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A New Synthesis of 3,4,5-Triamino-4H-1,2,4-triazole (Guanazine)

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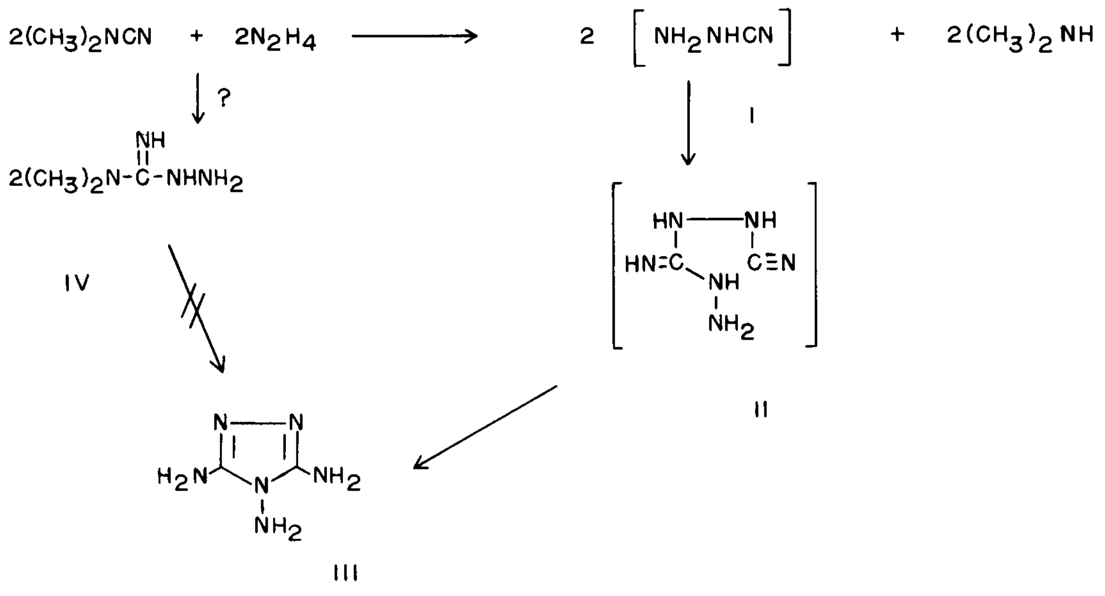
Guanazine has been prepared in low yield from thiosemicarbazide and lead oxide (1). Its salts have been prepared from cyanogen bromide (2) or cyanogen chloride (3) and hydrazine, and from cyanogen bromide and diaminoguanidine but are difficult to convert to the free base (2). It has now been found that hydrazine displaces dimethylamine from dimethylcyanamide to give a 75% yield of the free base of guanazine.

The reaction proceeds presumably by way of the reactive intermediate carbazonitrile I which dimerizes stepwise via 1-amino-3-cyanamidoguanidine (II) to guanazine (III). Support for this route over the alternative requiring 1,1-dimethyl-3-aminoguanidine (IV) as an intermediate was provided by the demonstration that under similar conditions 1,1-dimethyl-3-aminoguanidine (IV) did not self-condense to give guanazine (III). It is also likely that the other known methods of synthesis proceed via this same pathway, *e.g.* conversion of thiosemicarbazide by lead oxide to carbazonitrile, direct formation of carbazonitrile from cyanohalides and hydrazine, and formation of 1-amino-3-cyanamidoguanidine (II) from diaminoguanidine and cyanogen bromide.

The best yields of guanazine were obtained when hydrazine and an equimolar amount of dimethylcyanamide were heated on a steam bath for 20 hours. Slightly lower yields were obtained when the reaction was carried out in absolute ethanol or t-butyl alcohol. The basic gas evolved from the reaction was absorbed in water and shown to be dimethylamine by the sodium nitroprussideacetaldehyde spot test (4). Neither ammonia nor hydrazine gives a positive test with this reagent. The hydrochloride, hydrobromide and sulfate salts of guanazine were readily prepared from aqueous solutions of the base since the salts are less water soluble than the base.

Their melting points agree with those reported (2,3). When hydrazine hydrate and dimethylcyanamide were allowed to react, dark red solutions containing both N,N-dimethylurea (by hydrolysis of the dimethylcyanamide) and decreased yields of guanazine were obtained.

The guanazine prepared from dimethylcyanamide and hydrazine was shown to be identical (mixed melting point and infrared spectra) with that formed from thiosemicarbazide and lead oxide (1). Further-



more the hydrochloride salt was identical (mixed melting point and infrared spectra) with that formed from cyanogen chloride and hydrazine (3).

