The Synthesis of Derivatives of the Novel Pyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine Ring System.

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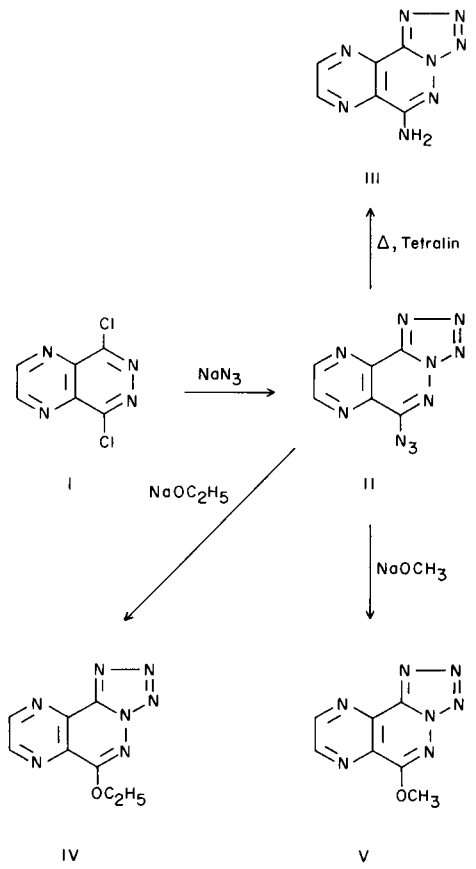
An examination of the literature revealed that neither the parent ring system nor a singlet substituted derivative of pyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine had been reported. With quantities of 5,8-dichloropyrazino-[2,3-*d*]pyridazine (I) (3) in hand it appeared feasible to prepare 6-azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (II). Thus when I was treated with sodium azide (2 moles) using dimethylsulfoxide as the solvent, II was obtained in 93% yield. The structure of II was established from an examination of the infrared spectrum. Strong absorption bands at 2160 and 2125 cm^{-1} were present characteristic of the azido stretching vibrations. These azido stretching vibrations disappeared when the spectrum of II was then taken in DMF as reported by Stanovnik and Tišler (4) thereby confirming the presence of at least one azido group. It is possible that the tetrazole ring may exhibit ring-chain tautomerism with the azido group. This has been reported by Stanovnik and Tišler (4), Temple and Montgomery (5) and Boyer and Miller (6). However, Itai and Kamiya (7) obtained 6-azidotetrazolo-[1,5-*b*]pyridazine when 3,6-dichloropyridazine was treated with sodium azide. Our reaction appears to be analogous. Additional evidence that II is correctly formulated is obtained from the NMR spectrum which shows two doublets centered at 9.26 δ. If the bis-azide were present, the molecule would be symmetrical and therefore C_2-H and C_3-H would show a singlet in the NMR spectrum. The tetrazole ring is present in compound II as well as in III, IV and V since absorption bands characteristic of the tetrazole ring (8) were observed (See Experimental). Additional evidence for the existence of the tetrazole ring in II was obtained by the conversion of II into III, IV and V.



6-Azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (II) was allowed to react with either sodium methoxide in methanol or sodium ethoxide in ethanol to give 6-methoxypyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (V) and 6-ethoxypyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (IV), respectively. These two nucleophilic displacement reactions of the azido group took place readily, giving yields of 70% of IV and 75% of V. When II was heated with tetralin, the azido group was reduced to the amino group and the product, 6-aminopyrazino[2,3-*d*]tetrazolo-[4,5-*b*]pyridazine (III) was obtained in 50% yield.

An examination of the infrared spectra of III, IV, and V revealed the absence of the azido stretching vibrations at 2160 and 2125 cm^{-1}, indicating that the azido group was no longer present. This is taken as additional evidence that in compounds III, IV and V the tetrazole ring is present rather than the tautomeric azido group. Furthermore, the strong infrared absorption bands characteristic of the tetrazole ring in the 1110-1000 cm^{-1} and the 790-730 cm^{-1} (8) region are present. Therefore, the evidence for the structures of II, III, IV and V as pyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazines is complete.

EXPERIMENTAL (9)

6-Azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (II).

To a magnetically stirred mixture of 0.2 g. (0.001 mole) of dry powdered 5,8-dichloropyrazino[2,3-*d*]pyridazine (I) (3) and 0.2 g.

of dry sodium azide was added *dropwise* 4 ml. of dimethylsulfoxide. [CAUTION--A larger scale preparation (0.5 g. of sodium azide and 0.5 g. of II) decomposed with flames upon addition of the dimethylsulfoxide. Larger quantities than 0.2 g. of reactants should be carefully cooled.] The solution was stirred for the 3 hours at room temperature. Ice was added to the suspension and 0.36 g. of a yellowish-white precipitate was collected by filtration. The precipitate was recrystallized from ethanol Norite) to give 0.2 g. (93%) of white needles of 6-azidopyrazino-[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (II), m.p. 193-194°; U.V. λ max (95% ethanol), 210 (ε, 16,950), 219 (sh) (ε, 16,750), 260 (ε, 9,700), 285 (ε, 7,625), 295 mμ (sh) (ε, 6,950); infrared cm^{-1}, 3450(m), 2250(w), 2200(m), 2160(s), 2125(s), 1600(w), 1550(m), 1500(s), 1460(m), 1425(s), 1375(s), 1350(s), 1300(s), 1295(m), 1245(s), 1195(m), 1135(m), 1130(m), 1120(m), 985(m), 910(w), 885(w), 729(w), 640(w), 545(w), 430(s), (potassium bromide); NMR spectrum (deuteriochloroform), 9.26 δ (C_2-H and C_3-H doublets).

