OD), 12407-89-5; adduct **9a** of **1b** (Z = OD), 12407-88-4; adduct **9a** of **1e** (Z = OD), 12407-94-2; adduct **9b** of **1d** (Z = OD), 12407-90-8; adduct **9b** of **1d** (Z = OEt), 12407-93-1; **11d**, 23430-66-2; **14a**, 1468-26-4; **14b**, 2083-04-7; **14c**, 2083-05-8; **14d**, 2278-15-1; **14e**, 22855-06-7; **15a**, 4730-46-5; **15b**, 23430-72-0; **15c**, 23110-95-4; **15d**, 22855-07-8; **15e**, 22855-08-9; **15f**, 22855-09-0; **15g**, 23465-14-7; **15h**, 23430-73-1; **16b**, 22699-23-6; **17**, 2683-90-1; **18**, 134-58-7; **19a**, 23431-04-1; **19b**, 22699-22-5; **20b**, 22699-24-7.

Pyridazines. XXXIII. Valence Isomerizations of Some Tetrazolo[1,5-*b*]pyridazines

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Several examples of valence isomerizations of fused tetrazolo rings of different tetrazolo[1,5-*b*]pyridazines and related systems into azido functions are presented. Valence isomerization could be induced by forming a new fused five- or six-membered hetero ring or by N oxidation.

Recently, we were able to show that fusion of an azolo ring, involving a pyridazine ring nitrogen at the bridgehead of the bicyclic system, caused spontaneous valence isomerization of tetrazolo[1,5-*b*]pyridazines into the corresponding azidopyridazines.[1-3]

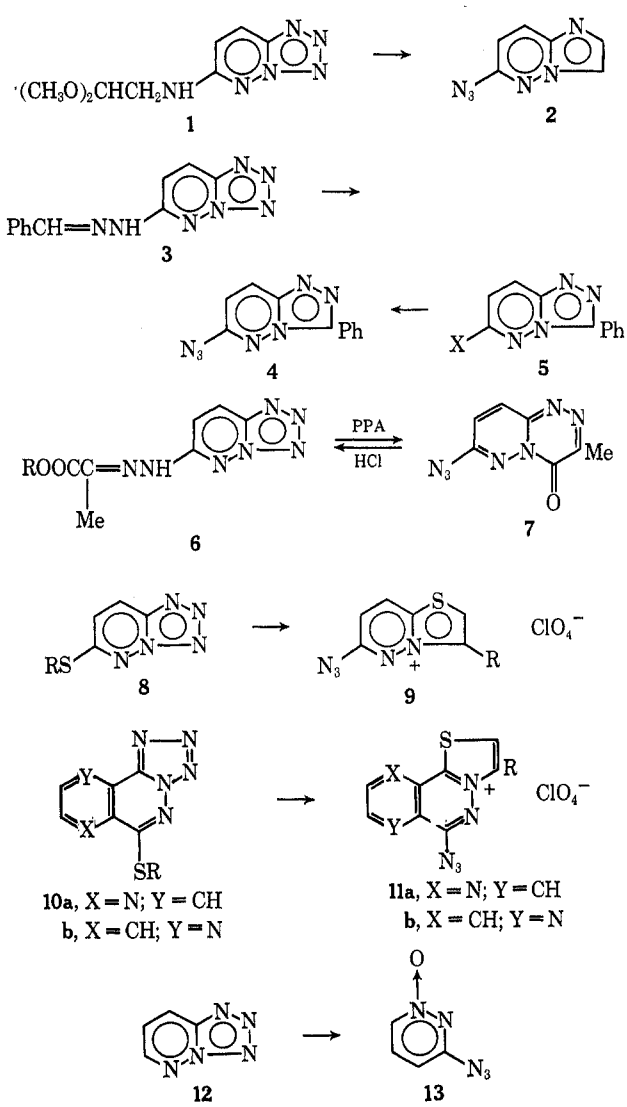
In order to test the generality of such valence isomerizations in the tetrazolopyridazine series, further experiments have been performed which include the formation of a fused azole or azine ring, a sulfur-containing five-membered ring, or an introduction of a N-oxide function.

