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The Synthesis of Imidazo[4,5-c]-, *s*-Triazolo[4,3-b]-, and Tetrazolo[1,5-b]pyridazines

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The adenine analog, 7-aminoimidazo[4,5-c]pyridazine (XII) and three other members of this previously unknown ring system have been prepared. The adenine analog, 8-aminotetrazolo[1,5-b]pyridazine (I) has also been prepared together with three other compounds in this ring system. The novel displacement of halogen in nitrogen heterocycles with phosphorus pentasulfide has been extended.

This work was undertaken in order to prepare the adenine analogs, 7-aminoimidazo[4,5-c]pyridazine (XII) and 8-aminotetrazolo[1,5-b]pyridazine (I).

Kuraishi (3) obtained a mixture of 4-amino-3,5-dichloropyridazine (II) and 5-amino-3,4-dichloropyridazine (XVI) from 3,4,5-trichloropyridazine (I) and alcoholic ammonia. For the synthesis of XII, II served as the starting material. When II was allowed to react with hydrazine without a solvent, the 4-amino-5-chloro-3-hydrazinopyridazine (V) was obtained isomer-free. Treatment of V with Raney Nickel gave 5-chloro-3,4-diaminopyridazine (VIII) in good yield. With ethyl orthoformate, VIII was smoothly converted into 7-chloroimidazo[4,5-c]pyridazine (XI). When XI was allowed to react with alcoholic ammonia under pressure, the adenine analog (XII) was obtained in 27% yield. The cyclization of VIII with carbon disulfide and sodium hydroxide gave 7-chloroimidazo[4,5-c]pyridazine-2-thiol (IX) in 70% yield. Compound IX was converted readily into 7-chloro-2-methylthioimidazo[4,5-c]pyridazine (VI) with methyl iodide and potassium hydroxide. Compound XI was also obtained by the Raney Nickel dethiation of IX. The structure of the adenine analog (XII) is certain since it is different from the adenine analog 4-aminoimidazo[4,5-d]pyridazine reported by Castle and Seese (4) and also by Carbon (5). The U.V. and I.R. spectra of XII also confirm the assigned structure. Had the 5-chlorine atom of II been replaced by hydrazine, then the previously known adenine analog 4-aminoimidazo-[4,5-d]pyridazine would have been obtained. Thus this sequence of reactions II, V, VIII, XI, XII establishes the constitution of V and each of the compounds that follow. Compounds XI, XII, IX and VI represent four examples of the previously unknown imidazo[4,5-c]-pyridazine ring system.

