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

CHEMISTRY OF DICYANDIAMIDE. IV. REACTION OF ACYLDICYANDIAMIDES WITH HYDROXYLAMINE AND CYANAMIDE

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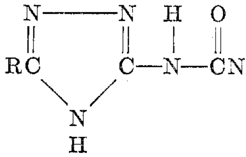
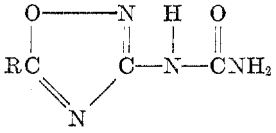
After it was found that acyldicyandiamides (1) reacted with hydrazine to yield 3-ureido-5-substituted-1,2,4,4*H*-triazoles (I) (2), the expansion of the reaction with other amino compounds such as hydroxylamine and cyanamide was undertaken.

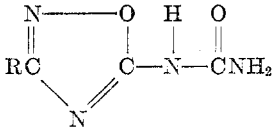
Reaction with hydroxylamine salts unexpectedly gave 3-ureido-5-substituted-1,2,4-oxadiazoles (II) although the isomeric 3-substituted-5-ureido-1,2,4-oxadiazoles (III) were the anticipated products, based on the reaction with hydrazine (2).



I

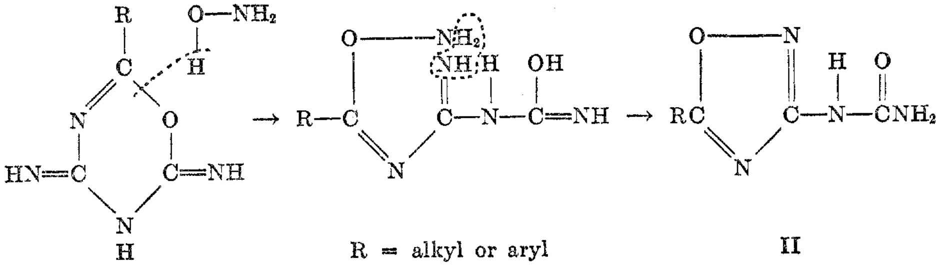


R = alkyl or aryl II



III

To explain the formation of the ureido derivative, the reaction can be best represented as occurring through the cyclic form of the acyldicyandiamide, as was postulated for the reaction with hydrazine (2).



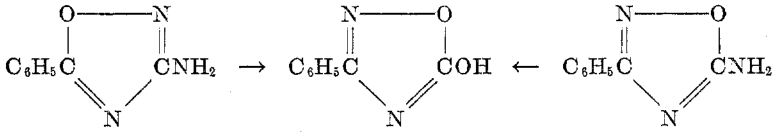
R = alkyl or aryl II

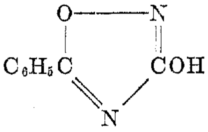
Evidence that the product was the 3-ureido-5-substituted-1,2,4-oxadiazole (II) was obtained by hydrolysis of the phenyl derivative.

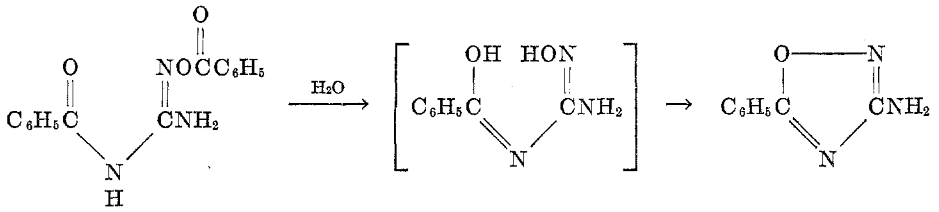
The known 3-amino-5-phenyl-1,2,4-oxadiazole (IV) (3) was one of the products isolated.

However, the issue was clouded by the simultaneous isolation of the known 3-phenyl-5-hydroxy-1,2,4-oxadiazole (V) (4, 5). It was subsequently found that hydrolysis of IV produced V. This apparent rearrangement was unexpected since hydrolysis of VI also produces V (6).

