New Syntheses of Condensed Heterocycles from Isoxazole Derivatives. III. *s*-Triazolo[4,3-*b*]pyridazines.

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The chemistry of the *s*-triazolo[4,3-*b*]pyridazine ring system has been studied for many years and a number of general synthetic schemes are available (1,2).

In connection with our continuing interest in isoxazole chemistry, we now wish to report a new synthesis of substituted *s*-triazolo[4,3-*b*]pyridazines which employs an isoxazolyltriazole as the precursor. The sequence consists of reductive ring opening of the isoxazole (IIIa,b and VIII) to the intermediate aminoketones (IV and IX) followed by treatment with alkali to give the substituted *s*-triazolo[4,3-*b*]pyridazine.

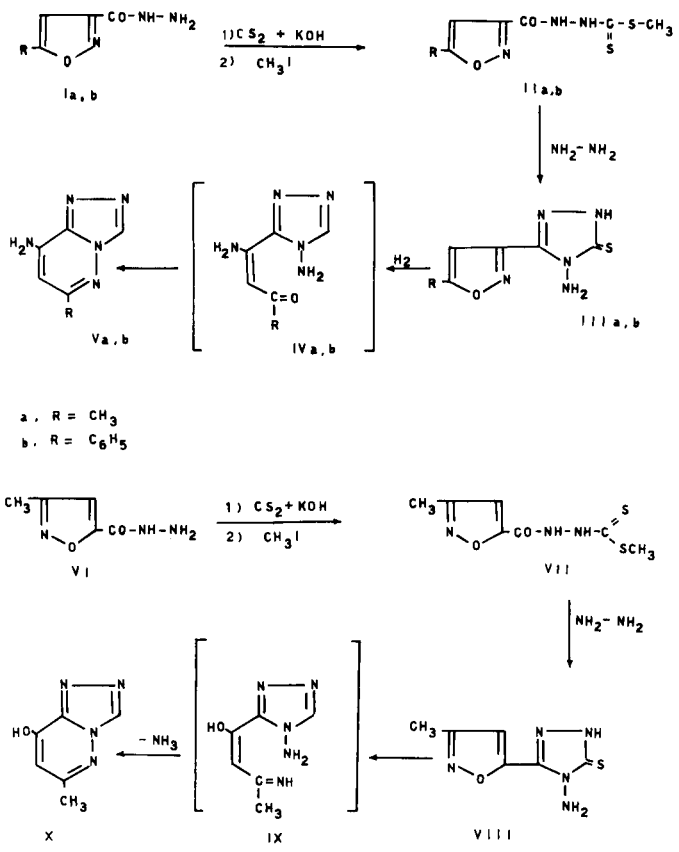
The isoxazolyl-triazoles of type III, were prepared *via* I → II → III and the reductive ring-opening of isoxazoles was carried out with W2 Raney Nickel in a Parr apparatus. By the route described, 8-amino-6-methyl- and 6-phenyl-*s*-triazolo[4,3-*b*]pyridazine (Va,b) and 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (X) were obtained.

The nmr spectrum of compound X showed absorption at δ 6.73 attributable to a OH proton rather than to a NH proton; the ir spectrum (potassium bromide) showed two weak bands at 2950 (NH) and at 1700 cm^{-1} (CO) and a wide band at about 2500 cm^{-1} (C-OH). This fact seems to confirm that the tautomeric equilibrium (C=O) ⇌ (-OH) is strongly displaced in the direction of the hydroxy form.

With regard to compounds of type IIIa,b and VII the structure of 1*H*-3-substituted-4-amino-*s*-triazole-5-thione was recently reported (3), while Hoggarth (4) reported the thiol structure for the same type of compounds.

To confirm whether the thione or thiol structure predominated, the uv spectra of IIIa, VIII and 1*H*-4-amino-3-phenyl-*s*-triazole-5-thione (4) λ max 252 and 288 (sh), 250 and 296 (sh), 250 and 285 (sh) respectively and those of their methyl derivatives (λ max 260, 274 and 256 respectively) were compared. The different pattern of uv spectra confirms the thione structure for the compounds IIIa,b and VIII; this structure was also supported by nmr spectra which showed the NH proton.

The structures of the compounds were determined by ir, uv, nmr spectra and by the fact that Va and X were identical in all respects (mixture m.p., ir, nmr) with authentic sample (5).



