The Synthesis of Imidazo[4,5-*d*]pyridazines. VI. *v*-Triazolo[4,5-*d*]pyridazines, Pyrazino[2,3-*d*]pyridazines and 7*H*-Imidazo[4,5-*d*]tetrazolo[1,5-*b*]pyridazine.

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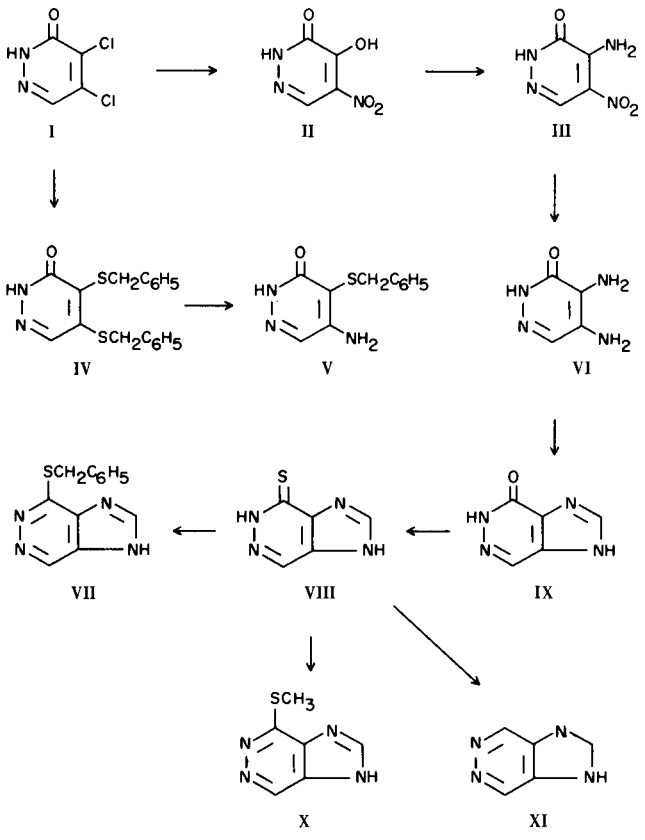
Several pyridazines have been prepared as intermediates in the synthesis of monosubstituted imidazo[4,5-*d*]pyridazines, monosubstituted *v*-triazolo[4,5-*d*]pyridazines and monosubstituted pyrazino[2,3-*d*]pyridazines. The new ring system, 7*H*-imidazo[4,5-*d*]tetrazolo[1,5-*b*]pyridazine (XIV) has been prepared unsubstituted. Furthermore, unsubstituted imidazo[4,5-*d*]pyridazine (XI) has been prepared. Calculations for XI and XIV were made by approximate SCF LCAO-MO with CNSO II theory.

Previous reports on the imidazo[4,5-*d*]pyridazine ring system have been concerned primarily with di- and trisubstituted imidazo[4,5-*d*]pyridazines (3-12). Only a few monosubstituted imidazo[4,5-*d*]pyridazines have been prepared (5-6). It is the purpose of this paper to report the synthesis of several monosubstituted imidazo[4,5-*d*]-pyridazines and intermediates leading thereto. With several intermediates in hand a number of monosubstituted *v*-triazolo[4,5-*d*]pyridazines were prepared.

4,5-Dichloro-6-pyridazone (I) (13) was allowed to react with benzyl mercaptan in the presence of sodium amide. 4,5-Bisbenzylthio-6-pyridazone (IV) (14) was obtained which, when treated with ethanolic ammonia in a rocking autoclave, gave 4-amino-5-benzylthio-6-pyridazone (V) rather than the expected 4,5-diamino-6-pyridazone (VI). The structure of V was established by removal of the benzylthio group with Raney nickel. The product was the known 4-amino-6-pyridazone (15). Therefore compound VI was prepared *via* II and III by the methods of Reicheneder and Dury (16-18).