Both isomers, IV, m.p. 164° (3) and VI, m.p. 153–154° (6) were on record. Since the recorded melting points differed by only 10°, supplementary evidence was obtained to substantiate the existence of the two isomers. The monoacetyl derivative of VI is reported to melt at 183–184° (6). Acetylation of IV gave a monoacetyl derivative melting at 150–152°.[1] The 3-amino-5-phenyl-1,2,4-oxadiazole (IV) had been obtained by Wieland and Bauer (3) by hydrolysis of N,O-dibenzoylhydroxyguanidine (VIII).


IV V VI


VII


VIII IV

The latter compound had been isolated as one of the products of the treatment of dihydroxyguanidine hydrobromide with benzoyl chloride and sodium bicarbonate. The oxadiazole of Wieland and Bauer (3) should have the structure as assigned, since any guanidine derivative must contain a carbon atom attached to three nitrogen atoms.

It appeared simpler to the authors to start directly with hydroxyguanidine to obtain an authentic sample of 3-amino-5-phenyl-1,2,4-oxadiazole (IV). Prätorius-Seidler (7) had treated hydroxylamine hydrochloride with cyanamide but had difficulty in isolating the rather unstable hydroxyguanidine hydrochloride. In the present work, hydroxylamine hydrochloride was allowed to react with aqueous cyanamide and the solution was treated with benzoyl chloride and sodium bicarbonate. Hydrolysis of the N,O-dibenzoylhydroxyguanidine (VIII) gave 3-amino-5-phenyl-1,2,4-oxadiazole (IV) which was identical (m.p., and infrared spectrum) with the hydrolysis product obtained from the phenyl ureido oxadiazole.

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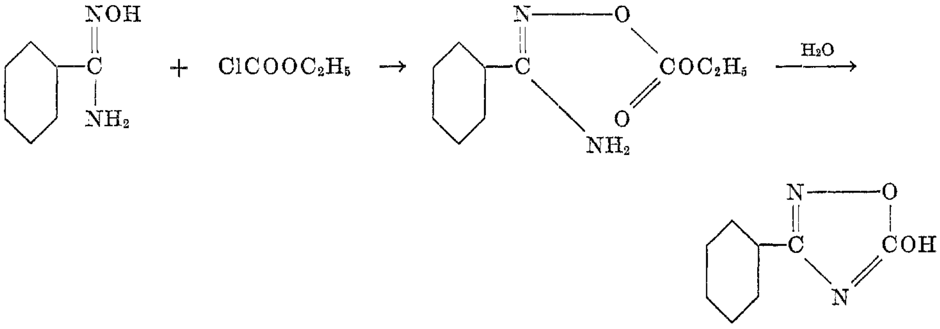
[1] It should be pointed out that the chemistry of these oxadiazoles is somewhat equivocal, since IV was isolated by hydrolysis of a by-product (3), and V, VI, and VII have been obtained from dioximes (5, 6). If rearrangement occurs as facilely as it appears from our experiments, the whole problem of the structure of these compounds could bear re-examination.

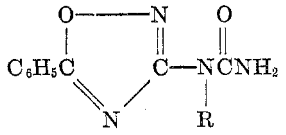
Both of the phenyl hydroxy oxadiazoles, V (4, 5) and VII (5), were on record. An authentic sample of 3-phenyl-5-hydroxy-1,2,4-oxadiazole (V) was obtained by the unambiguous procedure of Falk (4). This synthesis involved the treatment of benzamidoxime with ethyl chlorocarbonate, followed by hydrolysis.



V

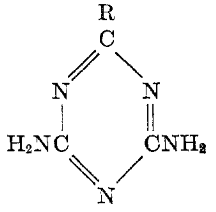
The authentic sample was identical with the compounds isolated from the hydrolysis of the phenyl ureido oxadiazole and the phenyl amino oxadiazole (comparison of m.p., mixture m.p., and infrared spectra).

The reactions of the substituted ureido-1,2,4-oxadiazoles were not studied extensively. The compounds were difficultly soluble in alkali and gave no colored complexes with copper or nickel salts as had the ureido-1,2,4,4*H*-triazoles (2). The phenyl derivative was alkylated with benzyl chloride and acylated with benzoyl chloride. No attempt was made to establish the structure of these derivatives of 3-ureido-5-phenyl-1,2,4-oxadiazole. It was assumed that the same hydrogen atom was replaced in both reactions and the products were arbitrarily assigned structure IX.