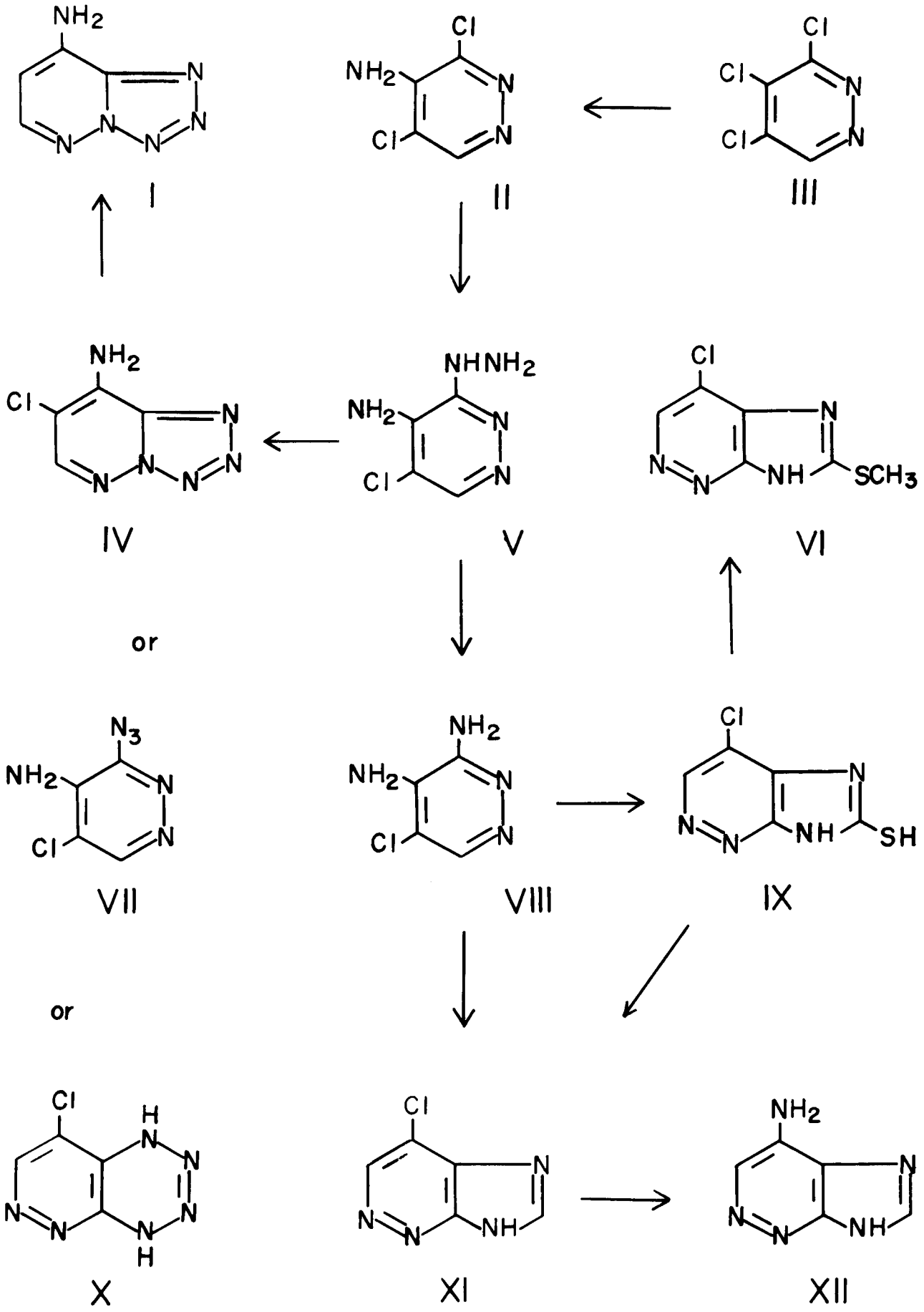
For the synthesis of the adenine analog, 8-aminotetrazolo[1,5-b]pyridazine (I), V was allowed to react with nitrous acid whereupon 8-amino-7-chlorotriazolo-[1,5-b]pyridazine (IV) was obtained. It was conceivable that 4-amino-3-azido-5-chloropyridazine (VII) might be the product, however the absence of an azide absorption in the 2160-2120 cm^{-1} region (6) of the infrared spectrum eliminated VII. Structure X was eliminated by the presence of the 299 mμ absorption band which is indicative of conjugation between the two rings. This conjugation is not possible in X. Furthermore the infrared spectra of the product from V and nitrous acid is quite similar to the infrared spectra of tetrazole (7), therefore structure IV was assigned on U.V. and I.R. spectral grounds (see experimental). Compound IV was smoothly dechlorinated with palladium on charcoal to the adenine analog I in 63% yield. The structure of I was also confirmed by the presence of the absorption band at 294 mμ.

The second product (XVI) from the mono-amination of 3,4,5-trichloropyridazine served as the starting material in the synthesis of the remainder of the tetrazolo[1,5-b]pyridazines and for the *s*-triazolo[4,3-b]-pyridazines.