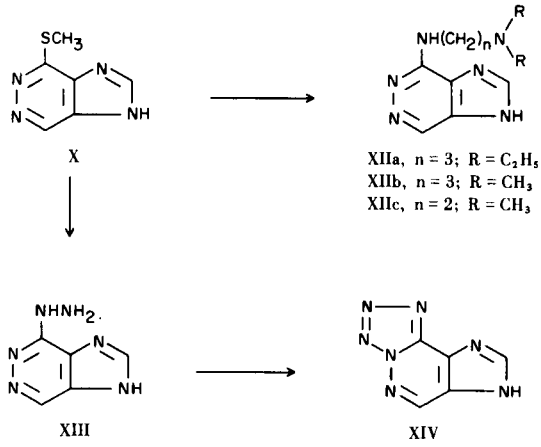
Treatment of 4,5-diamino-6-pyridazone (VI) (18) with ethyl orthoformate and acetic anhydride (8) gave imidazo-[4,5-*d*]pyridaz-4-one (IX) in about 90% yield. Attempts to chlorinate IX under a variety of chlorinating conditions failed to produce 4-chloroimidazo[4,5-*d*]pyridazine. The reaction of IX with phosphorus pentasulfide in boiling pyridine solution (19) gave imidazo[4,5-*d*]pyridazine-4-thione (VIII) in 76% yield. Compound VIII was methylated to give the known 4-methylthioimidazo[4,5-*d*]-pyridazine (X) in 73% yield which had previously been prepared by a different method (5). Compound VIII was readily *S*-benzylated with benzyl chloride in potassium hydroxide solution to give VII. Raney nickel dethiation of VIII afforded the unsubstituted imidazo[4,5-*d*]pyridazine (XI) in 52% yield. These transformations are detailed in Flow Sheet I.

FLOW SHEET I



4-Methylthioimidazo[4,5-*d*]pyridazine (X) served as the starting material for the preparation of three 4-dialkylaminoalkylaminoimidazo[4,5-*d*]pyridazines (XIIa-c) which have been screened for antimalarial activity and found inactive. Treatment of 4-methylthioimidazo[4,5-*d*]pyridazine (X) with hydrazine gave 4-hydrazinoimidazo[4,5-*d*]-pyridazine (XIII) in 69% yield. The reaction of XIII (20-21) with nitrous acid led to 7*H*-imidazo[4,5-*d*]-tetrazolo[1,5-*b*]pyridazine (XIV). The structural assignment of XIV was based upon the absence of absorption bands at 2160 and 2125 cm^{-1} characteristic of the azide group. These reactions are outlined in Flow Sheet II.