IX

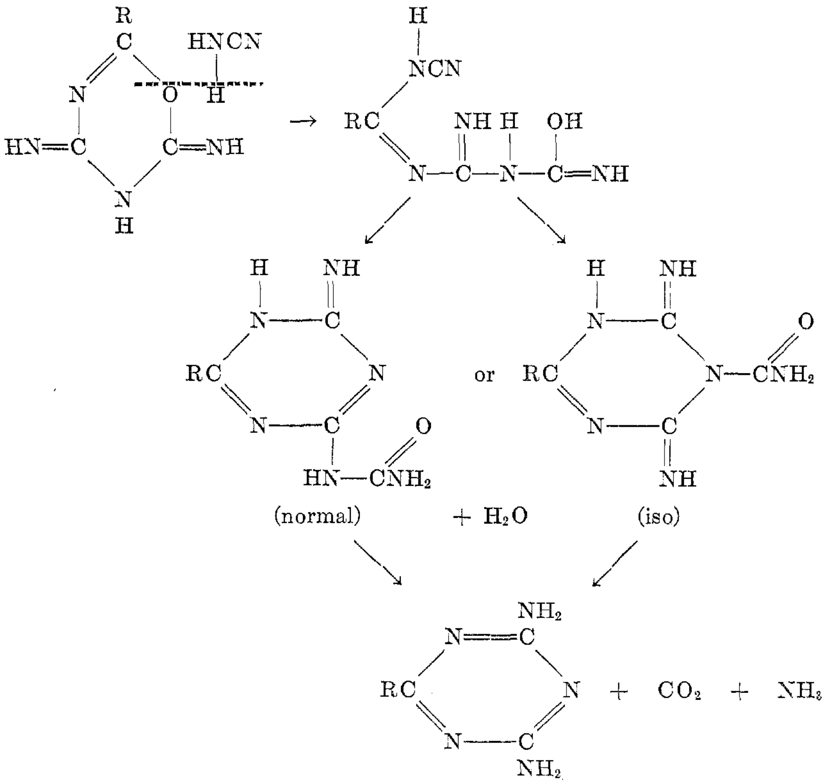
$R = C_7H_7,\ C_6H_5CO$



X

R = alkyl or aryl

Reaction of acyldicyandiamides with cyanamide gave guanamines (X) which are 2-substituted-4,6-diamino-*s*-triazines. A possible mechanism utilizing the oxadiazine form of the acyldicyandiamide is shown. Whether an intermediate normal or iso carbamyl derivative is formed or whether hydrolysis occurs before or after ring closure is not known.



X

R = alkyl or aryl

Acknowledgment: The authors wish to thank Dr. J. A. Kuck and his staff for microanalyses and Dr. J. E. Lancaster for infrared spectra.

EXPERIMENTAL[2]

I. PREPARATION OF OXADIAZOLES

3-Ureido-5-methyl-1,2,4-oxadiazole. A mixture of 63 g. (0.50 mole) of acetyldicyandiamide (1), 49.2 g. (0.30 mole) of hydroxylamine sulfate, and 150 ml. of water was stirred and refluxed for 40 minutes. During this time the solid changed in appearance and the liquid became reddish-brown in color. The yield of crude product, decomposing at 197–198° was 32.3 g. (45.5%). Recrystallization from hot water raised the decomposition point of the colorless, noncrystalline-appearing solid to 206–207°. An alkaline solution of the compound gave no colored copper or nickel complexes.

Anal. Calc'd for $C_4H_6N_4O_2$: C, 33.80; H, 4.25; N, 39.42.
Found: C, 33.89; H, 4.20; N, 39.44.

3-Ureido-5-n-amyl-1,2,4-oxadiazole. A stirred mixture of 91 g. (0.50 mole) of caproyldicyandiamide (1), 49.2 g. (0.30 mole) of hydroxylamine sulfate, and 900 ml. of 45% Cellosolve[3] was heated to reflux. Complete solution occurred. Heating was continued for 10

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[2] All melting points are uncorrected.

