[CONTRIBUTION FROM THE RESEARCH DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

CHEMISTRY OF DICYANDIAMIDE. III. REACTION OF ACYLDICYANDIAMIDES WITH HYDRAZINE

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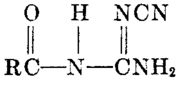
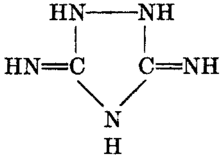
A previous communication discussed the preparation and certain simple reactions of acyldicyandiamides (I) (1). In continuation of this investigation it was of interest to learn whether acyldicyandiamides would undergo reaction with hydrazine.

It was known that dicyandiamide reacted with hydrazine (2) or its salts (3) to yield a product called guanazole which has been represented as 3,5-diimino-1,2,4-tetrahydrotriazole (II). A patent (4) has also described the preparation of acylguanazoles (III) from the reaction of dicyandiamide with hydrazide salts.



I



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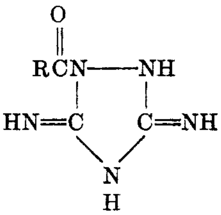

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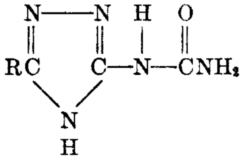
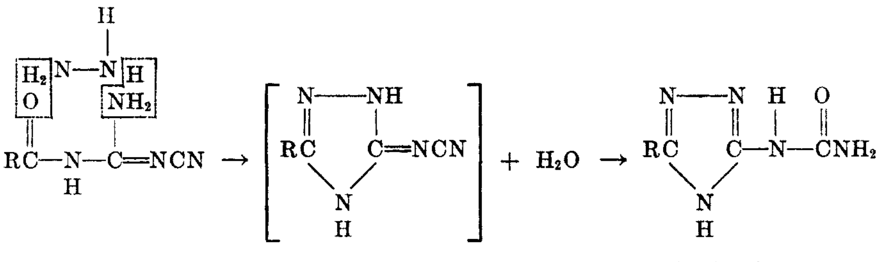


IV

Acyldicyandiamides (I) were found to react readily with hydrazine salts to yield 3-ureido-5-alkyl (or aryl)-1,2,4,4*H*-triazoles[1] (IV).

The unexpected formation of this type structure could be interpreted as resulting from the elimination of the elements of water from hydrazine and the carbonyl group of the cyanoguanylamide with subsequent hydrolysis of the nitrile group before or after ring closure by elimination of the elements of ammonia. However, in most experiments the condensation was carried out with hydrazine salts at about *p*H 6.5 which was not sufficiently acidic for hydrolysis of the nitrile group. The same product also resulted when free hydrazine was employed. Yet, if the nitrile group was not involved in the original reaction, the



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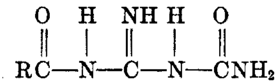
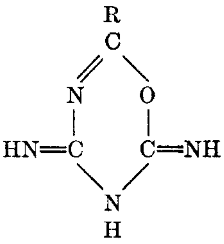
[1] The nomenclature of the 1,2,4-triazole derivatives is dependent upon which structural isomer is employed. In this paper the structure conforming to the 1,2,4,4*H*-configuration will be employed arbitrarily. It is recognized that the position of the hydrogen atoms is not fixed and that all of the possible tautomeric forms may exist.

identical product would have been anticipated from the condensation of hydrazine with the acylguanylurea (V) (1), but this postulated reaction did not occur. These facts were again suggestive that acyldicyandiamides could exist in isomeric forms, such as VI, which, as postulated previously (1), could be the reactive intermediate. With this interpretation the reaction with hydrazine did not involve hydrolysis of the cyano group but a rupture of the oxadiazine ring in such a manner as to create the ureido group.