Since earlier attempts[1] toward simultaneous formation of a fused imidazole ring were not successful, another approach to such conversion has been attempted. It was now possible to convert 6-dimethoxyethylaminotetrazolo[1,5-*b*]pyridazine (**1**) with polyphosphoric acid into the corresponding 6-azidoimidazo[1,2-*b*]pyridazine (**2**) (see Scheme I) and thus induce a complete elimination of the fused tetrazolo ring as is evident from infrared and nmr spectra. The presence of the tetrazolo isomer in a solution of deuteriochloroform could not be detected.

Similarly, the formation of a fused *s*-triazolo ring could be now extended by employing procedures designed previously for syntheses of simple *s*-triazolo[4,3-*b*]pyridazines[4] or *s*-triazolo[4,3-*a*]-1,3,5-triazines.[5] In this manner, the hydrazone **3** could be transformed into the bicyclic compound **4** by employing either the lead tetraacetate technique or by means of bromine. Here again, valence isomerization was discernible from spectral data and, in addition, from chemical transformations of compounds **5** (R = $NHNH_2$) with nitrous acid or (**5**, R = Cl) by means of sodium azide. As anticipated, in both cases no ring closure to a fused tetrazolo heterocycle occurred and only an azide group was formed (**4**).

A fused six-membered ring could be generated in the reaction of **6** (R = Et) with polyphosphoric acid, and once more the tetrazolo ring was isomerized to the azido group. The obtained bicyclic compound **7**, a representative of the newly discovered pyridazino[6,1-*c*]*as*-triazine system,[6] is susceptible to acid hydrolysis and as soon as the fused *as*-triazine ring was opened this resulted in immediate generation of the fused tetrazolo ring (**6**, R = H) from the azido group present in the starting compound.

SCHEME I



(1) A. Kovačič, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **5**, 351 (1968).
(2) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).
(3) B. Stanovnik, M. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968).
(4) A. Pollak and M. Tišler, *Tetrahedron*, **22**, 2073 (1966).
(5) M. Jelenc, J. Kobe, B. Stanovnik, and M. Tisler, *Monatsh. Chem.*, **97**, 1713 (1966).
(6) B. Stanovnik and M. Tišler, *J. Heterocycl. Chem.*, **6**, 413 (1969).

As an extension of the above reactions, compounds with a fused thiazolium ring were prepared in order to investigate further valence isomerization. Thiazolo[3,2-*b*]pyridazin-4-ium perchlorates **9** were formed from the corresponding sulfides of the type **8** and in their infrared spectra strong azide absorption bands were discernible. In contrast to earlier observations[7] no intermediate 3-hydroxy derivatives could be isolated when working in an organic solvent in the absence of a base. This can be ascribed to somewhat more rigorous reaction conditions which have to be employed in order to convert the sulfides into the bicyclic thiazolium salts. In order to establish the stability of this ring system, 6-azido-3-phenylthiazolo[3,2-*b*]pyridazin-4-ium perchlorate (**9**, R = Ph) has been submitted to various reactions. The compound was found to be stable in boiling water or boiling 20% hydrochloric acid after 2 hr.

Application of this reaction sequence to the isomeric substituted thiopyridotetrazolo[5,1-*b*]pyridazines **10a** and **10b** revealed that the anticipated valence isomerization proceeded in the same manner, and salts of both fused thiazolium systems **11a** and **11b** showed as solids strong azide absorption bands in the region 2137–2165 cm^{-1}, characteristic for the presence of azido groups.

Finally, direct N oxidation of tetrazolo[1,5-*b*]pyridazine (**12**) with concentrated hydrogen peroxide in polyphosphoric acid led to simultaneous N oxidation and ring opening and thus 3-azidopyridazine 1-oxide (**13**) could be detected and isolated in low yield.

