

Pyridazines. LIII. Hydrazinolysis of Some *s*-Triazolo[4,3-*b*]pyridazines

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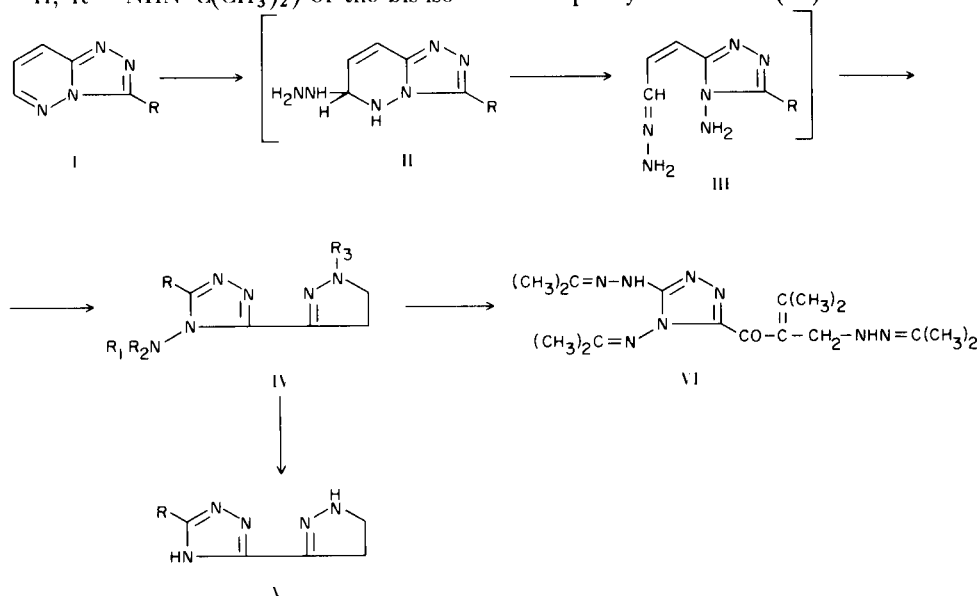
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Following our observations that the five-membered ring of some quaternized *s*-triazolo[4,3-*b*]pyridazines is cleaved under the influence of bases (1) we have investigated also the action of bases on other azoloazines and azinoazines with bridgehead nitrogen (2,3). However, in the last mentioned cases the six-membered ring was attacked and ring opening was followed by the isomerization of the unsaturated side chain.

We have now found that hydrazinolysis of *s*-triazolo[4,3-*b*]pyridazines follows a somewhat different pattern giving rise to 2'-pyrazolin-3'-yl-1,2,4-triazoles (IV). The products can be envisaged as resulting from addition of hydrazine to the 6C=5N bond (II), followed by bond cleavage (III) and cyclization of the hydrazone to the pyrazoline ring. The products were characterized by their acetyl or isopropylidene derivatives and their nmr spectra, which exhibit an AA'XX' pattern for the pyrazolinyl part, are consistent with the proposed structures.

In a similar manner 3-chloro-*s*-triazolo[4,3-*b*]pyridazine was transformed into the 4-amino-5-hydrazino compound (IV, R₁ = R₂ = R₃ = H, R = NHNH₂) which reacted, depending upon the quantity of acetone employed, to give either the isopropylidenehydrazone derivative (IV, R₁ = R₂ = R₃ = H, R = NHN=C(CH₃)₂) or the bis-isopropylidene compound (IV, R₃ = H, R = NHN=C(CH₃)₂, R₁ R₂ = (CH₃)₂C=) or the tetra-isopropylidene derivative (VI), the latter being formed by ring opening of the pyrazoline part of the molecule. Moreover, the 5-hydrazino group in the 4-amino-5-hydrazino compound (IV, R = NHNH₂, R₁ = R₂ = R₃ = H) could be transformed with one equivalent of nitrous acid into an azido group (IV, R = N₃, R₁ = R₂ = R₃ = H). Similarly, the 4-amino-5-hydrazino compound (IV, R = NHNH₂, R₁ = R₂ = R₃ = H) when treated with two equivalents of nitrous acid, or the 4-amino-5-azido compound (IV, R = N₃, R₁ = R₂ = R₃ = H) when reacting with equivalent amount of nitrous acid, both afforded the 5-azido derivative (V, R = N₃). Finally, the parent compound (V, R = H) could be prepared by nitrosation of the 4-amino derivative (IV, R = R₁ = R₂ = R₃ = H).

