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Cyclizations of 3,4,5-Triamino-*s*-triazole (Guanazine) and 3,4-Diamino-5-mercapto-*s*-triazole with Acetic Anhydride

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Cyclizations of either guanazine (I) or 3,4-diamino-5-mercapto-*s*-triazole (VI) with acetic anhydride leads to 3-amino-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole and 5-amino-2-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole, respectively, as well as their acetyl derivatives.

s-Triazolo-*s*-triazoles of the [4,3-b] system are relatively rare. Hoggarth (1) prepared what is probably 3,6-diphenyl-*s*-triazolo[4,3-b]-*s*-triazole from excess benzoyl chloride and 4,5-diamino-3-phenyl-*s*-triazole although no conclusive proof is given. Hoggarth's compound is similar physically to a diphenyl triazolotriazole prepared later by Bower and Doyle (2). Their synthesis, however, was totally ambiguous and no assignment could be made. More recently Gehlen and Robisch (3) have unequivocally synthesized a series of alkyl, aryl and acyl 3,5 and 6 substituted *s*-triazolo[4,3-b]-*s*-triazoles by acylation and ring closure of 4,5-diamino-*s*-triazoles. We have now prepared an amino substituted *s*-triazolo[4,3-b]-*s*-triazole starting with the readily available guanazine (I) (4).

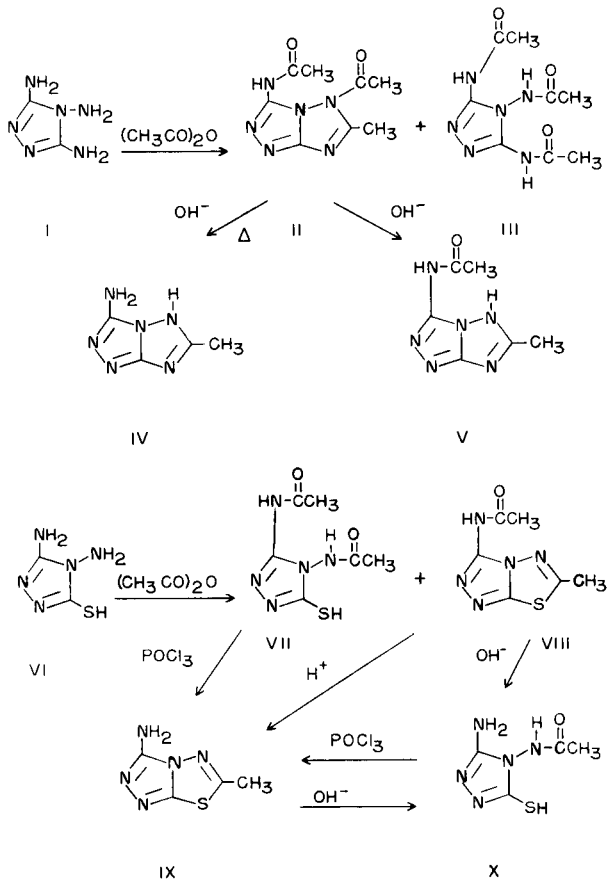
When the initially exothermic reaction between guanazine (I) and excess acetic anhydride was maintained at reflux for 5 minutes there was obtained a 50% yield of 3,4,5-triacetamido-*s*-triazole (III). When the mixture was refluxed for 2.5 hours there was obtained a 46% yield of 3-acetamido-5-acetyl-6-methyl-*s*-triazolo [4,3-b]-*s*-triazole (II) and lesser quantities of III. Treatment of II with two moles of dilute alkali at room temperature for one hour removed the nuclear acetyl to give 3-acetamido-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole (V). Both acetyl groups were removed from II with three moles of alkali at 100° for 2.5 hours giving 3-amino-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole (IV). The n.m.r. spectrum of IV in deuterated dimethylsulfoxide showed singlets for the methyl and primary amino groups at 7.63 and 3.50 τ respectively in the ratio of 3:2. The nuclear imino proton was too diffuse downfield to be seen. The U. V. absorption curve showed one maximum at 235 mμ (ϵ = 6,080).

s-Triazolo[3,4-b]-1,3,4-thiadiazoles were first described by Kanaoka (5). 4-Amino-5-mercapto-3-phenyl-*s*-triazole (6) was heated with various acyl and aroyl halides giving the corresponding amides which were ring closed with phosphoryl chloride. Another route to this ring system was provided by Sandström (7) who obtained 3,6-dimercapto-*s*-triazolo[3,4-b]-1,3,4-thiadiazole from a refluxing pyridine solution of carbon disulfide and thiocarbohydrazide.