EXPERIMENTAL

All melting points (Kofler) are uncorrected; ir (nujol mull), Perkin-Elmer Infracord 137 spectrophotometer; uv (ethanol), Beckmann DB (with recorder) spectrophotometer; nmr, Jeol C-60H spectrometer (TMS as internal reference).

Potassium Isoxazolyldithiocarbazates.

Isoxazolylcarboxylic acid hydrazide (0.01 mole) was added to a solution of potassium hydroxide (0.01 mole) in 100 ml. of absolute ethanol; the mixture was stirred for 30 minutes with carbon disulfide (0.012 mole) and the yellow solid was collected and washed with dry ether (yield *ca.* 92% for all three compounds described below).

Methyl Isoxazolyldithiocarbazates (IIa, IIb, VII).

Methyl iodide (0.01 mole) was added to a stirred solution of the potassium isoxazolyldithiocarbazate (0.01 mole) in 50 ml. of water. After one hour the white solid was filtered, washed with water and recrystallized.

Methyl 5-Methyl-3-isoxazolyldithiocarbazate (IIa).

White crystals from ethanol-water, m.p. 175° (yield 68%).

Anal. Calcd. for $C_7H_9N_3O_2S_2$: C, 36.37; H, 3.92; N, 18.18. Found: C, 36.81; H, 4.02; N, 17.90.

Methyl 5-Phenyl-3-isoxazolyldithiocarbazate (IIb).

White crystals from ethanol-water, m.p. 148°, (yield 70%).

Anal. Calcd. for $C_{12}H_{11}N_3O_2S_2$: C, 49.15; H, 3.78; N, 14.33. Found: C, 48.88; H, 3.93; N, 13.99.

Methyl 3-Methyl-5-isoxazolyldithiocarbazate (VII).

White crystals from benzene, m.p. 161°, (yield 78%).

Anal. Calcd. for $C_7H_9N_3O_2S_2$: C, 36.37; H, 3.92; N, 18.18. Found: C, 36.16; H, 4.18; N, 17.92.

1*H*-4-Amino-3-(3- and 5-isoxazolyl)-*s*-triazole-5-thione.

The solution of methyl isoxazolyldithiocarbazate (0.01 mole) in 50 ml. of ethanol was refluxed for 5 hours with hydrazine (0.012 mole). The precipitated was collected, dissolved in 10% aqueous alkali, the solution was acidified with dilute hydrochloric acid and the precipitated solid was recrystallized.

1*H*-4-Amino-3-(5-methyl-3-isoxazolyl)-*s*-triazole-5-thione (IIIa).

White needles from ethanol, m.p. 190-191° (yield 74%); ir cm^{-1}, 3320 and 3200 (NH_2); 3160 (NH); uv mμ, λ max 252 and 288 (sh); nmr (DMSO) δ, 2.50 (s, 3H, CH_3); 5.78 (s, 2H, NH_2); 6.72 (s, 1H, CH); 14.15 (broad, 1H, NH).

Anal. Calcd. for $C_6H_7N_5OS$: C, 36.55; H, 3.58; N, 35.52. Found: C, 36.20; H, 3.88; N, 35.41.

4-Amino-5-methylthio-3-(5-methyl-3-isoxazolyl)-*s*-triazole.

Colorless needles from benzene, m.p. 146°; uv mμ, λ max 260; ir cm^{-1}, 3180 and 3320 (NH_2); nmr (DMSO) δ, 2.52 and 2.63 2x (s, 3H, CH_3); 6.21 (s, 2H, NH_2); 6.82 (s, 1H, CH).

Anal. Calcd. for $C_7H_9N_5OS$: N, 33.17. Found: N, 33.03.

1*H*-4-Amino-3-(5-phenyl-3-isoxazolyl)-*s*-triazole-5-thione (IIIb).

White needles from ethanol, m.p. 193-194° (yield 72%); uv mμ λ max 261; ir cm^{-1}, 3330 and 3180 w (NH_2), 3130 (NH); nmr (DMSO) δ, 5.94 (s, 2H, NH_2); 7.50-8.20 (m, 5H, C_6H_5); 7.58 (s, 1H, CH); 13.80 (broad, 1H, NH).

