[Contribution from the Research Division, Stamford Research Laboratories, American Cyanamid Company]

CHEMISTRY OF DICYANDIAMIDE. V. STRUCTURES OF GUANAZO- AND PYRO-GUANAZOLES, AND REACTION OF DICYANDIAMIDE WITH 3-AMINO-5-SUBSTITUTED-1,2,4,4*H*-TRIAZOLES

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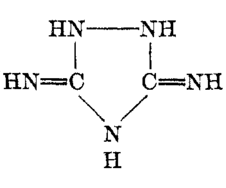
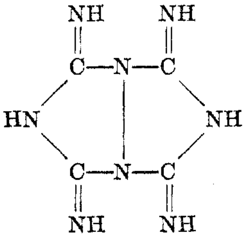
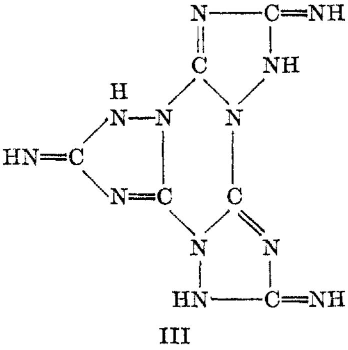
In 1894 Pellizzari (1) found that hydrazine hydrochloride and dicyandiamide reacted to yield a product which he called guanazole and which he represented as 3,5-diimino-1,2,4-tetrahydrotriazole (I). Later, in 1901, Pellizzari and Roncagliolo (2) found that either guanazole hydrochloride and dicyandiamide, or hydrazine hydrochloride and two equivalents of dicyandiamide yielded an infusible, relatively insoluble compound which they named guanazoguanazole and to which they assigned structure II.

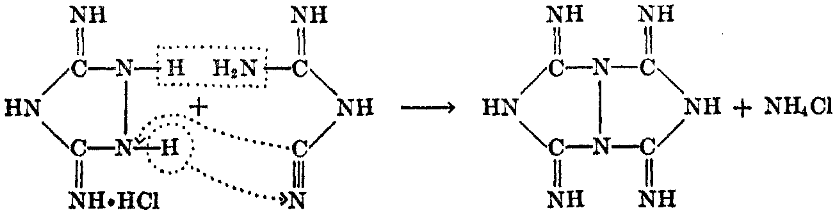

I


II

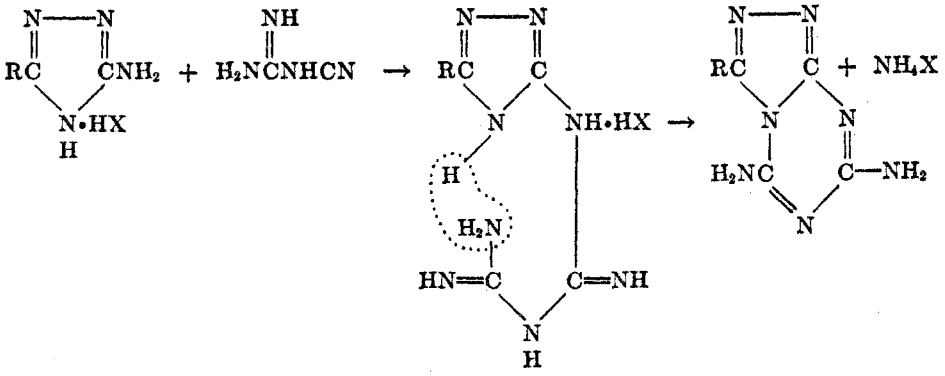
At a still later date Hofmann and Ehrhart found that when dicyandiamide and hydrazine hydrochloride (3) or hydrate (4) were heated to high temperatures or that when the isolated guanazole (4) was heated to a high temperature a product which these authors first called melamazine (3) and later pyroguanazole (4) was formed. This compound was assigned structure III (4) and the presence of an *s*-triazine ring was demonstrated by isolation of cyanuric acid through oxidation with alkaline permanganate (4).