It seems that the driving force for the described valence isomerizations of tetrazolopyridazines is due primarily to the electron-withdrawing influence of a π-excessive fused azolo ring (or N-oxide function). In this manner the fused tetrazolo ring becomes destabilized and the electron-donating azido group is formed.

Experimental Section

Melting points were taken on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as mulls in Nujol or as KBr disks, and nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer using tetramethylsilane as internal standard.

6-(1′,1′-Dimethoxyethylamino)tetrazolo[1,5-*b*]pyridazine (1).—After 6-chlorotetrazolo[1,5-*b*]pyridazine (1.55 g) was treated with aminoacetaldehyde dimethyl acetal (1.05 g) the mixture evolved heat and was warmed up to 80°. It was then heated on a water bath for 15 min and cooled; the precipitate was filtered off (1.80 g, 80%) and crystallized from ethanol, mp 129°.

Anal. Calcd for $C_8H_{12}N_6O_2$: C, 42.85; H, 5.39; N, 37.48. Found: C, 43.08; H, 5.45; N, 37.55.

6-Azidoimidazo[1,2-*b*]pyridazine (2).—The above acetal (1, 2.25 g) and polyphosphoric acid (20 g) were heated slowly up to 110° (about 1 hr) and this temperature was maintained then for 15 min. To the cooled reaction mixture crushed ice (30 g) was added and the mixture neutralized with solid sodium bicarbonate. The separated product was crystallized from a mixture of benzene and petroleum ether (1:3) and had mp 108° (yield 0.72 g, 45%). The compound was found to be identical with the specimen obtained from 6-hydrazinoimidazo[1,2-*b*]pyridazine after treatment with nitrous acid:[8] ir (KBr) 2132 cm^{-1} (N_3); nmr ($CDCl_3$) δ 2.41 (d, H_2), 2.29 (d, H_3), 3.51 (d, H_7), 2.27 (d, H_8), $J_{2,3} = 0.75$, $J_{7,8} = 9.15$ cps.

6-Benzylidenehydrazinotetrazolo[1,5-*b*]pyridazine (3).—This compound was prepared from 6-hydrazinotetrazolo[1,5-*b*]-pyridazine[1,9,10] and benzaldehyde in the usual way; mp 315–317° with partial decomposition over 310° (from N,N-dimethylformamide and ethanol, 3:1).

Anal. Calcd for $C_{11}H_9N_7$: C, 55.22; H, 3.79; N, 40.99. Found: C, 54.88; H, 4.02; N, 41.34.

6-Azido-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (4). A.—To a suspension of the above hydrazone (**3**, 1.2 g) in glacial acetic acid (25 ml), anhydrous sodium acetate (1.64 g) and a solution of bromine in glacial acetic acid (0.8 g in 2 ml) were added. The reaction mixture was heated up to 100°, left for 5 min at this temperature, and cooled. It was then poured on crushed ice (70 g); the separated product was filtered off and washed with iced water (69% yield). Crystallization was performed from ethanol: mp 168°; ir (KBr) 2141 cm^{-1} (N_3).

Anal. Calcd for $C_{11}H_7N_7$: C, 55.69; H, 2.97; N, 41.34. Found: C, 55.46; H, 3.29; N, 41.53.

The compound is identical with the product obtained either from a similar cyclization of the hydrazone with lead tetraacetate (B) or from treatment of 6-hydrazino compound with nitrous acid (C) or from 6-chloro compound after reaction with sodium azide (C).

B.—The hydrazone **3** (1.2 g) was suspended in glacial acetic acid (20 ml), lead tetraacetate (2.21 g) was added, and the mixture was heated to 75°. After 5 min at this temperature the reaction mixture was cooled and poured onto ice (50 g). The product, after crystallization from ethanol, was found to be identical with compounds described under A or C by comparison of mixture melting points and infrared spectra, mp 168°.

C.—The azido compound was equally well prepared by nitrozation of 6-hydrazino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (83% yield) or from 6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine by treatment with sodium azide in ethanol (67% yield). Both products were identical with compounds prepared as described in A or B.