[3] 2-Ethoxyethanol.

minutes, the solution was poured into ice-water, and the precipitated solid was filtered; the yield was 87 g. (89%). Decomposition occurred at 179–180°, and fusion with caproyldicyandiamide, m.p. 179–180° (1), gave a marked depression. Glittering colorless plates were obtained after recrystallization from aqueous propanol-2, and the decomposition point was raised to 185–186°. The product was alkali-soluble but gave no colored complexes with copper or nickel salts.

Anal. Calc'd for $C_8H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.27.
Found: C, 48.35; H, 7.00; N, 28.30.

3-Ureido-5-phenyl-1,2,4-oxadiazole. To a suspension of 131.6 g. (0.70 mole) of benzoyldicyandiamide (1) in 1500 ml. of water there was added a solution of 59 g. (0.85 mole) of hydroxylamine hydrochloride in 1500 ml. of water. The stirred mixture was heated but before reflux occurred the mass became so thick that an additional 500 ml. of water was added. After the mixture was refluxed for 30 minutes it was cooled and the colorless fluffy crystals were filtered; the yield was 141 g. (99%). Recrystallization from dilute Cellosolve did not alter the decomposition point of 239–240°. The material was alkali-soluble but formed no colored complexes with nickel or copper salts.

Anal. Calc'd for $C_9H_8N_4O_2$: C, 52.99; H, 3.92; N, 27.45.
Found: C, 52.92; H, 4.01; N, 27.39.

II. REACTIONS OF OXADIAZOLES

3-(1′-Benzyl)ureido-5-phenyl-1,2,4-oxadiazole. A solution of 16.5 g. (0.25 mole) of 85% potassium hydroxide in 300 ml. of water was prepared before the addition of 40.8 g. (0.20 mole) of 3-ureido-5-phenyl-1,2,4-oxadiazole and 31.6 g. (0.25) mole of benzyl chloride. After a short reflux period considerable solid separated. Heating was continued for a half hour, the excess benzyl chloride was removed under reduced pressure, and the mixture was poured into ice-water. Filtration gave 50 g. (86%) of slightly sticky solid which melted at 120–130°. Two recrystallizations, first from methanol and then butanol, gave fine needles, m.p. 189–190°.

Anal. Calc'd for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04.
Found: C, 65.16; H, 4.83; N, 19.09.

3-(1′-Benzoyl)ureido-5-phenyl-1,2,4-oxadiazole. To a suspension of 30.6 g. (0.15 mole) of 3-ureido-5-phenyl-1,2,4-oxadiazole in 300 ml. of pyridine there was slowly added 20.1 g. (0.20 mole) of benzoyl chloride while the temperature was maintained below 20°. After standing a day the now brown solution was warmed on a steam-bath for half an hour and poured into excess, cold, dilute hydrochloric acid. The precipitated oil soon solidified; the weight was 45 g. (98%). Softening occurred at 140° and the material gradually melted up to 165°. Recrystallization from a liter of boiling butanol gave 7 g. of colorless plates which decomposed at 220–223°. Evaporation of the filtrate gave a large quantity of viscous brown tar. A second recrystallization from 50–50 butanol-Cellosolve gave 5 g. of fine colorless needles which decomposed at 225–226°.

Anal. Calc'd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.18.
Found: C, 62.45; H, 4.00; N, 18.30.

3-Amino-5-phenyl-1,2,4-oxadiazole (IV) *and 3-phenyl-5-hydroxy-1,2,4-oxadiazole* (V). A mixture of 81.6 g. (0.40 mole) of 3-ureido-5-phenyl-1,2,4-oxadiazole, 41.3 g. (1.0 mole) of 97% sodium hydroxide, and 500 ml. of water was refluxed for 2½ hours. Ammonia was evolved and the solution became yellow. Distillation removed 100 ml. of water and on cooling 8 g. (12.5%) of light yellow needles of the amino compound separated, m.p. 162–164°. Recrystallization from hot water with decolorizing charcoal gave slender colorless needles, m.p. 164–165°; lit. (3) 164°. The compound was soluble in acid and reprecipitated by alkali.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.61; H, 4.38; N, 26.08.
Found: C, 59.54; H, 4.43; N, 26.27.