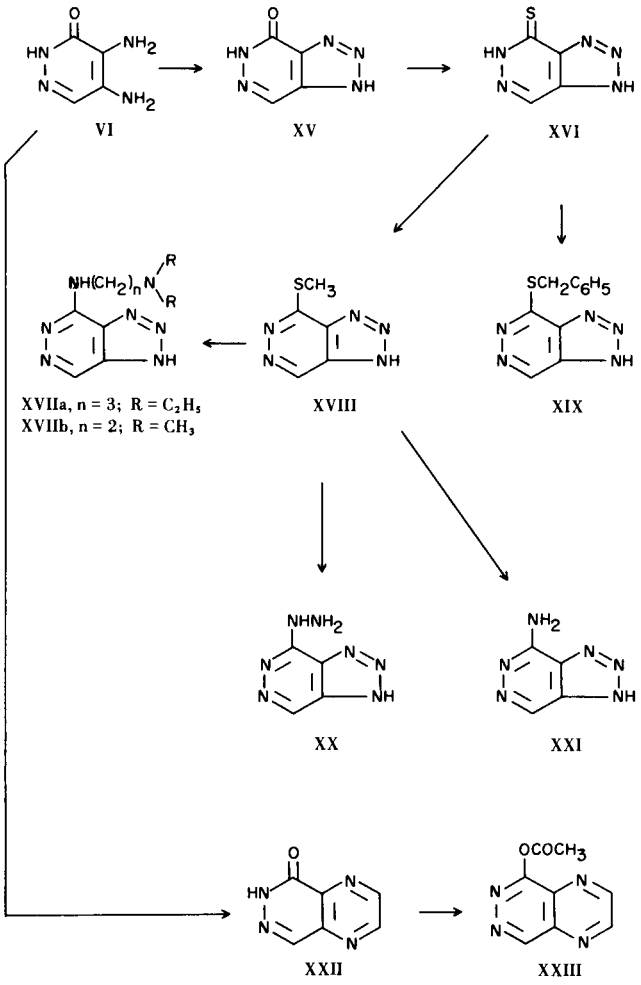
FLOW SHEET II



For the synthesis of *v*-triazolo[4,5-*d*]pyridazines, 4,5-diamino-6-pyridazone (VI) served as the starting material. Treatment of VI with nitrous acid (22) gave *v*-triazolo-[4,5-*d*]pyridaz-4-one (XV) in 90% yield. Phosphorus pentasulfide thiation (19) of XV gave *v*-triazolo[4,5-*d*]-pyridazine-4-thione (XVI) in 78% yield. Attempts to dethiate XVI with Raney nickel did not yield the expected unsubstituted *v*-triazolo[4,5-*d*]pyridazine. *S*-Benzylation of XVI with benzyl chloride in potassium hydroxide solution gave 4-benzylthio-*v*-triazolo[4,5-*d*]pyridazine (XIX), and XVI with methyl iodide in potassium hydroxide solution readily gave 4-methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII) in 83% yield. From XVIII the adenine analog, 4-amino-*v*-triazolo[4,5-*d*]pyridazine (XXI) was obtained in 59% yield by treatment of XVIII with aqueous ammonia in a pressure bottle. Treatment of XVIII with hydrazine produced 4-hydrazino-*v*-triazolo-[4,5-*d*]pyridazine (XX) in 76% yield. The reaction of nitrous acid with XX did not yield the desired *v*-triazolo-[4,5-*d*]tetrazolo[1,5-*b*]pyridazine. Treatment of XVIII with dialkylaminoalkylamines gave the two 4-dialkylaminoalkylamino-*v*-triazolo[4,5-*d*]pyridazines (XVIIa-b) which have been screened for antimalarial activity and found to be inactive.

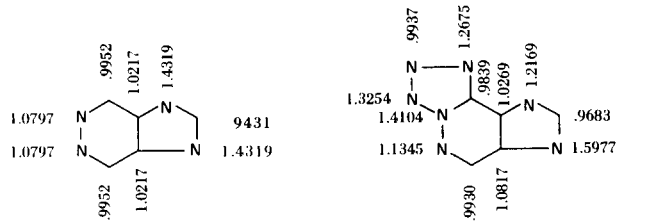
4,5-Diamino-6-pyridazone (VI) when allowed to react with aqueous glyoxal gave pyrazino[2,3-*d*]pyridaz-5-one (XXII) in 96% yield. Compound XXII was acetylated to give 5-acetoxypyrazino[4,5-*d*]pyridazine (XXIII). (U.V. λ max 276 mμ.) All attempts to chlorinate or thiate XXII were unsuccessful.

FLOW SHEET III

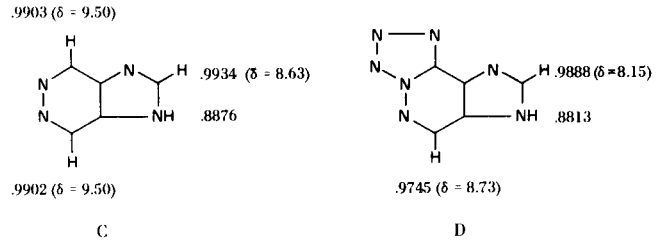


A discussion of approximate methods for obtaining self-consistent molecular orbitals for all valence electrons of large molecules has been presented by Pople, Santry, Segal and others (23-27). The simplest version of self-consistent molecular orbital theory involves the complete neglect of differential overlap (CNDO) between any two atomic orbitals. The method has been tested on polyatomic molecules and has been fairly successful in reproducing the orbitals and electron populations obtained by full LCAOSCF calculations (24). The SCFLCAO-MO with CNDO II (25) approximation method was used

in the calculation of electron densities for compounds XI and XIV. Approximate bond lengths and bond angles were obtained from tables compiled by Sutton (28). The charge densities shown in A were obtained by averaging the calculated values for positions 1 and 3; 4 and 7; 5 and 6; and 3a and 6a since the imidazole *H* is tautomeric. The original calculation was made assuming the imidazole *H* is fixed at position 1. The charge density of position 2 is as calculated. The π charge densities are shown below:



The σ charge densities on the hydrogen atoms are shown below:



If it is assumed that NMR chemical shifts are due mainly to electron densities around the hydrogen nucleus, these values are in agreement with the observed chemical shifts in deuterium oxide.

EXPERIMENTAL (29)

4,5-Dichloro-6-pyridazone (I).

This compound was prepared by the method of Mowry (13).

5-Hydroxy-4-nitro-6-pyridazone (II).

This compound was prepared by the method of Reicheneder and Dury (16).

5-Amino-4-nitro-6-pyridazone (III).

This compound was prepared by the method of Reicheneder and Dury (17).

4,5-Diamino-6-pyridazone (VI).

This compound was prepared by the method of Reicheneder and Dury (18).

4,5-Bisbenzylthio-6-pyridazone (IV).

This compound was prepared by the method of Castle and Kaji (14).