6-(α-Carbethoxyethylidenehydrazino)tetrazolo[1,5-*b*]pyridazine (6, R = Et).—6-Hydrazinotetrazolo[1,5-*b*]pyridazine (1.51 g) was suspended in ethanol (2 ml), the mixture was heated to boiling, and thereafter acetic acid (0.5 ml) and ethyl pyruvate (1.16 g) were added. The reaction mixture was heated under reflux for 5 min and cooled; the product was filtered off and washed with ethanol. After crystallization from ethanol and N,N-dimethylformamide (2:1) the pure compound melted at 245–247°; ir (KBr) 3425 cm^{-1} (NH) and 1727 cm^{-1} (CO).

Anal. Calcd for $C_9H_{11}N_7O_2$: C, 43.37; H, 4.45; N, 39.34. Found: C, 43.58; H, 4.44; N, 39.84.

In an analogous way, but using methyl pyruvate, the corresponding **6-(α-carbomethoxyethylidenehydrazino) analog** was prepared, mp 252–254°.

7-Azido-3-methylpyridazino[6,1-*c*]-*as*-triazin-4-one (7).—Compound **6** (R = Et) (2.49 g) was thoroughly mixed with polyphosphoric acid (25 g) and the mixture was slowly heated on an oil bath to 150° (about 1 hr) and then heated at this temperature for a further 20 min. The reaction mixture was cooled on ice, treated with crushed ice (40 g), and neutralized with solid sodium bicarbonate. The separated product was filtered off and washed with ice–water (yield 0.81 g, 39%). Upon crystallization from ethyl acetate and petroleum ether (1:3) the compound had mp 147–148°: ir (KBr) 2151 cm^{-1} (N_3), 1715 cm^{-1} (CO); nmr spectrum ($CDCl_3$) τ 3.15 (d, H_8), 2.26 (d, H_9), 7.40 (s, 3-CH_3); $J_{8,9} = 9.5$ cps.

Anal. Calcd for $C_7H_5N_7O$: C, 41.40; H, 2.48; N, 48.27. Found: C, 41.21; H, 2.66; N, 48.42.

An identical product is obtained also from the 6-(α-carbomethoxyethylidenehydrazino) derivative.

6-(α-Carboxyethylidenehydrazino)tetrazolo[1,5-*b*]pyridazine (6, R = H). A.—The bicyclic compound **7** (100 mg) was suspended in hydrochloric acid (1 ml of 20%) and the mixture was heated to boiling for 2 min. After cooling the separated product was filtered off and found to be identical with the compound as obtained under B (yield 93%). Crystallization was accomplished from 2 *N* hydrochloric acid: mp 251–252°; ir (KBr) 1681 cm^{-1} (CO).

Anal. Calcd for $C_7H_7N_7O_2$: C, 38.01; H, 3.19; N, 44.32. Found: C, 37.90; H, 3.32; N, 44.48.

B.—A suspension of 6-hydrazinotetrazolo[1,5-*b*]pyridazine (1.51 g) in ethanol (20 ml) was heated to boiling and thereafter glacial acetic acid (0.5 ml) and pyruvic acid (0.88 g) were added. The mixture was heated under reflux for 5 min and cooled; the

(7) B. Stanovnik, M. Tišler, and A. Vrbanič, *J. Org. Chem.*, **34**, 996 (1969).
(8) B. Stanovnik and M. Tisler, *Tetrahedron*, **23**, 387 (1967).
(9) N. Takahayashi, *J. Pharm. Soc.*, **76**, 765 (1956); *Chem. Abstr.*, **51**, 1192 (1957).
(10) T. Itai and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **11**, 348 (1963); *Chem. Abstr.*, **59**, 8734 (1963).

product was filtered off and washed with ethanol (yield 86%). Crystallization was performed from 2 *N* hydrochloric acid, mp 251–252°. The compound was identical with the sample as prepared under A.