Acidification of the original filtrate with acetic acid gave evolution of carbon dioxide and precipitation of the hydroxy compound; yield 54 g. (85%), m.p. 190–192°. Recrystallization from hot water with charcoaling gave colorless crystals, m.p. 196–199° [lit. (4) 198°, (5) 203–204°].

Anal. Calc'd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.29.
Found: C, 59.17; H, 3.65; N, 17.03.

3-Phenyl-5-hydroxy-1,2,4-oxadiazole (V). A mixture of 3 g. of 3-amino-5-phenyl-1,2,4-oxadiazole (IV), 6 g. of 99% sodium hydroxide, and 160 ml. of water was refluxed for 2½ hours. Ammonia was evolved and complete solution resulted. On cooling, 1 g. of starting material, m.p. 160–164°, crystallized. Acidification of the filtrate with acetic acid precipitated a solid which was recrystallized from hot water without drying. The colorless crystals, m.p. 200–203°, weighed 0.3 g. (10%). Fusion with the sample isolated previously gave a value of 196–200°. The infrared absorption spectra of the two samples were identical.

3-Acetamido-5-phenyl-1,2,4-oxadiazole. After a mixture of 2 g. (0.01 mole) of 3-amino-5-phenyl-1,2,4-oxadiazole, 1 g. of anhydrous sodium acetate, and 12.5 ml. of acetic anhydride was heated to reflux the resulting solution was poured over ice. The product separated as a brown solid, weight 2.2 g. (88%) and was recrystallized from benzene as shiny plates, m.p. 150–152°. The melting point of the isomer is 183–186° (6). Nitrogen analysis indicated the presence of only one acetyl group.

Anal. Calc'd for $C_{10}H_9N_3O_2$: N, 20.68. Found: N, 20.46.

III. PROOF OF STRUCTURE OF OXADIAZOLES

N,O-Dibenzoylhydroxyguanidine (VIII). Solid hydroxylamine hydrochloride (139 g., 2.0 moles) was added to 262 g. (2.0 moles) of a 32% aqueous cyanamide solution at room temperature. Within a short time an exothermic reaction occurred with evolution of some gas and with complete solution. The solution, based on Prätorius-Seidler's (7) finding that two equivalents of ammonium chloride were formed in the reaction, was assumed to contain about 0.66 mole of hydroxyguanidine hydrochloride. A portion was treated with benzoyl chloride and sodium bicarbonate, giving a solid which was recrystallized from ethanol, m.p. 148–153°. The remaining solution was treated concomitantly with 140 g. (1.0 mole) of benzoyl chloride and 168 g. (2.0 moles) of solid sodium bicarbonate at 15–20°. After the addition, 41.3 g. (1.0 mole) of 97% sodium hydroxide in 100 ml. of water was added to give an alkaline reaction. The solid which separated was filtered and washed with water. Examination showed that the material consisted of a mixture of powdery colorless solid, a tacky substance, and a granular pink solid. Recrystallization from ethanol gave fine colorless plates, m.p. 145–147°; wt. 21 g. Addition of water to the filtrate precipitated an additional 20 g. of slightly pink product; the total yield was 41 g. (28.8%, based on benzoyl chloride). The pure compound is reported to melt at 162–163° (3).

3-Amino-5-phenyl-1,2,4-oxadiazole (IV). Wieland and Bauer (3) had previously carried out this hydrolysis but gave few details. A mixture of 14 g. (0.05 mole) of crude N,O-dibenzoylhydroxyguanidine, 5 g. (0.12 mole) of 97% sodium hydroxide, and 200 ml. of water was stirred at 80° for a half hour. The solid changed in appearance during this time and filtration gave 4 g. (50%) of powdery colorless product, m.p. 159–164°. Recrystallization from ethanol gave fine needles, m.p. 164–165°. A mixture melting point with the previously isolated phenyl amino oxadiazole gave no depression, and comparison of the infrared spectra of the two samples showed them to be identical.