III

Since guanazole hydrochloride reacted with dicyandiamide to yield guanazoguanazole (2), the authors wondered whether the closely related 3-amino-5-substituted-1,2,4,4*H*-triazole salts (5) would also react with dicyandiamide. Reaction did occur giving high-melting and relatively insoluble products similar to guanazoguanazole. When it was found that reaction was successful the structure of the products became of interest. The structure of guanazoguanazole as assigned by Pellizzari and Roncagliolo (2) necessitated reaction as shown.



However, both guanazole (6) and 3-amino-5-alkyl-1,2,4,4*H*-triazoles (7, 8) are aromatic in character since they can be diazotized and coupled to yield azo dyes. These reactions demonstrate the presence of amino groups. Dicyandiamide is also known to react readily with aromatic amine salts to yield aryl biguanide salts (9). In consideration of these facts, the reaction of guanazole and aminotriazole salts with dicyandiamide appeared more logically to occur through an intermediate biguanide stage with formation of compounds structurally related to pyroguanazole.



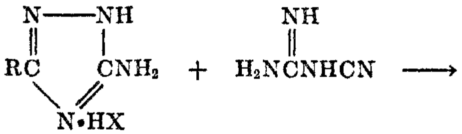
IV; R = NH_2 VI; R = NH_2

V; R = alkyl, aryl VII; R = alkyl, aryl

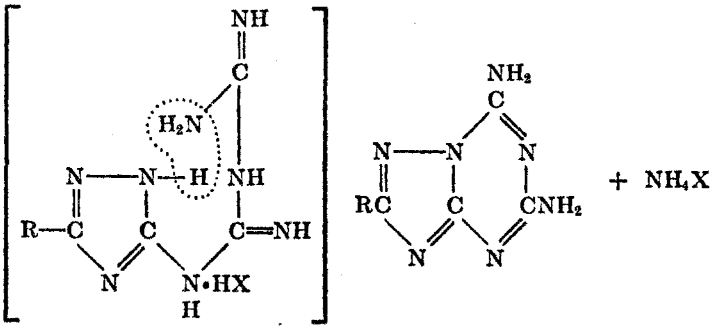
Since one of the hydrogen atoms of guanazole and 3-amino-5-substituted-1,2,4,4*H*-triazoles is not fixed another isomeric possibility (X, XI) must be considered.

In this connection pyroguanazole can also have structure III or XII, depending upon the structure of guanazole.

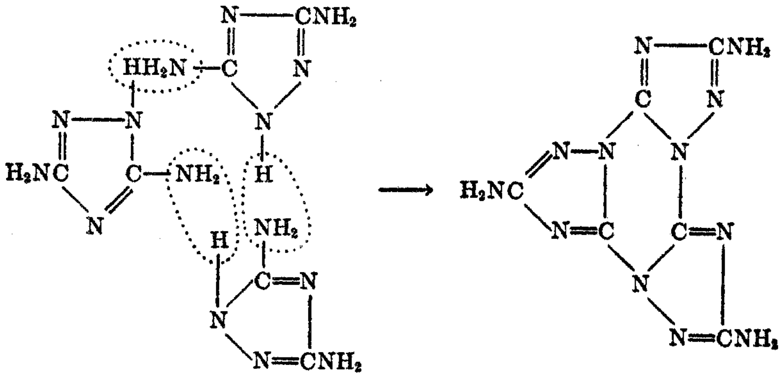
Hofmann and Ehrhart (4) isolated both cyanuric acid and nitrogen from the oxidation of pyroguanazole. The nitrogen could have come only from the hydrazine moiety. Therefore, the Hofmann and Ehrhart structure for pyroguanazole (III) requires modification since nitrogen evolution would have ruptured the triazine ring. Structure XII satisfactorily accounts for both nitrogen and cyanuric