The reaction of XVI with hydrazine gave 5-amino-4-chloro-3-hydrazinopyridazine (XIX) for which a satisfactory analysis was not obtained. However the structure was established by the conversion of XIX into 4-amino-5-chloropyridazine (XXIII) by treatment of XIX with copper sulfate. The melting point of XXIII was 70-73°, therefore it is different from the product described by Yanai (9) as 5-amino-3-chloropyridazine, m.p. 153-154.5°, thus it is certain that the 3-chlorine atom of XVI was replaced. When XIX was allowed to react with formic acid, 7-amino-8-chloro-*s*-triazolo-[4,3-b]pyridazine (XXI) was obtained. With palladium on charcoal, XXI was readily dechlorinated to give 7-amino-*s*-triazolo[4,3-b]pyridazine (XXIV). Furthermore when XIX was allowed to react with benzoyl chloride in pyridine solution, 7-amino-8-chloro-3-phenyl-*s*-triazolo[4,3-b]pyridazine (XVIII) was obtained.

The conversion of XIX into 7-amino-8-chlorotetrazolo[1,5-b]pyridazine (XXII) was accomplished by allowing XIX to react with nitrous acid. In this instance the cyclization could not proceed to give an analog of X and the infrared spectrum of XXII indicated the absence of an azide group, therefore XXII could not be 5-amino-3-azido-4-chloropyridazine. Compound XXII was readily dechlorinated with palladium on charcoal to 7-aminotetrazolo[1,5-b]pyridazine (XXV), thus a position isomer of the adenine analog I has been prepared. Structures XXII and XXV are consistent with the observed U.V. and I.R. spectra.

5-Amino-3,4-dichloropyridazine (XVI) reacted readily with anthranilic acid to give 3-amino-4-chloro-10H-pyridazino[3,2-b]quinazol-10-one (XV) or the alternate seven membered ring compound XIII. The structure of XV is analogous to the pyridine analog (10). The structure (XV) was assigned on the basis of the broad band in the ultraviolet spectra at 381-396 mμ indicative of three-ring conjugation. This type of conjugation is not possible in structure XIII and thus XIII was eliminated.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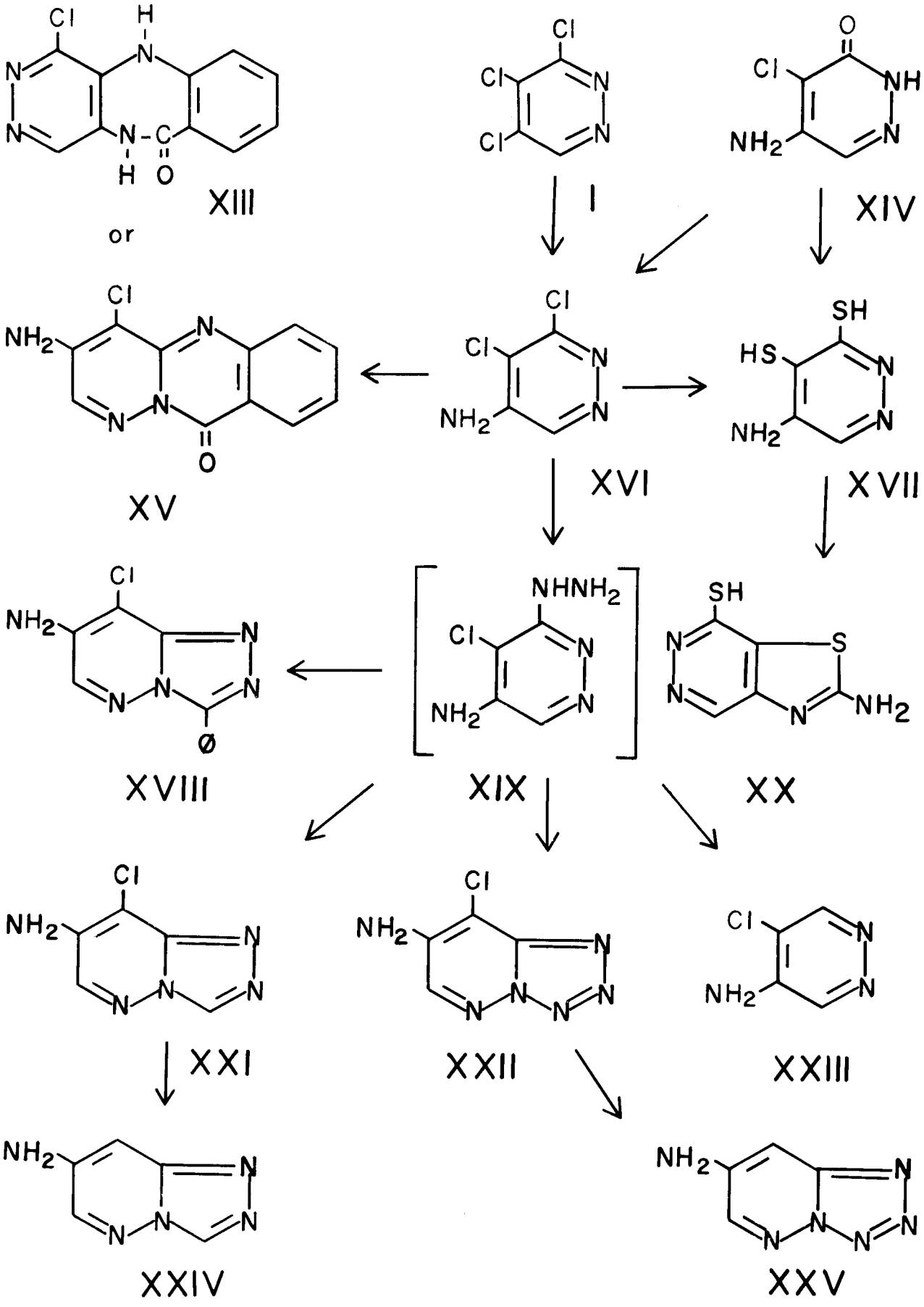
XIII
or
I
XIV
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XX
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XXIV
XXV