Recently Potts and Huseby (8) reported the cyclization of 3-substituted-4-amino-5-mercapto-*s*-triazoles with either carbon disulfide or cyanogen bromide to give respectively 2-mercapto- and 2-amino-5-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles. Our report describes the cyclization of 3,4-diamino-5-mercapto-*s*-triazole (9) with acetic anhydride to give 5-amino-2-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole (IX), a new derivative of this ring system.

Excess acetic anhydride and 3,4-diamino-5-mercapto-*s*-triazole in glacial acetic acid gave a mixture of the diacetamido mercapto triazole (VII) and 3-acetamido-6-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole (VIII). The diacetamido mercapto triazole (VII) was characterized on the basis of two different carbonyl absorptions in the infrared (5.85 and 5.92 μ) and a free SH group by the sodium azide-iodine spot test (10). The structure of the acetamido methyl triazolo thiadiazole (VIII) was determined by a negative SH test, no reaction in alkali at room temperature (therefore no nuclear acetyl), one carbonyl band in the infrared and acid hydrolysis to 3-amino-6-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole (IX). The latter was characterized on the basis of n.m.r. showing an aromatic type methyl at 7.18 τ and a protonated primary amine in trifluoroacetic acid at -1.66 τ in a ratio of 1:1. The infrared spectrum showed the typical guanidine type primary amino peaks at 3.10 and 3.28 μ and the ultraviolet spectrum had a λ max (H_2O) at 265 mμ (ϵ = 2,480).

The action of hot alkali on the acetamido methyl triazolo thiadiazole (VIII) not only hydrolyzed the amide but also opened the ring giving 3-amino-4-acetamido-5-mercapto-*s*-triazole (X) which was ring closed to the amino methyl triazolo thiadiazole (IX) with phosphoryl chloride and hydrolyzed back again into X with hot alkali, establishing the position of the acetyl group in X. Similarly the diacetamido mercapto triazole (VII) was directly converted into the amino methyl triazolo thiadiazole (IX) by phosphoryl chloride - the formed hydrochloric acid being responsible for the hydrolysis of the 3-acetamido group.



EXPERIMENTAL (11)

3-Acetamido-5-acetyl-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole (II).

Solid guanazine, 22.8 g. (0.2 mole) was treated with 125 ml. of acetic anhydride. The exothermic reaction was maintained at reflux for 2.5 hours and then evaporated to dryness in a rotary evaporator at 100°. The solidified mass was boiled with 75 ml. of ethanol and filtered hot retaining 10.5 g. of fine colorless flakes, m.p. 227-228°. Concentration of the mother liquor followed by crystallization of the product from ethanol gave an additional 10.2 g. totalling 20.7 g. (46.5%).

Anal. Calcd. for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.26; H, 4.13; N, 37.60.

3,4,5-Triacetamido-*s*-triazole (III).

Five g. (0.044 mole) of guanazine (I) was treated with 25 ml. of acetic anhydride and refluxed for 5 minutes. The resulting solution was dissolved in two volumes of ethanol and cooled for four days giving 3.3 g. of colorless grains, m.p. 278-280°. A second crop of 6 g. obtained from the mother liquor was combined with the first crop and recrystallized from methanol yielding 5.2 g. (50%) of colorless grains, m.p. 279-282°. Pellizzari and Repetto (12) reported a m.p. of 240°. Fractional crystallization of the mother liquor concentrates from the preparation of II above gave 30% yields of this triacetamido-*s*-triazole.

Anal. Calcd. for $C_8H_{12}N_6O_3$: C, 40.00; H, 5.04; N, 34.99. Found: C, 40.12; H, 5.09; N, 35.11.

3-Acetamido-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole (V).

A solution of 1.11 g. (0.005 mole) of II in 10 ml. of 1 *N* sodium hydroxide (0.01 mole) was maintained at room temperature for one hour, neutralized with 0.286 ml. (0.005 mole) of glacial acetic acid, concentrated to dryness at 30-40° and triturated with 55 ml. of ethanol. The remaining colorless solid was filtered, washed with ethanol and dried at 100° *in vacuo* leaving 0.5 g. (55%) of product, m.p. 275-277° dec.

Anal. Calcd. for $C_6H_8N_6O$: C, 40.00; H, 4.48; N, 46.65. Found: C, 40.34; H, 4.57; N, 46.44.

3-Amino-6-methyl-*s*-triazolo[4,3-b]-*s*-triazole (IV).

A solution of 33.3 g. (0.15 mole) of II in 225 ml. of 2 *N* sodium hydroxide (0.45 mole) was heated on a steam bath for 2.5 hours, neutralized with 8.6 ml. (0.15 mole) of glacial acetic acid and cooled. The formed colorless precipitate was filtered, washed with water and dried leaving 16.0 g. (80%) of product, m.p. 273-274° dec.