The above mentioned ring opening and formation of a pyrazole ring has been observed also with pyrimidines or pyrimidine nucleosides (4-7), as well as with some condensed pyrimidines, such as pyrazolo[3,4-*d*]pyrimidines (8) and pteridines (9). Similarly, quinoxalin-2(1*H*)one was converted with hydrazine into 2-methylbenzimidazole and *o*-phenylenediamine (10).



EXPERIMENTAL (11)

4-Amino-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (IV, R = R₁ = R₂ = R₃ = H).

A mixture of *s*-triazolo[4,3-*b*]pyridazine (I, R = H) (1.0 g.) and hydrazine hydrate (10 ml. of 100%) was heated under reflux for 10 hours. Upon evaporation *in vacuo* the residual oil was cooled and treated with ethanol (10 ml.) and left at room temperature for several hours. The product was the collected and crystallized from ethanol (yield 48%), m.p. 165°; ir (potassium bromide): 3215 cm⁻¹ (NH₂); nmr (DMSO-d₆, 122°): τ = 6.78 (m, -CH₂CH₂-), 1.78 (s, H₅), 4.0 (s, broad, NH).

Anal. Calcd. for C₅H₈N₆: C, 39.46; H, 5.30; N, 55.24. Found: C, 39.91; H, 5.15; N, 54.96.

The compound (0.76 g.) when heated with acetic anhydride (5 ml.) under reflux for 2 hours, formed a triacetyl derivative (IV, R = H, R₁ = R₂ = R₃ = CH₃CO), in 73% yield, m.p. 238-239° (from ethanol); ir (potassium bromide): 1727 and 1754 cm⁻¹ (CH₃CO-); nmr (DMSO-d₆, 80°): τ = 6.40 (m, -CH₂CH₂-), 1.21 (s, H₅), 7.71 (s, 6H of two COCH₃), 7.90 (s, 3H, CH₃CO).

Anal. Calcd. for C₁₁H₁₄N₆O₃: C, 47.48; H, 5.07. Found: C, 47.47; H, 4.73.

With acetone (reflux, 30 minutes) the isopropylidene derivative (IV, R = R₃ = H, R₁R₂ = (CH₃)₂C=), m.p. 155° (from ethanol and *N,N*-dimethylformamide, 2:1) was obtained.

Anal. Calcd. for C₈H₁₂N₆: C, 49.98; H, 6.29; N, 43.72. Found: C, 49.87; H, 5.96; N, 43.48.

4-Amino-5-hydrazino-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (IV, R = NHNH₂, R₁ = R₂ = R₃ = H).

The compound was prepared from I (R = Cl) in a similar manner as described above in 61% yield; m.p. 196-198°; nmr (DMSO-d₆, 119°): τ = 6.88 (m, -CH₂CH₂-), 4.45 (broad, NH).

Anal. Calcd. for C₅H₁₀N₈: C, 32.96; H, 5.53; N, 61.51. Found: C, 33.32; H, 5.31; N, 61.13.

The compound formed a hexaacetyl derivative (IV, R₁ = R₂ = R₃ = CH₃CO, R = (CH₃CO)₂N-N(COCH₃-)) when heated with excess of acetic anhydride for 2 hours; m.p. 182-183° (from ethanol and *N,N*-dimethylformamide, 2:1); nmr (DMSO-d₆, 100°): τ = 6.42 (m, -CH₂CH₂-), 7.60 (s, 6H, 2 CH₃CO), 7.67 (s, 6H, 2CH₃CO), 7.77 (s, 3H, CH₃CO), 7.90 (s, 3H, CH₃CO).

Anal. Calcd. for C₁₇H₂₂N₈O₆: C, 46.99; H, 5.10; N, 25.79. Found: C, 46.83; H, 5.13; N, 25.98.

With acetone the following isopropylidene derivatives could be prepared:

a) The Isopropylidenehydrazino Compound (IV, R = (CH₃)₂C=NHN-, R₁ = R₂ = R₃ = H).