Although the synthesis of the mono- and dibenzylidine derivatives have been reported, no structural assignments have been made (1,2). Repetition of the synthesis gave both the mono- and dibenzylidene derivatives as described. Examination of these by n.m.r. in hexamethylphosphoramide revealed, for the monobenzylidene derivative, four identical NH protons (two identical NH_2 groups) at 4.03 τ, the 3,4,5 phenyl protons centering at 2.40 τ, the 2,6 phenyl protons centering at 1.87 τ, and a single vinyl proton at 0.58 τ. The only structure compatible with these data is 3,5-diamino-4-benzylideneamino-4H-1,2,4-triazole. For the dibenzylidene derivative, there were two identical NH protons (one NH_2 group) at 3.08 τ, six 3,4,5 phenyl protons at 2.30 τ, four 2,6 phenyl protons at 1.80 τ, and two different vinyl protons at 0.38 and 0.58 τ. The phenyl protons of the dibenzylidene derivatives were more smeared than those of the monobenzylidene derivative, indicating a superimposition of two slightly different phenyl groups. The structure for the dibenzylidene derivative is therefore 5-amino-3,4-dibenzylideneamino-4H-1,2,4-triazole.

EXPERIMENTAL

Melting points were observed in liquid-heated capillary tubes and are corrected. Infrared spectra were compared on a Perkin-Elmer Infracord, Model 137B spectrophotometer using potassium bromide discs. The n.m.r. spectra were determined in hexamethylphosphoramide with internal tetramethylsilane on a Varian A-60 spectrometer.

Guanazine.

A mixture of 74 g. (1.0 mole) of dimethylcyanamide (American Cyanamid Co.) and 32.05 g. (1.0 mole) of hydrazine (Eastman 95 + %) was heated for 20 hours on a steam bath. The resulting solid mass was dissolved in the minimum amount of hot water, decolorized with carbon and treated with four volumes of ethanol. On cooling, faintly pink needles, 28.2 g. (50%), m.p. 260-261° dec., were obtained. Addition of more alcohol to the mother liquor and long standing produced a second crop of 14 g., m.p. 256-257° dec. giving a combined crude yield of 42.2 g. (75%). A sample recrystallized for analysis from aqueous ethanol melted at 262-263° dec.

Anal. Calcd. for $C_2H_6N_6$: C, 21.05; H, 5.30; N, 73.65. Found: C, 21.34; H, 5.35; N, 73.00.

The monohydrochloride salt was prepared by dissolving 2.2 g. (0.02 mole) of guanazine in 30 ml. of warm water and titrating to *p*H 7 with 1.7 ml. (0.02 mole) of concentrated hydrochloric acid. On cooling, filtering and washing with ethanol, there was obtained 2.1 g. of colorless rosettes, m.p. 276-277°, (lit. (3) m.p. 260-261°).

Anal. Calcd. for $C_2H_7N_6Cl$: C, 15.95; H, 4.68; N, 55.83; Cl, 23.55. Found: C, 16.29; H, 4.71; N, 55.86; Cl, 23.77.

The monohydrobromide salt was prepared in the same manner from 48% hydrobromic acid, giving colorless crystals, m.p. 271° dec. (lit. (2) m.p. 267°). The acid sulfate salt prepared similarly, gave colorless needles, m.p. 288-289° dec. (uncorrected m.p. 275°, lit (2) m.p., 275°).

Attempted Formation of Guanazine by Self-Condensation of 1,1-Dimethyl-3-aminoguanidine.

A suspension of 1 g. (0.004 mole) of 1,1-dimethyl-3-aminoguanidine hydriodide (5) in 10 ml. of ethanol was treated with 0.75 ml. of 6 N sodium hydroxide (0.0045 mole). The clear solution was heated on a steam bath under a reflux condenser for 72 hours, during which time no trace of evolved dimethylamine was detected. On cooling, no crystals of the alcohol insoluble guanazine appeared.

3,5-Diamino-4-benzylideneamino-1,2,4-triazole and 5-Amino-3,4-dibenzylidene-1,2,4-triazole.

Using the procedure of Stollé and Dietrich (1), both derivatives were obtained from the same reaction mixture. The monobenzylidene derivative separated as pale yellow needles from ethanol melting at 194-195° (lit. (1) m.p. 184°).

Anal. Calcd. for $C_9H_{10}N_6$: C, 53.45; H, 4.98; N, 41.56. Found: C, 53.62; H, 5.48; N, 41.14.

The dibenzylidene derivative when crystallized from aqueous methanol came out as yellow needles, m.p. 200-201° (lit. (1) m.p. 194°).

Anal. Calcd. for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.07; H, 5.01; N, 29.01.

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