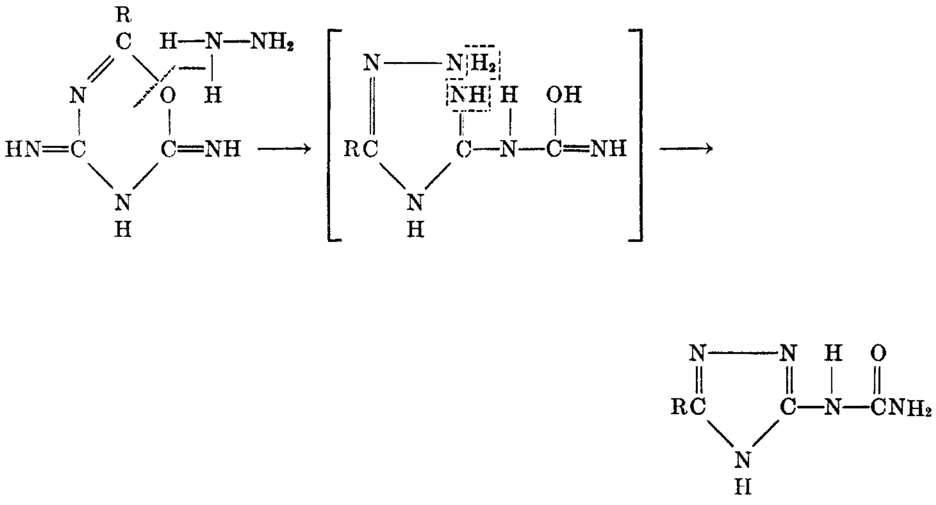


$$\mathrm{RC(=O)-NH-C(=NH)-NH-CNH_2(=O)}$$

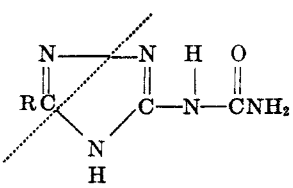
V



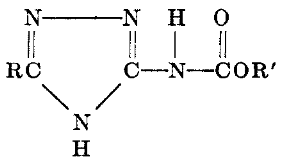
VI



The 3-ureido-5-substituted-1, 2, 4, 4*H*-triazoles were alkali-soluble and these solutions gave violet and orange complexes with copper and nickel salts in a manner similar to guanylurea (5). This complexing ability was not too unexpected since the guanylurea nucleus could be considered present by utilizing part of the triazole ring, VII.



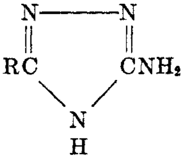
VII



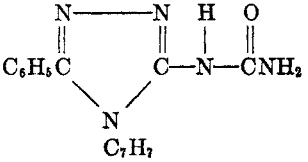
VIII

Evolution of ammonia occurred during recrystallization of certain samples from hydroxylated solvents. Prolonged heating resulted in the conversion of the amino to the alkoxy group, giving the triazole carbamate (VIII). This reaction substantiated the presence of the ureido group since in a simple example butyl carbamate is formed by heating urea with butanol (6).

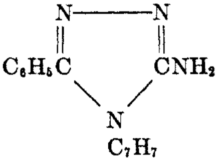
The 3-ureido-5-substituted-1,2,4*H*-triazoles could be alkylated and acylated. Hydrolysis of the benzylated phenyl derivative gave an alkali-insoluble amino compound which formed an alkali-soluble benzenesulfonamide. 3-Amino-5-substituted-1,2,4,4*H*-triazoles (IX) form metallic salts (7, 8), and it is suggested that the acidic hydrogen atom is on the nitrogen atom between the carbon atoms as in the cyclic imides. On this basis the structures of the benzylated derivative, its hydrolysis product, and the derived benzenesulfonamide are assigned structures X, XI, and XII. Infrared examination of XI confirmed the presence of a primary amino group. Although not proven, acylation was assumed to occur also on the 4-position.



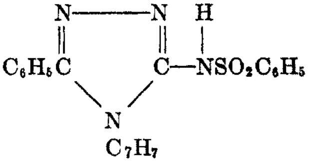
IX



X



XI



XII

Hydrolysis of the ureido compounds gave 3-amino-5-substituted-1,2,4,4*H*-triazoles (IX), certain of which were on record, and established the 1,2,4-triazole moiety.

Acknowledgment: The authors wish to thank Dr. J. A. Kuck under whose direction analyses were conducted and Mrs. M. Taylor for the infrared spectrum.

EXPERIMENTAL[2]

3-Ureido-5-methyl-1,2,4,4H-triazole. To a suspension of 104 g. (0.80 mole) of hydrazine sulfate in 400 ml. of water was added 34 g. (0.80 mole) of 95% sodium hydroxide. As soon as solution resulted 101 g. (0.80 mole) of acetyldicyandiamide (1) was added and the mixture heated. After refluxing for 30 minutes the mixture was cooled, and the colorless solid filtered and washed with water. The crude yield was 68 g. (60.5%). On gradual heating decomposition was not detected up to 310° but on immersion at 295° decomposition occurred. The compound dissolved in alkali and addition of nickel salts gave an orange solution while copper salts produced a violet color. Recrystallization from 50% Cellosolve gave non-crystalline-appearing solid which decomposed at 307° when immersed at that temperature.