6-Mercaptotetrazolo[1,5-*b*]pyridazine (8, R = H).—6-Chlorotetrazolo[1,5-*b*]pyridazine (1.55 g) was added to a solution of 0.03 mol of potassium hydrogen sulfide in ethanol (30 ml). The mixture was heated in a pressure vessel at 120° for 3 hr. The solvent was then evaporated and the residue dissolved in water, some charcoal was added, and after filtration the filtrate was acidified with concentrated hydrochloric acid. The separated product (70% yield) was for analysis dissolved in a solution of sodium carbonate, charcoaled, filtered, and acidified with concentrated hydrochloric acid, and washed with ice–water. The pure compound had mp 135–137°; ir (KBr) 2500 cm^{-1} (SH).

Anal. Calcd for $C_4H_3N_5S$: C, 31.38; H, 1.98; N, 45.75; S, 20.90. Found: C, 31.30; H, 2.15; N, 45.68; S, 20.75.

The **6-methylthio derivative (8, R = Me)** was prepared in the usual way in 67% yield; mp 169–170°.

Anal. Calcd for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 35.86; H, 3.34; N, 42.04; S, 19.33.

The **6-phenylthio derivative (8, R = Ph)** was obtained from the reaction with sodium thiophenolate in 60% yield, mp 128.5–129.5° (from ethanol).

Anal. Calcd for $C_{10}H_7N_5S$: C, 52.40; H, 3.08; N, 30.56; S, 13.96. Found: C, 52.10; H, 3.46; N, 30.80; S, 14.00.

6-Phenacylthiotetrazolo[1,5-*b*]pyridazine (8, R = $PhCOCH_2$).—A mixture of the mercapto compound (**8, R = H**; 0.765 g), ethanol (10 ml), and phenacyl bromide (1.0 g) was shaken at room temperature for 30 min and the product was then filtered off. Upon crystallization from a mixture of N,N-dimethylformamide and ethanol (1:4) the compound had mp 170–172° (yield 84%); ir (KBr) 1667 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_9N_5OS$: C, 53.14; H, 3.34; N, 25.82; S, 11.80. Found: C, 53.09; H, 3.57; N, 25.55; S, 11.81.

In an analogous way **6-acetonylthiotetrazolo[1,5-*b*]pyridazine (8, R = CH_3COCH_2)** was obtained in 78% yield; mp 124–125° (from ethanol and ethyl acetate, 1:1).

Anal. Calcd for $C_7H_7N_5OS$: C, 40.19; H, 3.37; N, 33.48; S, 15.30. Found: C, 40.33; H, 3.58; N, 33.54; S, 15.45.

6-Azido-3-phenylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (9, R = Ph).—The phenacylthio compound (**8, R = $PhCOCH_2$**) (1.35 g) was dissolved in 8 ml of concentrated sulfuric acid and the mixture was heated on a water bath for 3 hr. Upon cooling, the mixture was poured into diethyl ether (150 ml), the ethereal layer was decanted, and the residual oil was dissolved in water (20 ml). The insoluble part was filtered off and the filtrate was treated with perchloric acid (2 ml of 70%). The separated perchlorate salt was filtered off, washed with water, and thereafter crystallized from ethanol (yield 51%). The compound is hygroscopic: mp 170–172°; ir (KBr) 2169 cm^{-1} (N_3).

Anal. Calcd for $C_{12}H_8ClN_5O_4S$: C, 40.74; H, 2.28; N, 19.80. Found: C, 40.60; H, 2.47; N, 20.06.

By using the above procedure the **3-methyl analog (9, R = Me)** could be obtained in 26% yield, mp 140–141° (from ethanol); the compound is hygroscopic.

Anal. Calcd for $C_7H_6ClN_5O_4S$: C, 28.83; H, 2.08; N, 24.01; S, 10.99. Found: C, 28.72; H, 2.38; N, 23.86; S, 11.25.