Anal. Calcd. for $C_6H_2N_{10}$: C, 33.65; H, 0.94; N, 65.41. Found: C, 33.99; H, 1.18; N, 65.51.

6-Methoxypyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (V).

To a solution containing 0.066 g. of sodium in 9 ml. of anhydrous methanol was added 0.4 g. (0.002 mole) of 6-azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine. The solution was heated under reflux for 2 hours. The course of the reaction was followed using TLC with benzene as the developing agent. The product moved but the starting material did not. A yellowish-brown precipitate was collected by filtration, washed with water and recrystallized from methanol (Norite) to give 0.3 g. (75%) of white crystals of 6-methoxypyrazino[2,3-*d*]tetrazolo-[4,5-*b*]pyridazine, m.p. 220-221°; U.V. λ max (95% ethanol), 208 (ε, 17,250), 248 (ε, 13,950), 292 (ε, 6,475), 298 mμ (sh) (ε, 5,770); infrared cm^{-1}, 1620(s), 1560(m), 1525(s), 1475(m), 1450(m), 1425(m), 1375(s), 1350(s), 1300(w), 1295(w), 1235(m), 1200(m), 1170(m), 1150(w), 1110(s), 1065(m), 1025(m), 990(m), 965(m), 895(s), 790(m), 730(w), 685(w), 435(m), (potassium bromide); NMR spectrum (deuteriochloroform), 4.41 δ ($O\text{-}CH_3$ singlet), 9.33 δ (C_2-H and C_3-H doublets).

Anal. Calcd. for $C_7H_5N_7O$: C, 41.38; H, 2.09; N, 48.27. Found: C, 41.02; H, 2.19; N, 48.24.

6-Ethoxypyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (IV).

To a solution containing 0.066 g. of sodium in 9 ml. of anhydrous ethanol was added 0.4 g. (0.002 mole) of 6-azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine. The solution was heated under reflux with stirring for one hour. The course of the reaction was followed using TLC with benzene as the developing agent. The starting material did not move while the product did. A tan solid was collected by filtration, washed with water, dried and recrystallized from ethanol (Norite) to give 0.3 g. (70%) of long white needles of 6-ethoxypyrazino[2,3-*d*]tetrazolo[4,5-*b*]-pyridazine, m.p. 201-202°; U.V. λ max (95% ethanol), 209 (ε, 14,150), 248 (ε, 8,125), 284 (ε, 6,025), 298 mμ (sh) (ε, 4,175); infrared cm^{-1}, 3050(w), 2990(m), 1610(s), 1560(m), 1525(s), 1460(m), 1450(s), 1375(s), 1360(m), 1340(s), 1315(m), 1290(m), 1225(m), 1200(w), 1170(s), 1110(s), 1060(s), 1015(s), 980(m), 915(w), 890(m), 865(m), 815(w), 790(s), 730(m), 685(m), 595(w), 485(w), 435(s), (potassium bromide); NMR spectrum (deuteriochloroform), 1.66 δ (CH_3 triplet), 4.86 δ (OCH_2 quartet), 9.26 δ (C_2-H and C_3-H doublets).

Anal. Calcd. for $C_8H_7N_7O$: C, 44.24; H, 3.24; N, 45.14. Found: C, 44.06; H, 2.89; N, 45.00.

6-Aminopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (III).

To 4 ml. of distilled tetralin was added 0.4 g. (0.002 mole) of 6-azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine (II). The suspension was placed in an oil bath which was preheated to 160°. After one minute the suspension became clear and bubbles of nitrogen were evolved. After 10 minutes nitrogen evolution had ceased. Heating was continued an additional 35 minutes. After cooling, the dark brown precipitate was removed by filtration. The precipitate was digested twice by heating with 25 ml. portions of chloroform. The mother liquor was decanted and discarded. The residue was recrystallized from water (Norite), m.p. 315° dec.; infrared cm^{-1}; 3440(s), 3315(s), 2925(m), 2850(w), 1625(s), 1515(s), 1475(w), 1375(w), 1360(m), 1280(s), 1216(w), 1110(m), 1065(w), 1025(w), 998(m), 885(w), 785(w), 675(w), 428(m) (potassium bromide).

Anal. Calcd. for $C_6H_4N_8$: C, 38.30; H, 2.14; N, 59.55. Found: C, 38.45; H, 2.35; N, 59.57.

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