Anal. Calcd. for $C_{11}H_9N_5OS$: C, 50.96; H, 3.50; N, 27.02. Found: C, 50.74; H, 3.50; N, 27.08.

4-Amino-5-methylthio-3-(5-phenyl-3-isoxazolyl)-*s*-triazole.

White needles from ethanol, m.p. 224-225°; uv mμ, λ max 274; nmr (DMSO) δ, 2.70 (s, 3H, CH_3); 6.30 (s, 2H, NH_2); 7.40-8.65 (m, 5H, C_6H_5); 7.65 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.74; H, 4.06; N, 25.63. Found: C, 52.84; H, 4.19; N, 25.42.

1*H*-4-Amino-3-(3-methyl-5-isoxazolyl)-*s*-triazole-5-thione (VIII).

White needles from water, m.p. 195° (yield 73%); uv mμ, λ max 250 and 296 (sh); ir cm^{-1}, 3330 and 3210 (NH_2); 3100 (NH); nmr (DMSO) 2.37 (s, 3H, CH_3); 5.91 (s, 2H, NH_2); 7.22 (s, 1H, CH); 13.90 (broad, 1H, NH).

Anal. Calcd. for $C_6H_7N_5OS$: C, 36.55; H, 3.58; N, 35.52. Found: C, 36.24; H, 3.55; N, 35.68.

4-Amino-5-methylthio-3-(3-methyl-5-isoxazolyl)-*s*-triazole.

White needles from ethanol, m.p. 212°; uv mμ, λ max 274; ir cm^{-1}, 3240, 3250 w (NH_2); nmr (DMSO) δ, 2.34 and 2.64 2x (s, 3H, CH_3); 6.28 (s, 2H, NH_2); 7.15 (s, 1H, CH).

Anal. Calcd. for $C_7H_9N_5OS$: N, 33.17. Found: N, 32.94.

1*H*-4-Amino-3-phenyl-*s*-triazole-5-thione.

Uv mμ, λ max 250 and 285 (sh); nmr (DMSO) δ, 5.85 (s, 2H, NH_2), 7.54-8.25 (m, 5H, C_6H_5), 14.10 (broad, 1H, NH).

4-Amino-5-methylthio-3-phenyl-*s*-triazole (4).

Uv mμ, λ max 256; nmr (DMSO) δ, 2.64 (s, 3H, CH_3), 6.22 (s, 2H, NH_2), 7.52-8.35 (m, 5H, C_6H_5).

s-Triazolo[4,3-*b*]pyridazines (Va, Vb, X).

Compound IIIa or VIII (0.01 mole) in 200 ml. of ethanol or IIIb in 200 ml. of methanol was hydrogenated with 2 g. of W2 Raney-Ni, in a Parr apparatus at 45-50 psi at room temperature.

After 18 hours the catalyst was removed and the solution was evaporated under reduced pressure; 20 ml. of 20% potassium hydroxide was added and the mixture was stirred for 15 minutes at room temperature. The solid was collected, washed with water and recrystallized.

8-Amino-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (Va).

White crystals from water, m.p. 222° (yield 49%; uv, ir and nmr spectra were identical with those of an authentic sample obtained by another method (5).

Anal. Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.96. Found: C, 47.99; H, 4.78; N, 46.70.

8-Amino-6-phenyl-*s*-triazolo[4,3-*b*]pyridazine (Vb).

White needles from ethanol-water, m.p. 274-275° (yield 56%); ir cm^{-1}, 3320, 3260, 3100, 1660; nmr (DMSO) δ, 6.48 (s, 1H, CH); 7.20-7.80 (m, 7H, C_6H_5 and NH_2); 9.32 (s, 1H, CH).

Anal. Calcd. for $C_{11}H_9N_5$: C, 62.55; H, 4.30; N, 33.16. Found: C, 62.43; H, 4.33; N, 33.50.

8-Hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (X).

Needles from acetic acid, m.p. 303-304° (yield 59%); nmr (DMSO) δ, 2.43 (s, 3H, CH_3); 6.40 (s, 1H, C_7H); 6.73 (broad, 1H, OH); 9.45 (s, 1H, C_3H); ir (potassium bromide) cm^{-1}, 2950 (NH); 2500 broad (OH); 1700 (CO); uv mμ, λ max 290; uv, ir and nmr spectra were identical with those of an authentic sample obtained by another method (5).

Acknowledgment.

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