4-Amino-5-benzylthio-6-pyridazone (V).

4,5-Bisbenzylthio-6-pyridazone (IV) (14) (3.39 g., 0.01 mole) was suspended in 250 ml. of absolute ethanol saturated in the cold with ammonia and heated in a rocking autoclave at 210° for 30 hours. The brown reaction mixture was heated with Norite and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was extracted four times with ∿ 50 ml. portions of ether, and the ether extracts were discarded. The solid residue was chromatographed on 100 g. of Wohlm neutral grade alumina in a 25 mm column using ethyl acetate-ethanol (10:1) as the eluant. Recrystallization of the product from methanol afforded white plates, m.p. 248° dec.; U.V. λ max (95% ethanol), 207 (ε, 36,415), 216 (ε, 27,490), 227 (ε, 22,550), 311 mμ (ε, 4,230); NMR (deuterium oxide-sodium deuteroxide) δ 7.71 (C_3-H singlet), δ 7.24 (singlet, phenyl), δ 3.92 (singlet, benzylic -CH_2-).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.55; H, 4.78; N, 17.90.

Imidazo[4,5-*d*]pyridaz-4-one (IX).

4,5-Diamino-6-pyridazone (VI) (18) (5 g., 0.041 mole) was dissolved in 30 ml. of acetic anhydride and 30 ml. of ethyl orthoformate. The mixture was heated under reflux for 1.5 hours. After 5-10 minutes reflux a solid product began to separate. The reaction was cooled and evaporated nearly to dryness under reduced pressure. The residue was dissolved in ammonium hydroxide solution, treated with Norite and filtered. The filtrate was acidified to *p*H 5 with acetic acid while the solution was still hot, and then allowed to cool. The white solid was collected, purified by acid-base precipitation, yield 4.9 g. (80%), m.p. > 300°; U.V. λ max (0.1 *N* sodium hydroxide), 212 mμ (ε, 26,170); NMR (deuterium oxide-sodium deuteroxide) δ 8.74 (singlet C_7H), δ 8.06 (singlet C_2H).

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.18. Found: C, 44.39; H, 3.25; N, 41.18.

Imidazo[4,5-*d*]pyridazine-4-thione (VIII).

Finely powdered imidazo[4,5-*d*]pyridaz-4-one (IX) (6 g., 0.044 mole) was dissolved in 300 ml. of dry pyridine and the mixture was heated under reflux with stirring. Twenty g. of phosphorus pentasulfide were added slowly and the mixture was heated in an oil bath at 130-135° for 3 hours. The excess pyridine was evaporated under reduced pressure and 300 ml. of ice water was added to the residue. The mixture was allowed to come to room temperature and then heated on a steam bath for one hour. A small amount of sodium hydroxide was added to dissolve all of the suspended solids and the solution was heated, treated with Norite and filtered. The filtrate was acidified with concentrated hydrochloric acid to *p*H 1 and allowed to cool. The solid residue amounted to 5.1 g. (76%), m.p. > 300°. Purification was accomplished by acid-base precipitation; U.V. λ max (0.1 *N* sodium hydroxide), 213 mμ (ε, 39,180); NMR (deuterium oxide-sodium deuteroxide) δ 9.02 (singlet C_7H), δ 8.17 (singlet C_2H).

Anal. Calcd. for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.49; H, 2.74; N, 36.72.

4-Methylthioimidazo[4,5-*d*]pyridazine (X) (5).

This known compound has been prepared by a route different from that described (5). Powdered imidazo[4,5-*d*]pyridazine-4-thione (VIII) (15 g., 0.099 mole) was dissolved in 180 ml. of 0.5 *N* potassium hydroxide solution to which 5.45 ml. of methyl iodide was added slowly. The mixture was stirred at room temperature

for 5 hours. After 30 minutes solid product began to separate. The mixture was cooled in the refrigerator and the solid was collected, washed well with ice water and dried. The residue was recrystallized from ethanol (Norite) and 11.0 g. (73%), m.p. 235-236° was obtained (lit. (5) m.p. 230-232°); U.V. λ max (95% ethanol), 222 (ε, 17,040), 272 mμ (ε, 9,600); NMR (deuterium oxide-sodium deuteroxide) δ 9.22 (singlet C_7H), δ 8.32 (singlet C_2H), δ 2.80 (singlet $-SCH_3$).

Anal. Calcd. for $C_6H_6N_4S$: C, 43.36; H, 3.63; N, 33.70. Found: C, 43.40; H, 3.96; N, 33.70.