6-Mercaptopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = H).—To an ethanolic solution of potassium hydrogen sulfide, prepared from 1.7 g of potassium hydroxide in 30 ml of ethanol and then saturated with hydrogen sulfide, the 6-chloro compound[11] (10a, R = Cl) (2.04 g) was added and the reaction mixture was heated in an autoclave at 120° for 3 hr. The separated product was filtered off and dissolved in 0.5 *N* potassium hydroxide, the solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid. For analysis a sample was repeatedly purified by dissolution in potassium hydroxide and subsequent acidification, mp 260° dec.

Anal. Calcd for $C_7H_4N_6S$: C, 41.18; H, 1.98; N, 41.17; S, 15.67. Found: C, 41.02; H, 2.23; N, 41.02; S, 15.89.

6-Mercaptopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = H).—This compound was obtained by the same procedure as described above for the isomeric **10a** (R = H): mp 205° dec; ir (KBr) 2268 cm^{-1} (SH).

(11) B. Stanovnik, A. Krbavčič, and M. Tišler, *J. Org. Chem.* **32**, 1139 (1967).

Anal. Calcd for $C_7H_4N_6S$: C, 41.18; H, 1.98; S, 15.67. Found: C, 41.36; H, 2.08; S, 15.44.

6-Methylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = Me).—A solution of compound **10a** (R = H; 51 mg) in aqueous sodium hydroxide (2.5 ml of 0.1 *N*) was treated with methyl iodide (50 mg) and the mixture was shaken in a sealed flask at room temperature during 30 min. The crude product was separated, washed with water, and dried. Upon crystallization from water and ethanol (1:1) the compound had mp 246–247°.

Anal. Calcd for $C_5H_6N_6S$: C, 44.04; H, 2.77; N, 38.52; S, 14.67. Found: C, 44.46; H, 2.97; N, 38.60; S, 14.57.

The isomeric **6-methylthiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = Me)** was prepared in essentially the same way (yield 77%), mp 283–285°.

Anal. Calcd for $C_5H_6N_6S$: C, 44.04; H, 2.77; N, 38.52; S, 14.67. Found: C, 44.27; H, 2.91; N, 38.43; S, 14.48.

6-Acetonylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = CH_3COCH_2).—The potassium salt of **10a** (R = K) (1.21 g), prepared by addition of equimolar quantity of 0.1 *N* potassium hydroxide, was treated with ethanol (12 ml) and bromoacetone (0.7 g). The mixture was shaken at room temperature during 1 hr; the product was filtered off, washed with ice–water, and crystallized from N,N-dimethylformamide and ethanol (3:1): mp 210°; yield 60%; ir (KBr) 1715 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8N_6OS$: C, 46.16; H, 3.10; N, 32.30; S, 12.30. Found: C, 46.38; H, 3.30; N, 32.64; S, 12.45.

Similarly **6-acetonylthiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = CH_3COCH_2)** was obtained in 49% yield: mp 227° (from ethanol); ir (KBr) 1721 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8N_6OS$: C, 46.16; H, 3.10; N, 32.30; S, 12.30. Found: C, 46.23; H, 3.09; N, 32.04; S, 11.92.

6-Phenacylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = $PhCOCH_2$).—A mixture of **10a** (R = H; 0.51 g), ethanol (8 ml), and phenacyl bromide (0.5 g) was shaken at room temperature during 1 hr; the product was separated by filtration, washed with ethanol, and crystallized from a mixture of N,N-dimethylformamide and ethanol (2:1) (yield 80%): mp 244°; ir (KBr) 1675 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{10}N_6OS$: C, 55.90; H, 3.13; N, 26.08; S, 9.93. Found: C, 55.74; H, 3.43; N, 25.92; S, 10.32.

The isomeric **6-phenacythiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = $PhCOCH_2$)** was prepared in an analogous way in 64% yield: mp 231–232° (from ethanol and N,N-dimethylformamide, 2:1); ir (KBr) 1675 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{10}N_6OS$: C, 55.90; H, 3.13; N, 26.08; S, 9.93. Found: C, 55.61; H, 3.44; N, 26.01; S, 9.93.