VIII; R = NH_2
IX; R = alkyl, aryl

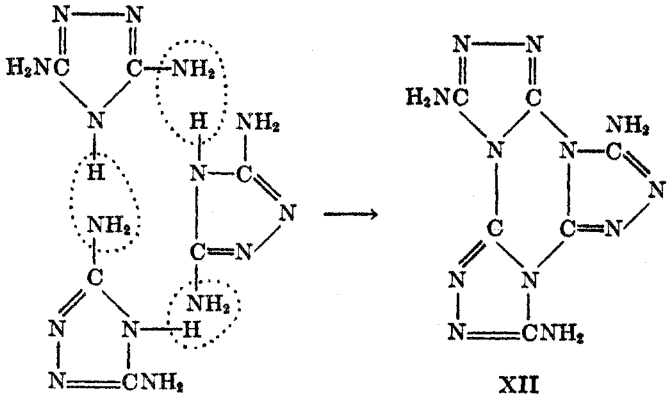


X; R = NH_2
XI; R = alkyl, aryl



III

or



XII

acid. Therefore pyroguanazole should be named 3,7,11-triamino-tris-*s*-triazolo[4,3-*a*, 4,3-*c*, 4,3-*e*]-*s*-triazine.

Pellizzari and Roncagliolo furnished evidence of a negative nature that guanazoguanazole did not possess the symmetrical structure II they assigned. They found that acetylation of guanazoguanazole with excess acetic anhydride gave a mixture of the di- and tri-acetyl derivatives (2). In the present work excess benzoic anhydride gave only a tribenzoyl derivative. On the basis of Pellizari and Roncagliolo's structure the introduction of four acyl groups would have been anticipated but with the newly proposed structures, VI and X, three would be all that should be expected. Information from the acid hydrolysis of guanazoguanazole would not have been helpful regarding its structure since by this procedure Pellizzari and Roncagliolo (2) removed only an amino group. However, by employing the technique of Hofmann and Ehrhart (6), oxidation of guanazoguanazole gave both cyanuric acid and nitrogen. This evidence established the structure of guanazoguanazole as VI and, the compound should be named 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine.

Based on the reassigned structures of pyroguanazole and guanazoguanazole, the structure of guanazole as 3,5-diamino-1,2,4,4*H*-triazole (IV) arbitrarily assigned by Stollé and Dietrich (6), is substantiated.

Evidence for the presence of the triazine ring in the newly described substituted aminotriazole-dicyandiamide condensation products was also obtained. Comparison of the infrared spectra of guanazoguanazole with the new compounds showed that all exhibited a characteristic isotriazine band[1] at about 775 cm.$^{-1}$. Oxidation of the methyl compound gave nitrogen and an intermediate which on further hydrolysis produced cyanuric acid. On this basis the compounds are assigned structure VII and named 3-substituted-5,7-diamino-*s*-triazolo[4,3-*a*]-*s*-triazines.

Acknowledgement. The authors are indebted to Mrs. C. F. Willey and Mrs. M. M. Taylor for the infrared spectra, and to Dr. J. A. Kuck and his staff for microanalyses.

EXPERIMENTAL[2]

3,5,7-Triamino-s-triazolo[4,3-a]-s-triazine (VI). The general procedure of Pellizzari and Roncagliolo (2) was employed. A stirred mixture of 105 g. (1.0 mole) of hydrazine dihydrochloride, 168 g. (2.0 moles) of dicyandiamide, and 160 ml. of water was heated. At 51° the heat source was removed and the temperature continued to rise. By intermittent cooling the temperature was kept below 75°. After the exothermic reaction subsided, the solution was refluxed eight hours, during which time a colorless solid separated. The infusible product was filtered, washed with water, and air-dried; yield, 139 g. (83.4%). The compound showed absorption at 776 cm.$^{-1}$ which was indicative of an isotriazine type structure.

When hydrazine sulfate was substituted for the hydrochloride the yield was only 34%.

3,5,7-Tribenzamido-s-triazolo[4,3-a]-s-triazine. A mixture of 1.5 g. (0.009 mole) of 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine and 20.5 g. (0.09 mole) of benzoic anhydride was heated in a large test tube with an oil-bath for several hours at a temperature of 185–200°. Complete

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[1] Oral communication from N. B. Colthup, Stamford Research Laboratories, American Cyanamid Company.