4-Benzylthioimidazo[4,5-*d*]pyridazine (VII).

Imidazo[4,5-*d*]pyridazine-4-thione (VIII) (1.0 g., 6.6 mmoles) was dissolved in 6.6 ml. of 1 *N* potassium hydroxide. Benzyl chloride (0.835 g., 6.6 mmoles) was added dropwise with stirring. The stirring was continued for 1 hour at room temperature during which time a solid separated which was collected and washed with water. The residue was recrystallized from benzene (Norite), yield 0.98 g., (62%), m.p. 199-200°; U.V. λ max (95% ethanol), 218 (ε, 20,590), 273 mμ (ε, 10,690); NMR (deuterium oxide-sodium deuteroxide) δ 9.31 (singlet C_7H), δ 8.48 (singlet C_2H), δ 7.33 (singlet, phenyl), δ 4.62 (singlet, benzylic $-CH_2-$).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.14. Found: C, 59.71; H, 4.29; N, 23.21.

Imidazo[4,5-*d*]pyridazine (XI).

Imidazo[4,5-*d*]pyridazine-4-thione (VIII) (3 g., 0.0197 mole) was pulverized and suspended in 50 ml. of absolute ethanol. About 18 g. of Raney nickel (grade T-1) (32) suspension was added, and the mixture was heated under reflux for 5 hours with stirring. The Raney nickel was removed by filtration while hot and washed with 3 x 75 ml. of hot water (The Raney nickel was heated with the water.), yield 1.31 g. (52%) (crude). The product was recrystallized from ethyl acetate (Norite), m.p. 279-280° dec.; U.V. λ max (95% ethanol), 203 (ε, 41,000), 216 (sh) (ε, 16,430), 249 (sh) (ε, 5,690), 280 mμ (ε, 2,120); NMR (deuterium oxide) δ 9.51 (singlet C_4 and C_7H), δ 8.52 singlet C_2H).

Anal. Calcd. for $C_5H_4N_4 \cdot \frac{1}{2}H_2O$: C, 46.51; H, 3.90; N, 43.39. Found: C, 46.34; H, 4.02; N, 42.94.

4-(3-Diethylaminopropylamino)imidazo[4,5-*d*]pyridazine Dihydrochloride (XIIa).

4-Methylthioimidazo[4,5-*d*]pyridazine (X) (1.5 g., 9.0 mmoles) was dissolved in 15 ml. of absolute ethanol and to this mixture was added 2.4 g. (18 mmoles) of 3-diethylaminopropylamine. The reaction mixture was heated in a pressure bottle in an oil bath maintained at 140-150° for 8 hours. After cooling and opening, 200 ml. of ether was added and the product (1.41 g., 63%), was obtained, m.p. 206.5-208°. The compound was analyzed as the hydrochloride prepared by dissolving the free base above in absolute ethanol which was saturated by dry hydrogen chloride. The excess ethanolic hydrogen chloride was removed by evaporation *in vacuo* and repeated evaporation with benzene eliminated all excess hydrogen chloride. The product was recrystallized from absolute ethanol-anhydrous ether to yield a *very hygroscopic* product which decomposed at 129-131°; U.V. λ max (95% ethanol), 208 (ε, 30,350), 260 mμ (ε, 7,500).

Anal. Calcd. for $C_{12}H_{20}N_6 \cdot 2HCl \cdot H_2O$: C, 42.48; H, 7.13; N, 24.77. Found: C, 42.63; H, 7.07; N, 24.74.

4-(3-Dimethylaminopropylamino)imidazo[4,5-*d*]pyridazine Dihydrochloride (XIIb).

4-Methylthioimidazo[4,5-*d*]pyridazine (X) (0.5 g., 3 mmoles), 0.34 g. (3 mmoles) of 3-dimethylaminopropylamine and 5 ml. of absolute ethanol were treated as described above for XIIa. The yield of the dihydrochloride was 0.55 g. (62%), m.p. 277-279° dec.; U.V. λ max (95% ethanol), 212 (ε, 43,230), 258 mμ (ε, 20,680).

Anal. Calcd. for $C_{10}H_{16}N_6 \cdot 2HCl$: C, 40.97; H, 6.19; N, 28.66. Found: C, 40.89; H, 6.18; N, 28.38.

4-(2-Dimethylaminoethylamino)imidazo[4,5-*d*]pyridazine Dihydrochloride (XIIc).