A mixture of the starting compound (IV, R = NHNH₂, R₁ = R₂ = R₃ = H) (0.364 g., 0.002 mole), methanol (5 ml.) and acetone (0.108 g., 0.002 mole) was heated under reflux for 30 minutes. Upon cooling, the separated product was collected and crystallized from ethanol (61% yield), m.p. 202°; nmr (DMSO-d₆, 100°): τ = 6.82 (m, -CH₂CH₂-), 4.20 (broad, NH), 8.03 (s, CH₃) and 8.07 (s, CH₃).

Anal. Calcd. for C₈H₁₄N₈: C, 43.23; H, 6.35; N, 50.42. Found: C, 43.55; H, 6.56; N, 50.74.

b) The bis-Isopropylidene Derivative (IV, R = (CH₃)₂C=NNH-, R₃ = H, R₁R₂ = (CH₃)₂C=).

This compound was obtained in essentially the same way as above, but using 2 equivalents of acetone and the mixture was heated 2 hours under reflux. The oily residue after evaporation of

the solvent was treated with ethyl acetate and upon standing on ice overnight the separated crystals were collected and crystallized from a mixture of chloroform and *n*-hexane (1:4), m.p. 125-127° (49% yield); mass spectrum: M⁺: calcd. 262.1654, found 262.1652.

c) 4-Isopropylideneamino-5-isopropylidenehydrazino-3-(α -isopropylidene- β -isopropylidenehydrazinopropionyl)-1,2,4-triazole (VI).

The starting compound (182 mg.) and acetone (5 ml.) were heated under reflux for 3 hours. The solvent was evaporated *in vacuo* and the residue (320 mg.) was crystallized twice from ethanol, m.p. 195°; ir (potassium bromide): 1712 cm⁻¹ (CO). Mass spectrum: M⁺ = 360; nmr (DMSO-d₆): τ = 6.75 (s, CH₂), 8.15 (s, -N=C(CH₃)₂), 7.76 and 7.80 (s, -N=C(CH₃)₂), 8.82 (s, C=C(CH₃)₂).

Anal. Calcd. for C₁₇H₂₈N₈O: C, 56.63; H, 7.83; N, 31.11. Found: C, 56.68; H, 7.34; N, 30.95.

4-Amino-5-phenyl-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (IV, R = C₆H₅, R₁ = R₂ = R₃ = H).

The same procedure as described above for the synthesis of IV (R = R₁ = R₂ = R₃ = H) was applied, but starting with 3-phenyl-*s*-triazolo[4,3-*b*]pyridazine. The product had m.p. 252-253° (from ethanol) (yield 29%). Mass spectrum: M⁺ calcd. 228.1123, found 228.1116; nmr (DMSO-d₆, 126°): τ = 6.75 (m, -CH₂CH₂-), 1.90 and 2.55 (m, C₆H₅-), 3.75 (broad, NH).

The product formed a triacetyl derivative (IV, R = C₆H₅, R₁ = R₂ = R₃ = CH₃CO), m.p. 214° (from ethanol); ir (potassium bromide): 1748 and 1727 cm⁻¹ (COCH₃); mass spectrum: M⁺ calcd. 354.1440, found 354, 1417; nmr (DMSO-d₆): τ = 6.35 (m, -CH₂CH₂-), 2.40 (m, C₆H₅), 7.65 (s, 6H, 2 COCH₃), 7.86 (s, CH₃CO).

3-(2'-Pyrazolin-3'-yl)-1,2,4-triazole Hydrochloride (V, R = H. HCl).

The 4-amino compound (IV, R = R₁ = R₂ = R₃ = H) (0.3 g.) was dissolved in water (3 ml.) and treated with concentrated hydrochloric acid (1 ml.) and thereafter with a solution of sodium nitrite (0.1 g. in 1 ml. water). After standing on ice for 1 hour, the product was collected and crystallized from ethanol (yield 63%), m.p. 198-199°.

Anal. Calcd. for C₅H₈ClN₅: C, 34.60; H, 4.65; N, 40.34. Found: C, 34.87; H, 4.64; N, 40.20.

5-Azido-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (V, R = N₃).