[2] All melting points are uncorrected.

solution occurred with the formation of a deep orange color. The solid that resulted on cooling was triturated thoroughly with ether to dissolve the benzoic acid and excess anhydride. The tan powder weighed 2.9 g. (67.0%) and melted at 172–175°. The material was insoluble in ethyl acetate and soluble in hot acetic acid and butanol, but was difficult to recrystallize. The crude product was analyzed for nitrogen and gave a value which indicated the presence of three benzoyl groups.

Anal. Calc'd for $C_{25}H_{18}N_8O_3$: N, 23.4. Found: N, 23.1.

Oxidation of 3,5,7-triamino-s-triazolo(4,3-a]-s-triazine. Attempts to oxidize 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine with hot alkaline permanganate (4) were unsuccessful; nitrogen was evolved but cyanuric acid was not formed.

A stirred slurry of 25 g. (0.15 mole) of 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine in 400 ml. of water to which was added 50 ml. (0.90 mole) of 96.5% sulfuric acid was heated to reflux. A solution of 36 g. (0.22 mole) of potassium permanganate in 750 ml. of water was gradually added. The permanganate color was discharged as added and the slurry became yellow. A gas identified as nitrogen (passage through caustic and failure to support combustion) was evolved. After 480 ml. (23 g.) of permanganate was added the color was no longer discharged, and the mixture was refluxed eight hours. An additional 2.0 g. (0.01 mole) of 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine was then added to the purple mixture and refluxing was continued another eight hours. The yellow slurry was filtered hot and the filtrate was concentrated to approximately half its volume. On cooling, 12 g. of nearly colorless crystals separated. Further concentration of the filtrate gave an additional gram of product. The infusible material gave an amethyst-colored precipitate with ammonia and cupric ions, a test for cyanuric acid (10). A portion was recrystallized from hot water and infrared and nitrogen analyses proved the identity as cyanuric acid. The yield was 62%.

Anal. Calc'd for $C_3H_3N_3O_3$: N, 32.5. Found: N, 32.3.

5,7-Diamino-3-methyl-s-triazolo[4,3-a]-s-triazine. A turbid solution resulted when a mixture of 52 g. (0.53 mole) of crude 3-amino-5-methyl-1,2,4,4*H*-triazole (5), 50.4 g. (0.60 mole) of dicyandiamide, 53 g. (0.53 mole) of concentrated hydrochloric acid, and 200 ml. of water was heated to reflux. Decolorizing charcoal was added, the solution was filtered, and refluxing of the clear filtrate was continued. After almost an hour finely divided solid began to separate. Heating was continued a half-hour longer and, although the quantity of material was not large, the mixture bumped badly. The colorless solid was filtered, washed with water, and the filtrate was refluxed an additional four hours but no more product separated. The compound decomposed at 345–346°; yield, 12 g. (14.0%). Recrystallization from two liters of boiling water gave fine, colorless needles with no change in the decomposition point. Although a sample was dried in an Abderhalden pistol with acetone, the product was a monohydrate. Infrared absorption occurred at 770 cm.$^{-1}$, indicative of an isotriazine structure.

Anal. Calc'd for $C_5H_7N_7 \cdot H_2O$: C, 32.78; N, 53.55; H_2O, 9.83.
Found:[3] C, 32.56; N, 53.59; H_2O, 9.74.

Later attempts to repeat the preparation in water were unsuccessful but use of Methyl Cellosolve[4] gave yields as high as 49%.