With the availability of XVI and XIV the novel nucleophilic displacement reaction of halogen with phosphorus pentasulfide (11) was extended. When XVI was allowed to react with phosphorus pentasulfide in pyridine solution, the 5-aminopyridazine-3,4-dithiol (XVII) was obtained in 64% yield. However when XIV was allowed to react with phosphorus pentasulfide under similar conditions, XVII was obtained in only 21% yield. It has been our experience in the pyridazine ring system as well as in several other heterocyclic ring systems that halogen is displaced more readily than oxygen with phosphorus pentasulfide.

In order to give further proof of the structure of XVII, it was allowed to react with cyanogen bromide to give the alkali-soluble 2-aminothiazolo[4,5-d]pyridazine-7-thiol (XX).

EXPERIMENTAL (12)

4-Amino-3,5-dichloropyridazine (II) and 5-Amino-3,4-dichloropyridazine (XVI).

The procedure of Kuraishi (3) was modified and scaled up. A stainless steel reaction vessel (1.7 l. capacity) was charged with 123 g. (0.67 mole) of 3,4,5-trichloropyridazine (Caution! Produces severe blisters.) and 1.25 l. of about 18% absolute ethanolic ammonia. The reaction mixture was heated at 125° in a rocking autoclave for 5 hrs. The crude reaction mixture (107 g.) was separated into 38 g. (35%) of II (m.p. 151°) and 42 g. (38%) of XVI (m.p. 178°). II was soluble in chloroform while XVI was only slightly soluble. Final purification was accomplished by chromotography on alumina.

4-Amino-5-chloro-3-hydrazinopyridazine (V).

A solution containing 38 g. (0.23 mole) of II dissolved in 130 ml. of 95% hydrazine was heated on the steam bath for 3 hrs. After cooling and the addition of water (130 ml.), the crystals were collected and recrystallized from water. There was obtained 20.8 g. (56%) of V, m.p. 201-202° dec.

Anal. Calcd. for $C_4H_6ClN_5$: C, 30.09; H, 3.77; N, 43.88. Found: C, 30.68; H, 3.93; N, 44.09.

U.V. λ max (95% C_2H_5OH) 218-220 (ε, 19,750); 266 (ε, 11,500); 288-294 mμ (ε, 10,000).