Anal. Calc'd for $C_4H_7N_5O$: C, 34.04; H, 4.96; N, 49.62.

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[2] All melting points are uncorrected.

Found: C, 34.21; H, 4.82; N, 49.45.

Under similar conditions to that described above but employing acetylguanylurea (1) in place of acetyldicyandiamide no 3-ureido-5-methyl-1,2,4,4*H*-triazole was obtained. The infusible solid isolated appeared to be acetoguanide (1).

3-Ureido-5-n-amyl-1,2,4,4H-triazole. A mixture of 25.50 g. (0.6 mole) of 95% sodium hydroxide, 78.0 g. (0.60 mole) of hydrazine sulfate, 91.0 g. (0.50 mole) of caproyldicyandiamide (1), 550 ml. of water, and 350 ml. of Cellosolve was heated to boiling. When reflux occurred almost complete solution resulted, followed immediately by the formation of a rather granular precipitate. Heating was continued 5 minutes, and the mixture was cooled and the colorless solid filtered; yield 91.0 g. (92.5%). Decomposition could not be detected on gradual heating but when the compound was immersed at 223–224° it melted to a clear liquid which evolved gas and resolidified. Violet- and orange-colored complexes were obtained when alkaline solutions were treated with copper and nickel salts. Recrystallization from a large volume of 80% ethanol gave a fine powder which decomposed as before at 223–224° when immersed at that temperature. When the material was heated in Methyl Cellosolve, ammonia was evolved.

Anal. Calc'd for $C_8H_{15}N_5O$: C, 48.73; H, 7.61; N, 35.53.

Found: C, 48.96; H, 7.63; N, 35.53.

When caproylguanylurea nitrate (1) and hydrazine sulfate with enough added caustic to liberate the hydrazine were heated in water, the isolated product was caproguanide (1).

3-Ureido-5-phenyl-1,2,4,4H-triazole. A mixture containing 91. g. (0.22 mole) of 97% sodium hydroxide, 23.2 g. (0.22 mole) of hydrazine dihydrochloride, 37.6 g. (0.20 mole) of benzoyldicyandiamide, and 1500 ml. of water was refluxed for 30 minutes. Complete solution did not occur at any time and the solid increased greatly in bulk. After cooling, filtration gave a quantitative yield (41.0 g.) of fluffy colorless product which decomposed at 234–236°. Recrystallization from 50% Cellosolve gave fibrous needles. Decomposition varied with the rate of heating and with moderately rapid heating decomposition occurred at 239–240°. The compound was alkali-soluble and addition of copper sulfate produced a deep violet color while nickel salts gave a deep orange color. With concentrated solutions both the copper and nickel complexes crystallized from solution.

Anal. Calc'd for $C_9H_9N_5O$: C, 53.20; H, 4.43; N, 34.43.

Found: C, 53.25; H, 4.25; N, 34.40.

When an aqueous mixture of 0.20 mole of benzoyldicyandiamide, 0.20 mole of hydrazine sulfate, and 0.40 mole of sodium hydroxide was heated for 15 minutes much ammonia was evolved and a 76% yield of 3-ureido-5-phenyl-1,2,4,4*H*-triazole, m.p. 239–240° was obtained.

3-(N-Carbo-2′-ethoxyethoxyamino)-5-phenyl-1,2,4,4H-triazole. A suspension of 40.6 g. (0.20 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole in 300 ml. of Cellosolve was heated to reflux. Within a short time ammonia was strongly evolved and after 30 minutes a clear solution formed. Heating was continued for a total of 5 hours. Evaporation of the solvent on a steam-bath gave 52 g. (94%) of tan product, m.p. 122–125°. The compound was alkali-soluble and reprecipitated by addition of acid. Two recrystallizations from ethanol with decolorizing charcoal gave colorless needles, m.p. 149–150°.

Anal. Calc'd for $C_{13}H_{16}N_4O_3$: C, 56.52; H, 5.79; N, 20.29.

Found: C, 56.50; H, 5.73; N, 20.43.

3-(N-Carbobutoxyamino)-5-phenyl-1,2,4,4H-triazole. A mixture of 40.6 g. (0.20 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole and 500 ml. of butanol was heated to reflux. After about 4 hours a clear solution resulted but ammonia was still being evolved, so heating was continued for an additional 4 hours. Evaporation of the solution gave 51.0 g. (98%) of tan solid, m.p. 141–145°. The alkali-soluble product was recrystallized twice from methanol with the aid of decolorizing charcoal. The colorless needles now melted at 161–162°.

Anal. Calc'd for $C_{13}H_{16}N_4O_2$: C, 60.00; H, 6.15; N, 21.53.