4-Methylthioimidazo[4,5-*d*]pyridazine (X) (0.5 g., 3 mmoles), 0.54 g. (6 mmoles) of 2-dimethylaminoethylamine and 5 ml. of absolute ethanol were treated as described above for XIIa. The yield of dihydrochloride was 0.51 g. (61%), m.p. 270-270.5° dec.; U.V. λ max (95% ethanol), 213 (ε, 22,800), 258 mμ (ε, 8,500).

Anal. Calcd. for $C_9H_{14}N_6 \cdot 2HCl$: C, 38.71; H, 5.79; N, 30.11. Found: C, 38.64; H, 5.70; N, 30.09.

4-Hydrazinoimidazo[4,5-*d*]pyridazine (XIII).

4-Methylthioimidazo[4,5-*d*]pyridazine (X) (0.5 g., 3 mmoles) was dissolved in 6 ml. of 95% hydrazine. The solution was heated under reflux for 7 hours, cooled, and 50 ml. of water was added. A white solid separated which was collected by filtration and recrystallized from water (Norite), yield 0.31 g. (69%), m.p. > 300°; U.V. λ max (water), 210 (ε, 17,450), 252 mμ (ε, 7,610); NMR (deuterium oxide-sodium deuteroxide) δ 8.98 (singlet C_7H), δ 8.19 (singlet C_2H).

Anal. Calcd. for $C_5H_6N_6$: C, 39.99; H, 4.03; N, 55.98. Found: C, 39.85; H, 4.16; N, 56.12.

7*H*-Imidazo[4,5-*d*]tetrazolo[1,5-*b*]pyridazine (XIV).

4-Hydrazinoimidazo[4,5-*d*]pyridazine (XIII) (1.21 g., 8.1 mmoles) was dissolved in 15 ml. of water containing 2.5 ml. of concentrated sulfuric acid. The solution was cooled in ice to < 10°. A cold aqueous solution containing 1.4 g. of sodium nitrite in 5 ml. of water was added at such a rate to maintain the temperature < 10°. The mixture was stirred for 1 hour at < 10° and then allowed to come to room temperature. The mixture was heated on the steam bath for 0.5 hour. The solution was cooled and a white solid was collected, yield 1.07 g. (83%). The product was recrystallized from water (Norite); U.V. λ max (water), 206 (ε, 30,730), 277 mμ (ε, 6,060); NMR (deuterium oxide-sodium deuteroxide) δ 8.75 (singlet C_6H), δ 8.17 (singlet C_8H).

Anal. Calcd. for $C_5H_3N_7$: C, 37.27; H, 1.87; N, 60.86. Found: C, 37.31; H, 2.02; N, 60.85.

ν-Triazolo[4,5-*d*]pyridaz-4-one (XV).

To 30 g. (0.242 mole) of 4,5-diamino-6-pyridazone (VI) was added 500 ml. of water and 60 ml. of concentrated sulfuric acid. The solution was cooled to < 10° and a solution of 34.2 g. of sodium nitrite in 100 ml. of water was added at a rate slow enough to maintain the temperature below 10°. The mixture was stirred for 1 hour at < 10°, then allowed to rise to room temperature. The mixture was heated on the steam bath for one hour and then allowed to stand overnight in the refrigerator. The solid product was recrystallized from water (Norite), m.p. > 300°, yield 30 g. (91%); U.V. λ max (0.1 *N* sodium hydroxide), 211 (ε, 28,860), 230 (sh) (ε, 16,600), 312 mμ (ε, 10,480); NMR (deuterium oxide-sodium deuteroxide) δ 9.07 (singlet C_7H).

Anal. Calcd. for $C_4H_3N_5O$: C, 35.04; H, 2.21; N, 51.08. Found: C, 35.32; H, 2.32; N, 51.01.

ν-Triazolo[4,5-*d*]pyridazine-4-thione (XVI).

ν-Triazolo[4,5-*d*]pyridaz-4-one (XV) (4.5 g., 0.033 mole) was

added to 165 ml. of pyridine and the mixture was heated to reflux temperature. Phosphorus pentasulfide (16.5 g., 0.074 mole) was added slowly in small portions to the refluxing solution. The solution was heated under reflux for an additional 1.5 hours and then allowed to cool slightly. The excess pyridine was removed by evaporation under reduced pressure. The brown viscous residue was added to ∿300 ml. of ice-water mixture. The mixture was heated on the steam bath, and then sodium hydroxide pellets were added to bring all the solids into solution. After treating the solution with Norite, the volume was reduced to ∿75 ml. by boiling. The solution was then acidified with concentrated hydrochloric acid to ∿*p*H 1 and allowed to stand overnight in the refrigerator, yield 3.92 g. (78%) crude, m.p. $>300°$. The product was purified by acid-base precipitation (Norite); U.V. λ max (0.1 *N* sodium hydroxide), 215 (ε, 39,160), 298 mμ (ε, 3,880); NMR (deuterium oxide-sodium deuteroxide) δ 9.37 (singlet C_7H).