Infrared spectrum, cm^{-1}, 3470 (m), 3300 (s), 3230 (m), 3180 (m), 2950 (m), 1643 (s), 1588 (s), 1518 (w), 1473 (s), 1338 (w), 1304 (m), 1268 (w), 1247 (w), 1139 (m), 1081 (m), 1004 (w), 910 (m), 882 (m), 857 (w), 764 (m), 734 (m).

The picrate was prepared in the usual manner, m.p. 199-200°.

Anal. Calcd. for $C_{10}H_5ClO_7N_8$: C, 30.90; H, 2.31; N, 28.82. Found: C, 30.59; H, 2.34; N, 28.29.

5-Chloro-3,4-diaminopyridazine (VIII).

A suspension containing 9 g. (0.0565 mole) of V and approximately 3 g. of freshly prepared Raney Nickel in 600 ml. of absolute ethanol was hydrogenated at atmospheric pressure and at room temperature until about 1.4 l. of hydrogen was absorbed. After removal of the catalyst, the filtrate was evaporated at room temperature under a stream of compressed air. The residue was recrystallized from water (charcoal) and collected as the hemihydrate, m.p. 194-196°.

Anal. Calcd. for $C_4H_5ClN_4 \cdot 1/2H_2O$: C, 31.20; H, 3.91; N, 36.48. Found: C, 31.48; H, 4.35; N, 36.88.

A picrate of VIII was prepared from the hemihydrate and recrystallized from water, m.p. 266°.

Anal. Calcd. for $C_{10}H_6ClN_7O_7 \cdot 1/2H_2O$: C, 31.36; H, 2.35; N, 25.61. Found: C, 31.84; H, 2.83; N, 25.42.

The VIII hemihydrate was dried under reduced pressure over phosphorus pentoxide for 5 hrs. at 95°. The anhydrous VIII m.p. 205° was obtained in 85% yield from V.

Anal. Calcd. for $C_4H_5ClN_4$: C, 33.21; H, 3.46; N, 38.76. Found: C, 33.54; H, 3.74; N, 38.72.

U.V. λ max (95% C_2H_5OH) 214-218 (ε, 20,300); 264 (ε, 11,250); 295 mμ (ε, 11,370).

Infrared spectrum cm^{-1}, 3420 (s), 3330 (s), 3060 (s), 1658 (m), 1633 (s), 1613 (m), 1568 (m), 1533 (s), 1473 (s), 1423 (w), 1338 (m), 1300 (m), 1291 (m), 1140 (w), 1105 (m), 1074 (m), 1036 (w), 920 (s), 899 (m), 849 (m), 720 (m).

7-Chloroimidazo[4,5-c]pyridazine (XI).

Method I.

One g. (0.0069 mole) of VIII was suspended in 20 ml. (0.13 mole) of freshly distilled ethyl orthoformate and heated under reflux for 1 hr. After cooling, the crystals were collected, washed with ether and recrystallized from acetone, yield 0.9 g. (84%) m.p. >360°.

Anal. Calcd. for $C_5H_3ClN_4$: C, 38.84; H, 1.94; N, 36.24. Found: C, 39.20; H, 2.51; N, 36.45.

A picrate was prepared from XI and recrystallized from water, m.p. 139-140° dec.

Anal. Calcd. for $C_{11}H_6ClN_7O_7 \cdot H_2O$: C, 32.89; H, 1.99; N, 24.41. Found: C, 32.69; H, 2.12; N, 24.87.

Method II.