Anal. Calcd. for $C_4H_6N_6$: C, 34.78; H, 4.38; N, 60.84. Found: C, 34.88; H, 4.10; N, 60.87.

3,4-Bis-acetamido-5-mercapto-*s*-triazole (VII) and 3-Acetamido-6-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole (VIII).

A suspension of 65.6 g. (0.5 mole) of VI (9) in 350 ml. of boiling glacial acetic acid was treated with 325 ml. of acetic anhydride over the course of 1.25 hours, refluxed for 3 hours and concentrated to a yellow solid in a rotary evaporator over steam. The cake was dissolved in 500 ml. of hot absolute ethanol, decolorized and cooled yielding colorless crystals of VIII weighing 42 g., m.p. 197-199°. Concentration of the mother liquor gave a crop of crude material, m.p. 230-260° which on fractional crystallization from chloroform gave 19.2 g. (18%) of VII m.p. 285° and an additional 10.2 g. of VIII (53% total yield). A sample of VII was extracted again with boiling chloroform leaving colorless crystals, m.p. 289-290°; positive SH test (10) and two absorption peaks at 5.85 and 5.92 μ.

Anal. (VII) Calcd. for $C_6H_9N_5SO_2$: C, 33.48; H, 4.22; N, 32.54; S, 14.89. Found: C, 33.10; H, 4.43; N, 32.40; S, 15.21.

Recrystallization of a sample of VIII from ethanol gave flat plates, m.p. 199-200°; negative SH test, one carbonyl absorption band at 5.95 μ and no reaction with 1 *N* sodium hydroxide at room temperature.

Anal. (VIII) Calcd. for $C_6H_7N_5SO$: C, 36.54; H, 3.57; N, 35.51; S, 16.26. Found: C, 36.71; H, 3.78; N, 35.39; S, 16.21.

4-Acetamido-3-amino-5-mercapto-*s*-triazole (X).

From VIII.

A mixture of 6 g. (0.03 mole) of VIII in 70 ml. of 1.29 *N* sodium hydroxide (0.09 mole) was heated on a steam bath for 2 hours, filtered, cooled and treated with 3.45 ml. (0.06 mole) of glacial acetic acid. After cooling the product was filtered, washed with water and dried leaving 3.2 g. (62%), m.p. 240-270°. Three recrystallizations raised the melting point to 284-285°. The product gave a positive test for a free SH group and the infrared curve showed a primary amine doublet at 2.95 and 3.05 μ.

Anal. Calcd. for $C_4H_7N_5SO$: C, 27.74; H, 4.08; N, 40.44; S, 18.52. Found: C, 27.80; H, 4.18; N, 40.54; S, 18.47.

From IX.

A suspension of 4.65 g. (0.03 mole) of IX in 70 ml. of 1.29 *N* sodium hydroxide (0.09 mole) was heated and worked up as above. The first crop was crude material, m.p. 235-240°, and was set aside. Concentration of the mother liquor under vacuum to half volume and cooling gave 2.3 g. of colorless crystals, m.p. 285°, which showed no depression of melting point when mixed with the product from VIII above.

3-Amino-6-methyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole (IX).

From VII.

One gram of VII was treated with 10 ml. of phosphoryl chloride and refluxed for 1 hour. The mixture was freed of excess phosphoryl chloride under vacuum, dissolved in water and neutralized with dilute alkali. The tan precipitate was filtered, washed with water and recrystallized from dilute ethanol with decolorization to give 0.5 g. of colorless rods, m.p. 305-308° dec.

From VIII.

A suspension of 39.4 g. (0.2 mole) of VIII in 500 ml. of 1 *N* hydrochloric acid was heated on a steam bath for 1.5 hours, neutralized with 49.2 g. of sodium acetate and cooled. The product was filtered, washed with water and dried leaving pink crystals weighing 26 g. (84%), m.p. 300-303°. A sample recrystallized from water gave colorless crystals, m.p. 301-303°.

From X.

A mixture of 0.87 g. (0.005 mole) of X and 10 ml. of phosphoryl chloride was refluxed and worked up as described for the preparation from VII above. The product (0.3 g., m.p. 305°) was identical to the above two by mixed melting point and infrared absorption curves. Spectral data and analyses on the product melting at 301-303° are as follows. The n.m.r., using trifluoroacetic acid as solvent showed

two singlets at 7.18 and -1.66 τ in a ratio of 1:1, the infrared revealed the guanidino type amine peaks at 3.10 and 3.28 μ; and the ultraviolet had one absorption band at λ max 265 mμ (ϵ = 2,480).

Anal. Calcd. for $C_4H_8N_6S$: C, 30.95; H, 3.25; N, 45.13; S, 20.66. Found: C, 30.95; H, 3.61; N, 45.36; S, 20.62.

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