Anal. Calcd. for $C_4H_3N_5S$: C, 31.37; H, 1.97; N, 45.73. Found: C, 31.58; H, 2.18; N, 45.43.

4-Benzylthio-*v*-triazolo[4,5-*d*]pyridazine (XIX).

v-Triazolo[4,5-*d*]pyridazine-4-thione (XVI) (0.5 g., 3.3 mmoles) was dissolved in 3.3 ml. of 1 *N* potassium hydroxide. The solution was stirred rapidly during the dropwise addition of 0.42 g. (3.3 mmoles) of benzyl chloride. The solution was stirred for 2 hours at room temperature, whereupon a brown gummy mass separated from the solution. Ethanol (∿50 ml.) was added to the mixture at the boiling point to effect solution. A small amount of black solid remained undissolved. This was separated by filtration and discarded. The ethanolic filtrate was evaporated to dryness *in vacuo*. The solid product was recrystallized from benzene (Norite), yield 0.23 g. (29%), m.p. 188.5-189.5°; U.V. λ max (95% ethanol), 208 (ε, 36,670), 285 mμ (ε, 7,400).

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.30; H, 3.73; N, 28.78. Found: C, 54.27; H, 3.74; N, 28.92.

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII).

v-Triazolo[4,5-*d*]pyridazine-4-thione (XVI) (3.0 g., 0.0198 mole) was suspended in 18 ml. of 1 *N* potassium hydroxide solution. To this mixture 4 ml. of methyl iodide was added slowly. The mixture was stirred for 5 hours at room temperature, cooled, and the product was collected by filtration, washed well with ice water and dried, yield crude, 2.75 g. (83%). The product was recrystallized from hot water (Norite), m.p. 210.5-211.5° dec.; U.V. λ max (95% ethanol), 206 (ε, 25,530), 219 (sh) (ε, 17,530), 275 mμ (ε, 20,770); NMR (deuterium oxide-sodium deuteroxide) δ 9.39 (singlet C_7H), δ 2.75 (singlet $-SCH_3$).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.92; H, 3.01; N, 41.89. Found: C, 36.08; H, 3.14; N, 42.19.

4-Hydrazino-*v*-triazolo[4,5-*d*]pyridazine (XX).

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII) (2.0 g., 11.9 mmoles) was dissolved in 20 ml. of 95% hydrazine. The solution was heated under reflux for 8 hours and then evaporated to dryness *in vacuo*. The residue was recrystallized from water (Norite), yield 1.42 g. (76%), m.p. $>300°$; U.V. λ max (water), 223 (sh) (ε, 18,130), 263 mμ (ε, 8,490); NMR (deuterium oxide-sodium deuteroxide) δ 8.95 (singlet C_7H).

Anal. Calcd. for $C_4H_5N_5$: C, 31.79; H, 3.33; N, 64.88. Found: C, 31.85; H, 3.44; N, 64.95.

4-Amino-*v*-triazolo[4,5-*d*]pyridazine (XXI).

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII) (0.5 g., 2.98 mmoles) was dissolved in 5 ml. of aqueous ammonia and this solution was heated with stirring in a glass bottle at 120-130° for 8 hours. The pressure bottle was allowed to cool, opened, and the contents were evaporated to dryness *in vacuo*. The residue was dissolved in dilute ammonium hydroxide, treated with Norite and the filtrate was neutralized to *p*H 6-8 with dilute hydrochloric acid. The solid was collected and recrystallized by dissolving in dilute ammonium hydroxide solution, neutralizing with dilute hydrochloric acid to *p*H 5-7 and allowing the crystals to separate, yield 0.24 g. (59%), m.p. $>360°$; U.V. λ max (water), 214 (ε, 23,390), 259 (ε, 8,690), 275 (sh) (ε, 6,850), 285 (sh) mμ (ε, 3,900); NMR (deuterium oxide-sodium deuteroxide) δ 9.17 (singlet C_7H).