Found: C, 59.91; H, 6.13; N, 21.78.

3-Ureido-4-methyl-5-phenyl-1,2,4,4H-triazole. To a stirred solution containing 40.6 g. (0.20 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole and 12.75 g. (0.30 mole) of 97% sodium hydroxide in 300 ml. of water was slowly added 37.8 g. (0.30 mole) of methyl sulfate while the temperature was maintained below 40°. Before addition was completed solid began to separate. The mixture was warmed to 50° for a short time, excess alkali was added, and after cooling to 10°, the colorless solid was filtered. Acidification of the filtrate gave a 17% recovery of unchanged triazole. The methylated product weighed 17.0 g. (39%) and decomposition occurred at 218–220° on gradual heating, with softening below this temperature. Two recrystallizations from 25% Cellosolve gave noncrystalline-appearing solid which decomposed as before at 218–220°.

Anal. Calc'd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.06; N, 32.25.
Found: C, 55.41; H, 5.11; N, 32.23.

3-Ureido-4-benzyl-5-phenyl-1,2,4,4H-triazole. A stirred mixture of 20.3 g. (0.10 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole, 4.25 g. (0.10 mole) of 97% sodium hydroxide, 12.65 g. (0.10 mole) of benzyl chloride, and 100 ml. of 50% Cellosolve was refluxed for 30 minutes. During the heating period the benzyl chloride disappeared and the mixture became almost neutral. After pouring into ice-water a gum separated which soon solidified. Filtration gave 28.6 g. (97.5%) of alkali-insoluble product, m.p. 175–180°. Recrystallization first from Cellosolve and then butanol gave glittering needles which decomposed at 234–235°.

Anal. Calc'd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.11; N, 23.89.
Found: C, 65.67; H, 5.03; N, 23.72.

3-Amino-4-benzyl-5-phenyl-1,2,4,4H-triazole. A mixture containing 13.2 g. (0.20 mole) of 85% potassium hydroxide, 29.3 g. (0.10 mole) of 3-ureido-4-benzyl-5-phenyl-1,2,4,4*H*-triazole, and 100 ml. of 50% Cellosolve was refluxed for 19 hours during which time ammonia was evolved. After pouring into ice-water a quantitative yield (25.0 g.) of colorless solid, m.p. 133–136° was obtained. The material was soluble in acid and was reprecipitated by alkali. Recrystallization from methanol gave beautiful needles, m.p. 137–138°, but on drying in an Abderhalden pistol the crystals became chalky in appearance and now melted at 140–141°. Infrared absorption showed strong absorption of 4 bands in the 3100–3500 $cm.^{-1}$ region which is associated with a primary amino group.

Anal. Calc'd for $C_{15}H_{14}N_4$: C, 72.00; H, 5.60; N, 22.40.
Found: C, 72.03; H, 5.70; N, 22.28.

3-Benzenesulfonamido-4-benzyl-5-phenyl-1,2,4,4H-triazole. To a solution of 3.5 g. (0.014 mole) of 3-amino-4-benzyl-5-phenyl-1,2,4,4*H*-triazole in 50 ml. of pyridine was added 4.15 g. (0.023 mole) of benzenesulfonyl chloride. The solution became yellow but no heat was evolved. After warming at 60° for 30 minutes the solution was poured over ice. On standing a quantitative yield (5.46 g.) of light yellow solid separated; m.p. 180–188°. Two recrystallizations from ethanol gave fine, colorless crystals; m.p. 200–202°. The compound was soluble in alkali and was reprecipitated by acid.

Anal. Calc'd for $C_{21}H_{18}N_4O_2S$: C, 64.61; H, 4.61; N, 14.35.
Found: C, 64.60; H, 4.73; N, 14.58.

3-Ureido-4-benzoyl-5-phenyl-1,2,4,4H-triazole. Complete solution occurred after heating to reflux 20.8 g. (0.10 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole in 350 ml. of pyridine. The solution was cooled to 0° and 15.5 g. (0.11 mole) of benzoyl chloride was added. After standing at room temperature for 5 days the solution was warmed on a steam-bath for 30 minutes and poured into a large volume of dilute hydrochloric acid. The precipitated solid weighed 20.2 g. (66.5%) and decomposed at 208–211°. Recrystallization of the alkali-insoluble product from a large volume of 50% Cellosolve gave small colorless plates decomposing at 216–218°.

Anal. Calc'd for $C_{16}H_{13}N_5O_2$: C, 62.54; H, 4.23; N, 22.80.
Found: C, 62.45; H, 4.39; N, 22.66.