6-Azido-3-methylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (11a, R = Me).—The acetonyl compound (**10a**, R = CH_3COCH_2; 1.0 g) was heated in concentrated sulfuric acid (10 g) on a water bath for 2 hr. The cooled reaction mixture was poured slowly into ice-cold ether (100 ml). The ethereal layer was decanted, the residual oil was dissolved in water (25 ml), and the perchlorate salt was precipitated with dropwise addition of 70% perchloric acid. The salt was filtered off and washed with water and hot ethanol (yield 20%): mp 236°; ir (KBr) 2137 cm^{-1} (N_3).

Anal. Calcd for $C_{10}H_7ClN_6O_4S$: C, 35.05; H, 2.06; N, 24.52; S, 9.36. Found: C, 35.26; H, 2.38; N, 24.27; S, 9.55.

Following the above procedure the following compounds were prepared.

6-Azido-3-phenylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11a, R = Ph) was obtained in 51% yield: mp 135°; ir (KBr) 2165 cm^{-1} (N_3).

Anal. Calcd for $C_{15}H_9ClN_6O_4S$: C, 44.51; H, 2.24; N, 20.76. Found: C, 44.28; H, 2.61; N, 20.94.

6-Azido-3-methylpyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11b, R = Me) had mp 195°, ir (KBr) 2155 cm^{-1} (N_3).

Anal. Calcd for $C_{10}H_7ClN_6O_4S$: C, 35.05; H, 2.06; S, 9.36. Found: C, 35.47; H, 2.33; S, 9.26.

6-Azido-3-phenylpyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11b, R = Ph) melted at 203–204° dec; ir (KBr) 2137 cm^{-1} (N_3).

Anal. Calcd for $C_{15}H_9ClN_6O_4S$: C, 44.51; H, 2.24; N, 20.76. Found: C, 44.67; H, 2.48; N, 20.79.

3-Azidopyridazine 1-Oxide (13).—A suspension of tetrazolo[1,5-*b*]pyridazine (**12**, 1.21 g) in polyphosphoric acid (10 ml) was treated under stirring dropwise with 1 ml of 85% hydrogen peroxide and the mixture was left to stand at room temperature

in the dark for 4 days. During this period the evolution of gases ceased and a clear solution was obtained. The reaction mixture was diluted with water (50 ml) and neutralized with solid sodium bicarbonate. In addition, 30 ml of water was added and the whole extracted with six portions of 50 ml of chloroform. The combined extracts were dried over anhydrous sodium sulfate and then evaporated to dryness to obtain 0.83 g of a residue.

By thin layer chromatography on silica gel, using commercially available plates (DC-Fertigplatten Kieselgel F 254, Merck) and developing them with ethyl acetate, it could be shown that the obtained product was a mixture of the starting compound (R_f 0.59) and 3-azidopyridazine 1-oxide (R_f 0.45) (detection in uv light).

A solution of 300 mg of the crude product in 3 ml of chloroform was separated on a chromatoplate with the above-mentioned absorbent, and the part containing the azide was separated and the compound eluted with chloroform. Upon evaporation of the solvent 12 mg of the residue which consisted of practically pure 3-azidopyridazine 1-oxide[10] was obtaind (yield 2.4%); mp 151–152° and mixture melting point with an authentic specimen obtained from nitrosation of 3-hydrazinopyridazine 1-oxide[12] was undepressed. Moreover, ir spectra of both products were identical [2179 and 2146 cm^{-1} (N_3) and 1263 cm^{-1} (N–O)].