Anal. Calcd. for $C_4H_4N_6$: C, 35.26; H, 2.96; N, 61.77. Found: C, 35.20; H, 3.08; N, 61.78.

4-(3-Diethylaminopropylamino)-*v*-triazolo[4,5-*d*]pyridazine (XVIIa).

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII) (1.5 g., 8.94 mmoles), 2.49 g. (19 mmoles) of 3-diethylaminopropylamine and 15 ml. of absolute ethanol were heated in a glass pressure bottle with stirring at an oilbath temperature of 140-150° for 8 hours. The pressure bottle was opened after cooling and 500 ml. of anhydrous ether was added. The product initially separated as an oily residue which solidified upon cooling and scratching. The product was collected by filtration (2.03 g., 90% crude yield) and was recrystallized from absolute ethanol-absolute ether (Norite), m.p. 217-218° dec.; U.V. λ max (95% ethanol), 202 (ε, 32,780), 225 (sh) (ε, 19,950), 278 mμ (ε, 8,590).

Anal. Calcd. for $C_{11}H_{19}N_7$: C, 52.98; H, 7.68; N, 39.33. Found: C, 52.87; H, 7.53; N, 39.03.

4-(2-Dimethylaminoethylamino)-*v*-triazolo[4,5-*d*]pyridazine Monohydrochloride (XVIIb).

4-Methylthio-*v*-triazolo[4,5-*d*]pyridazine (XVIII) (0.5 g., 2.98 mmoles), 0.54 g. (6 mmoles) of dimethylaminoethylamine and 5 ml. of absolute ethanol were treated as described for XVIIa above. In this instance the free base was converted into the dihydrochloride by treatment of an absolute ethanol solution with dry hydrogen chloride, crude yield 0.65 g. (89%). The product was recrystallized from absolute ethanol-anhydrous ether (Norite), m.p. 295° dec.; U.V. λ max (95% ethanol), 204 (ε, 39,040), 229 (sh) (ε, 17,890), 268 (ε, 6,970), 318 (sh) mμ (ε, 2,300).

Anal. Calcd. for $C_8H_{13}N_7 \cdot HCl$: C, 39.42; H, 5.79; N, 40.24. Found: C, 39.05; H, 6.13; N, 40.11.

Pyrazino[2,3-*d*]pyridaz-5-one (XXII).

4,5-Diamino-6-pyridazone (VI) (10 g., 0.0792 mole) was pulverized and suspended in 250 ml. of methanol. To this suspension was added slowly 14 ml. (0.0964 mole) of a 40% aqueous solution of glyoxal. The mixture was heated under reflux for 5 hours. After 30 minutes the suspension dissolved, and after ∿2 hours solid began to separate from the reaction mixture. The reaction mixture was cooled and the solid was collected by filtration, yield 11.6 g. (96%) crude. Recrystallization of the product from absolute ethanol-ligroin (60-90° b.p.) (Norite) gave a product with m.p. 245-246° dec.; U.V. λ max (95% ethanol), 204 (ε, 34,570), 249 (ε, 10,790), 307 mμ (ε, 3,950), (0.1 *N* sodium hydroxide), 213 (ε, 18,450), 256 (ε, 16,130), 312 (ε, 4,310), 342 mμ (ε, 4,240); NMR (deuterium oxide) δ 9.29 (doublet C_2H), δ 9.22 (doublet C_3H), δ 8.67 (singlet C_8H).

Anal. Calcd. for $C_6H_4N_4O$: C, 48.64; H, 2.73; N, 37.83. Found: C, 48.45; H, 2.74; N, 37.95.

5-Acetoxypyrazino[2,3-*d*]pyridazine (XXIII).

Pyrazino[2,3-*d*]pyridaz-5-one (XXII) (0.5 g., 3.37 mmoles) was suspended in 5 ml. of acetic anhydride and heated under reflux for 1.5 hours. After a few minutes all the solid dissolved. The excess acetic anhydride was removed by evaporation *in vacuo* and the solid residue was recrystallized from benzene, yield 0.54 g., (82%), m.p. 145-146°; U.V. λ max (absolute ethanol), 204 (ε, 29,725), 250 (ε, 15,430), 276 mμ (ε, 11,300); NMR (deuterioacetone) two doublets, δ 9.23 (J = 2 cps), δ 9.18 (J = 2 cps) C_2H and C_3H respectively, δ 8.53 (singlet C_8H), δ 2.72 (singlet $-COCH_3$).

Anal. Calcd. for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.77; H, 3.39; N, 29.56.

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