of ether. The ether solution was dried and distilled. The yield of  $\gamma$ -aminobutyronitrile, boiling at 80–82° (10 mm.), was 6.3 g. (42%). The hydrochloride of a small sample of  $\gamma$ -aminobutyronitrile was made and was found to melt at 143–145°. Goldberg and Kelly<sup>9</sup> reported a boiling point of 95–97° (20 mm.) for  $\gamma$ -aminobutyronitrile and a melting point of 138–140° for  $\gamma$ -aminobutyronitrile hydrochloride.

**N-(2-Cyanoethyl)- $\gamma$ -aminobutyronitrile.**—A 200-ml. flask was fitted with stirrer, condenser and addition funnel, and 6.3 g. (0.075 mole) of  $\gamma$ -aminobutyronitrile and 10 ml. of ether were placed in it. Acrylonitrile (4.0 g., 0.075 mole) was added dropwise for two hours to the stirred solution, temperature being maintained at 30°. After all acrylonitrile had been added, the solution was stirred at room temperature for 14 hours and for 1 hour on a steam-bath. Ethanolic hydrogen chloride was then added to the cooled ether solution until precipitation was complete. The precipitate was filtered and recrystallized from 90 ml. of absolute ethanol, giving 11.5 g. (88.5% of theory) of N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile hydrochloride melting at 133–134°.

*Anal.* Calcd. for  $C_7H_{12}N_3Cl$ : N, 24.2. Found: N, 24.3, 24.2.

**Spermidine Trihydrochloride.**—A 500-ml. glass Parr pressure flask was charged with 5.0 g. (0.029 mole) of N-(2-cyanoethyl)- $\gamma$ -aminobutyronitrile hydrochloride, 0.2 g. of platinum oxide catalyst,<sup>12</sup> 20 ml. of ethanolic hydrogen

(1) Abstracted in part from a thesis by Morris Danzig, presented to the Graduate Faculty of the University of Miami in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, June, 1951.

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