Registry No.—**1**, 23439-79-4; **3**, 23406-38-4; **4**, 23406-39-5; **6**, R = H, 23406-40-8; **6**, R = Et, 23406-41-9; **7**, 23406-42-0; **8**, R = H, 23439-80-7; **8**, R = Me, 23406-43-1; **8**, R = Ph, 23406-44-2; **8**, R = Ph-$COCH_2$, 23406-45-3; **8**, R = CH_3COCH_2, 23406-46-4; **9**, R = Me, 23439-81-8; **9**, R = Ph, 23406-47-5; **10a**, R = H, 23406-48-6; **10a**, R = Me, 23406-49-7; **10a**, R = $PhCOCH_2$, 23439-82-9; **10a**, R = CH_3COCH_2, 23439-83-0; **10b**, R = H, 23439-84-1; **10b**, R = Me, 23406-50-0; **10b**, R = $PhCOCH_2$, 23439-85-2; **10b**, R = CH_3COCH_2, 23410-93-7; **11a**, R = Me, 23410-94-8; **11a**, R = Ph, 23410-95-9; **11b**, R = Me, 23410-96-0; **11b**, R = Ph, 23439-86-3.

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The Kinetics of Deuteration of Imidazole[1]

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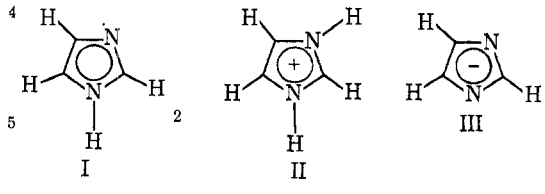
Rates of deuteration of imidazole in heavy aqueous solution were measured at various pD values at 65 and 70° for the 2 position and at 180 and 190° for the 4(5) position. Parallel rate-determining proton abstractions from the conjugate acid of imidazole by OD^- and by D_2O leading to an ylide intermediate accounted for the observed pD-rate profile for 2-position deuteration. These paths, together with proton abstraction from the imidazole molecule by OD^-, accounted for the 4(5)-position profile. The relative reactivities of hydrogen exchange sites in imidazole and other heterocycles were interpreted in terms of CNDO/2 ylide or anion stabilities.

In recent years, considerable attention has been focussed upon the relative electrophilic reactivities of various ring sites in aromatic heterocyclic compounds.[2,3] These electrophilic reactivities depend both upon the nature of the substrate and the nature of the electrophile. The case of imidazole (I) is of particular interest because the 4(5) position is said to be more reactive in iodination than the 2 position,[4] while the reverse is true for deuteration.[5] In order that different positions of a given substrate be compared for the same or different electrophilic reagents, it is important that the detailed kinetics of substitution for each site and each reaction be known. For example, imidazole may exist in the conjugate acid II or conjugate base III forms in addition to that of the molecule I. Kinetic



I II III

data could indicate which of these forms undergoes attack. The kinetics of iodination of imidazole has been studied in depth,[4,6,7] whereas that for the deuteration of imidazole has not been presented in comparable detail.[5,8,9] Thus, Harris and Randall[5] reported the kinetics of protonation of the 2 position of 1-methylimidazole, Olofson, Thompson, and Michelman[10] the rate of deuteration of the 2 positions of 1,3-dimethylimidazolium and other dialkylazolium cations, and Haake, Bauscher, and Miller[11] the rate of deuteration of 1,3,4-trimethylimidazolium cation. However, no kinetic studies of hydrogen exchange in the 4 and 5 positions of imidazole have been reported, and no detailed mechanistic analyses presented for either the 2 or the 4 and 5 positions. Accordingly, the purpose of this investigation was to study the kinetics of deuteration of the 2 and the equivalent 4 and 5 positions in imidazole, to propose mechanisms compatible with these rate laws and interpret the observed deuteration reactivities according to mechanistic and theoretical arguments.

Experimental Section

Materials.—Imidazole was recrystallized three times from benzene, mp 90.0°. Deuterium chloride (38% in D_2O), sodium deuterioxide (40% in D_2O), and heavy water (99.5%), obtained from Merck Sharp and Dohme of Canada Ltd., Volk Radiochemical, and International Chemical and Nuclear Corporation, were used without further purification. Reagent grade sodium chloride was also used without further purification.

Kinetic Runs.—All kinetic runs were made in heavy water solution. DCl or NaOD were added to adjust the pD of the solution from 0 to 14. The ionic strength of the solution was set

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