5,7-Diamino-3-n-amyl-s-triazolo(4,3-a]-s-triazine. After heating to reflux a mixture of 29.0 g. (0.13 mole) of 3-amino-5-*n*-amyl-1,2,4,4*H*-triazole nitrate (5), 16.8 g. (0.20 mole) of dicyandiamide, and 50 ml. of water, a clear solution formed. The mixture was refluxed for four hours, solid having appeared after a half hour. After cooling, filtration gave 10 g. (35%) of colorless plates which decomposed at 315–316°. Recrystallization from 500 ml. of Cellosolve[4] gave fine plates which decomposed as before at 315–316° when immersed in an oil-bath at 300°. On gradual heating decomposition occurred at a lower temperature. The compound gave infrared absorption at 775 cm.$^{-1}$.

Anal. Calc'd for $C_9H_{15}N_7$: C, 48.87; N, 44.34.
Found:[3] C, 48.81; N, 44.62.

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[3] Van Slyke wet combustion method.

[4] Methyl Cellosolve is 2-methoxyethanol; Cellosolve is 2-ethoxyethanol; both are trade marks of Carbide and Carbon Chemicals Co.

5,7-Diamino-3-phenyl-s-triazolo[4,3-a]-s-triazine. A mixture containing 48.0 g. (0.30 mole) of 3-amino-5-phenyl-1,2,4,4*H*-triazole (5), 30.0 g. (0.30 mole) of concentrated hydrochloric acid, 42.0 g. (0.50 mole) of dicyandiamide, and 100 ml. of water was heated to reflux. Within a short time solid began to separate from the hot solution. Refluxing was continued for three hours, the mixture was cooled, and the colorless solid filtered; yield, 31.0 g. (45.5%). Decomposition occurred at 375–376°. Treatment of the filtrate with nitric acid gave a 40% recovery of 3-amino-5-phenyl-1,2,4,4*H*-triazole as the nitrate (5). The product was insoluble in most solvents but recrystallization of a portion from dimethylformamide gave small colorless crystals decomposing as before at 375–376°. Infrared absorption occurred at 771 cm.$^{-1}$.

Anal. Calc'd for $C_{10}H_9N_7$: C, 52.85; H, 3.99; N, 43.15.

Found: C, 53.04; H, 4.11; N, 42.99.

Fusion of 3-amino-5-phenyl-1,2,4,4*H*-triazole with dicyandiamide at 150–160° for 2½ hours gave a 54% yield, and fusion of the hydrochloride (5) at 160–170° for a similar period gave a 77% yield.

Oxidation of 5,7-diamino-3-methyl-s-traizolo[4,3-a]-s-triazine. To a stirred refluxing mixture of 33.0 g. (0.18 mole) of 5,7-diamino-3-methyl-*s*-triazolo[4,3-*a*]-*s*-triazine hydrate in 200 ml. of water containing 25 ml. of 96.5% sulfuric acid was added, in the course of eight hours, a solution containing 11.5 g. of potassium permanganate in 500 ml. of water. The permanganate color was very slowly discharged to a yellow-brown. During oxidation a gas identified as nitrogen (passage through caustic and failure to support combustion) was evolved. After standing overnight the mixture was refluxed an additional hour and was filtered hot to remove some yellow amorphous solid. On cooling, 4.0 g. of orange solid, m.p. 230–235°, deposited. Concentration of the filtrate to about 150 ml. gave an additional 5.5 g. of pink product, m.p. 230–240°. Two recrystallizations from hot water of a previous preparation gave colorless solid which underwent decomposition at 278–280°. Infrared examination showed the presence of a triazine, possibly as an isocyanurate. Without further study the crude intermediate (9.5 g.) was refluxed for five hours with 25 ml. of concentrated sulfuric acid which had been diluted with 50 ml. of water. The resulting yellow solution was cooled and diluted with 50 ml. of water. On standing 0.75 g. of colorless, infusible crystals separated. The compound gave the characteristic amethyst-colored precipitate with cupric ions and ammonia (10) for cyanuric acid. Infrared analysis confirmed the materal as cyanuric acid.

SUMMARY

1. New structures have been proposed for guanazo- and pyro-guanazoles.

2. Dicyandiamide reacts with 3-amino-5-substituted-1,2,4,4*H*-triazoles to yield condensed triazolo-triazines.

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