3-Phenyl-5-hydroxy-1,2,4-oxadizaole (V). The general procedure of Falk (4) was followed. To a stirred solution of 45 g. (0.33 mole) of benzamidoxime (8) in 250 ml. of acetone there was added slowly 40 g. (0.37 mole) of ethyl chlorocarbonate at 5–10°. During this time colorless crystals of the amidoxime hydrochloride separated. A solution containing 15 g. (0.37 mole) of 97% sodium hydroxide in 75 ml. of water was then gradually added, causing solution and formation of another precipitate which slowly dissolved in the acetone. The stirred mixture was allowed to warm to room temperature and the aqueous layer removed. On cooling 30 g. of shiny plates of the carbethoxy derivative separated from the acetone, m.p. 118–122°; lit. (4) 127°. Dilution of the acetone filtrate precipitated an additional 33 g. of product; the total yield was 63 g. (91.5%).

The crude carbethoxybenzamidoxime (59 g., 0.28 mole) was added to 350 ml. of water containing 16 g. (0.38 mole) of 97% sodium hydroxide. After about 5 minutes of refluxing a light yellow solution formed which was treated with decolorizing carbon, filtered, cooled, and acidified with excess acetic acid. The crude product weighed 33 g. (72%); m.p. 188–192°. Recrystallization from hot water gave 20 g. (66%) of pure compound, m.p. 201–203° [lit. (4) 198°; (5) 203–204°]. Mixture melting point determinations and comparison of the infrared spectrum of this compound with the two other isolated samples of 3-phenyl-5-hydroxy-1,2,4-oxadiazole showed all three to be identical.

IV. PREPARATION OF GUANAMINES

Acetoguanamine. A stirred mixture of 36 g. (0.28 mole) of acetyldicyandiamide (1) and 70 g. (0.28 mole) of 17% aqueous cyanamide was refluxed for 20 minutes. At the end of this time evolution of carbon dioxide had ceased and the mixture was allowed to cool. The filtered solid was slurried with dilute caustic (16 g. of 97% sodium hydroxide in 250 ml. of water) for 15 minutes and the mixture was allowed to stand for an hour before filtration. The caustic treatment removed any starting material and/or hydroxy-*s*-triazines. The crude product was recrystallized from hot water giving colorless plates of the hydrate which crumbled to a powder on drying, m.p. 269–270° [lit. (9) 265°]. The yield of purified product was 4 g. (12.3%).

Hexanoguanamine. To 18.2 g. (0.10 mole) of caproyldicyandiamide (1), dissolved in 100 ml. of 95% ethanol at 75%, was added 40 g. (0.22 mole) of 24% aqueous cyanamide. The mixture was refluxed for an hour during which time carbon dioxide was evolved. The clear solution was cooled and 40 g. of a 10% sodium hydroxide solution plus excess water was added. The colorless precipitate weighed 4.7 g. (26%) and recrystallization from methanol gave fine crystals, m.p. 169–171°.

Anal. Calc'd for $C_8H_{15}N_5$: C, 53.03; H, 8.28; N, 38.67.
Found: C, 52.93: H, 8.04; N, 38.68.

Benzoguanamine. A stirred mixture of 94 g. (0.50 mole) of benzoyldicyandiamide (1), 85 g. (0.50 mole) of 25% aqueous cyanamide, and 500 ml. of water was heated and held at 90° for 20 minutes, during which time carbon dioxide was evolved. The mixture was cooled, and the solid was filtered and washed with dilute caustic followed by water. Acidification of the filtrate gave 18 g. (19.2%) of benzoguanide (1). The crude benzoguanamine, m.p. 214–215°, weighed 70 g. (75%). Recrystallization from 10% Cellosolve gave small colorless crystals, m.p. 224–226° [lit. (10) 220°; (11) 225°].

SUMMARY

1. Acyldicyandiamides reacted with hydroxylamine salts to yield 3-ureido-5-substituted-1,2,4-oxadiazoles.
2. Hydrolysis of 3-amino-5-phenyl-1,2,4-oxadiazole gave 3-phenyl-5-hydroxy-1,2,4-oxadiazole.
3. Acyldicyandiamides reacted with cyanamide to yield guanamines.

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