3-Amino-5-methyl-1,2,4,4H-triazole. A mixture of 70.5 g. (0.50 mole) of 3-ureido-5-methyl-1,2,4,4*H*-triazole, 62.0 g. (1.50 moles) of 97% sodium hydroxide, and 300 ml. of water was refluxed for 3 hours during which time ammonia was evolved. The yellow solution was treated with decolorizing charcoal, filtered, and the filtrate acidified with excess acetic acid which liberated carbon dioxide and precipitated a solid. After filtration the filtrate, which contained an appreciable quantity of the water-soluble product, was evaporated to dryness. The combined dried solids were extracted with acetonitrile in a Soxhlet extractor giving 24.0 g. (49%) of crude product. Recrystallization from acetonitrile gave small colorless crystals; m.p. 146–148°; lit (7) 148°.

3-Amino-5-n-amyl-1,2,4,4H-triazole. After dissolving 69 g. (0.35 mole) of 3-ureido-5-*n*-amyl-1,2,4,4*H*-triazole in a solution which contained 32 g. (0.75 mole) of 95% sodium hydroxide in 250 ml. of water, the resulting yellow solution was refluxed. Ammonia was rapidly evolved and after heatingfor 5 hours, decolorizing charcoal was added, and the solution was filtered, cooled, and acidified with excess nitric acid. Carbon dioxide was strongly evolved and on further cooling crystals separated. The nitrate was filtered and washed first with ice-water and then acetone with resulting loss of product. The yield was 29 g. (38%) and decomposition occurred at 138–139°. Recrystallization from acetone did not change the decomposition point of the needles. Treatment of a concentrated aqueous solution of the nitrate with ammonia precipitated the free base. Recrystallization from hot water gave shiny plates, m.p. 130–132°.

Anal. Calc'd for $C_7H_{14}N_4 \cdot HNO_3$: C, 38.70; H, 6.91; N, 32.25.
Found: C, 38.84; H, 6.92; N, 32.20.

3-AMINO-5-PHENYL-1,2,4,4H-TRIAZOLE

By acid hydrolysis. Complete solution occurred after refluxing a mixture of 20.3 g. (0.10 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole, 60 g. (0.60 mole) of concentrated hydrochloric acid, 250 ml. of water, and 100 ml. of dioxane for 5 hours. On cooling 8.0 g. of slender needles separated. The material, m.p. 163–164°, gave a strongly acidic reaction in water and changed to a noncrystalline-appearing solid. Excess alkali was added which dissolved the material and acetic acid precipitated a solid, m.p. 238–240°. A mixture melting point with starting material gave no depression. Recovery of 3-ureido-5-phenyl-1,2,4,4*H*-triazole as the hydrochloride was 33.5%.

Evaporation of the filtrate gave 24 g. of tan solid which was not completely dry. Addition of alkali to a portion dissolved in water evolved ammonia due to the ammonium chloride formed during hydrolysis. The solid was dissolved in a small volume of hot water, the solution decolorized with charcoal, and the filtrate diluted with an equal volume of concentrated hydrochloric acid. Filtration gave colorless fine needles of 3-amino-5-phenyl-1,2,4,4*H*-triazole hydrochloride which decomposed at 253–254°; lit (8) m.p. 252°. A portion of the hydrochloride was dissolved in water, the solution was made alkaline with sodium hydroxide, and excess nitric acid was added. Filtration of the insoluble nitrate gave noncrystalline-appearing solid which decomposed at 208°; lit (8) m.p. 203°. Another portion of the hydrochloride was warmed with excess ammonia solution. The free base melted at 187–188°; lit (8) m.p. 188°; (9) m.p. 186–187°.

By alkaline hydrolysis. A solution of 40.6 g. (0.20 mole) of 3-ureido-5-phenyl-1,2,4,4*H*-triazole and 33 g. (0.50 mole) of 85% potassium hydroxide in 250 ml. of water was refluxed for 3 hours during which time ammonia was evolved. The solution was treated with decolorizing charcoal, filtered, and cooled. Excess nitric acid was added slowly which caused evolution of carbon dioxide and precipitation of the nitrate. Filtration gave 43 g. (96%) of product decomposing at 205°. Recrystallization from hot water raised the decomposition point to 208–209°; lit (8) m.p. 208°.

SUMMARY

Acyldicyandiamides react with hydrazine salts to yield 3-ureido-5-substituted-1,2,4,4*H*-triazoles.

STAMFORD, CONNECTICUT

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