A. The compound was obtained from IV (R = NHNH₂, R₁ = R₂ = R₃ = H) in the manner as described above but employing 2 equivalents of sodium nitrite, m.p. 153-154° (from ethanol) (47% yield); ir (potassium bromide): 2151 cm⁻¹ (N₃); mass spectrum: M⁺ calcd. 178.0707, found 178.0707.

B. The 5-azido-4-amino compound (IV, R = N₃, R₁ = R₂ = R₃ = H) when treated with one equivalent of sodium nitrite in acid solution afforded the same product as described under A.

4-Amino-5-azido-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (IV, R = N₃, R₁ = R₂ = R₃ = H).

The compound was prepared according to the above procedure from equivalent amounts of IV (R = NHNH₂, R₁ = R₂ = R₃ = H) and sodium nitrite, m.p. 167°; ir (potassium bromide): 2160 cm⁻¹ (N₃); mass spectrum: M⁺ calcd. 193.0831, found 193.0830; nmr (DMSO-d₆, 61°): τ = 6.32 (m, -CH₂CH₂-), 4.0 (broad, NH).

4,5-Diamino-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (IV, R = NH₂, R₁ = R₂ = R₃ = H).

In a boiling solution of the 4-amino-5-azido compound (IV,

R = N₃, R₁ = R₂ = R₃ = H) (0.193 g.) in ethanol (10 ml.) hydrogen sulfide was introduced for 20 minutes. The separated product (0.116 g., 69%) was crystallized from ethanol and *N,N*-dimethylformamide (3:1), m.p. 198-200°; mass spectrum: M⁺ calcd. 167.0889, found 167.0926.

5-Amino-3-(2'-pyrazolin-3'-yl)-1,2,4-triazole (V, R = NH₂).

The compound was prepared by the above procedure from the 5-azido derivative (V, R = N₃), m.p. 230-231° (from ethanol and *N,N*-dimethylformamide, 5:1); mass spectrum: M⁺ 152.

Anal. Calcd. for C₅H₈N₆: C, 39.46; H, 5.30; N, 55.24. Found: C, 39.22; H, 5.52; N, 55.58.

3,6-Dihydrazino-*s*-triazolo[4,3-*b*]pyridazine.

3,6-Dichloro-*s*-triazolo[4,3-*b*]pyridazine (12) (5.0 g.) and hydrazine hydrate (50 ml. of 100%) were heated under reflux for 10 hours. After standing on ice overnight the product which separated was collected and washed with water. It was crystallized from 50% ethanol (yield 42%), m.p. 240°; nmr (DMSO-d₆), 150°): τ = 3.45 (d, H₇), 2.51 (d, H₈), 6.8 (broad, NH); J_{7,8} = 9.4 Hz.

Anal. Calcd. for C₅H₈N₈: C, 33.33; H, 4.48; N, 62.20. Found: C, 33.38; H, 4.50; N, 61.90.

3,6-Diazido-*s*-triazolo[4,3-*b*]pyridazine.

The above dihydrazino compound (1 g.) was suspended in hydrochloric acid (5 ml. of 1 *N*), the mixture cooled on ice and a solution of sodium nitrite (0.8 g. in 8 ml. of water) was added dropwise. The product was collected and crystallized from ethanol (yield 63%), m.p. 151-153°; ir (potassium bromide): 2174 cm⁻¹ (N₃); nmr (TFAA): τ = 2.70 (d, H₇), 1.75 (d, H₈); J_{7,8} = 9.5 Hz.

Anal. Calcd. for C₅H₂N₁₀: C, 29.72; H, 0.99. Found: C, 30.20; H, 1.42.

3,6-Diamino-*s*-triazolo[4,3-*b*]pyridazine.

Hydrogen sulfide was bubbled into a boiling solution of the above diazido compound (1 g.) in ethanol (20 ml.) during 15 minutes. Upon cooling the product was separated and crystallized

from water (58% yield), m.p. over 300°; ir (potassium bromide): 3344 and 3205 cm⁻¹ (NH₂).

Anal. Calcd. for C₅H₆N₆: C, 39.99; H, 4.03; N, 55.98. Found: C, 39.59; H, 4.08; N, 56.30.

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