A mixture of 4.2 g. (0.0225 mole) of IX and approximately 3 g. of Raney Nickel in 250 ml. of absolute ethanol was heated on the steam bath for 5 hrs. After removal of the catalyst, the filtrate was evaporated on the steam bath under reduced pressure. The residue was recrystallized from acetone giving 0.5 g. (14%) of XI. This compound was shown to be identical with the sample of XI as prepared above by mixed melting points of the picrates and by comparison of the infrared spectra, cm^{-1}, 3090 (m), 3060 (m), 2970 (m), 2730 (s), 2670 (s), 2535 (s), 1858 (w), 1613 (m), 1563 (m), 1473 (s), 1408 (m), 1388 (s), 1343 (w), 1294 (s), 1251 (m), 1248 (m), 1239 (m), 1220 (s), 1215 (s), 1191 (w), 1146 (m), 1094 (m), 1081 (m), 987 (w), 973 (w), 944 (s), 927 (m), 898 (w), 886 (w), 863 (s), 722 (w).

U.V. λ max (abs. C_2H_5OH) 212 (ε, 20,200); 260 (ε, 11,500); 272 (ε, 12,000); 305 mμ (sh) (ε, 3,500).

7-Aminoimidazo[4,5-c]pyridazine (XII).

A mixture of 2.5 g. (0.0162 mole) of XI in 250 ml. of 95% ethanol saturated with ammonia at 0-5° was heated in a stainless steel reaction vessel in a rocking autoclave at 210-220° for 25 hrs. After removal of the solvent, the residue was recrystallized from water giving 0.6 g. (27%) of solid, m.p. 335-338° dec.

U.V. λ max (abs. C_2H_5OH) 208-218 (ε, 20,300); 260 (ε, 11,870); 300 mμ (ε, 15,850).

Infrared cm^{-1}, 3515 (m), 3355 (s), 3225 (s), 3035 (s), 2500 (w), 1678 (s), 1638 (s), 1568 (s), 1523 (w), 1483 (m), 1453 (s), 1368 (s), 1320 (s), 1250 (m), 1157 (m), 1096 (m), 1066 (w), 928 (s), 888 (m), 864 (m), 781 (w), 723 (s).

Anal. Calcd. for $C_5H_5N_5 \cdot 1/5H_2O$: C, 43.27; H, 3.92; N, 50.48; H_2O, 2.35. Found: C, 43.40; H, 3.43; N, 50.02; H_2O, 2.46.

In some instances a monohydrate was obtained which liberated water at about 240°, melting with decomposition at 290-295°. This compound was somewhat efflorescent. The ultraviolet spectrum was identical to that described above. The infrared spectrum was nearly identical.

Anal. Calcd. for $C_5H_5N_5 \cdot H_2O$: C, 39.21; H, 4.57; N, 45.75; H_2O, 11.76. Found: C, 39.37; H, 4.55; N, 45.72; H_2O, 7.8.

7-Chloroimidazo[4,5-c]pyridazine-2-thiol (IX).

A mixture of 4.45 g. (0.0308 mole) of VIII, 26 ml. (0.43 mole) of carbon disulfide, 50 ml. (0.62 mole) of dry pyridine and 2.5 g. (0.0625 mole) of crushed sodium hydroxide was heated for 1.5 hrs. After removal of the solvent under reduced pressure, the residue was dissolved in water and acidified with concentrated hydrochloric acid. The precipitated crystals were collected and washed with water giving 4.0 g. (70%) of the product, m.p. >350° dec. The analytical sample was purified by recrystallization from a large amount of 80-90% ethanol.

U.V. λ max (abs. C_2H_5OH) 205 (ε, 15,100); 238 (ε, 17,000); 250 (ε, 18,600); 333 mμ (ε, 22,100).

Infrared cm^{-1}, 3040 (w), 2980 (w), 2700 (w), 2330 (w), 1788 (w), 1628 (m), 1578 (m), 1503 (s), 1433 (m), 1348 (m), 1260 (m), 1230 (m), 1204 (s), 1179 (s), 1068 (s), 990 (m), 940 (w), 909 (w), 898 (m), 874 (w), 769 (w), 724 (m), 710 (m).

Anal. Calcd. for $C_5H_3ClN_4S \cdot 1/2H_2O$: C, 30.67; H, 2.04; N, 28.62. Found: C, 30.85; H, 1.95; N, 28.61.

The anhydrous compound was obtained by further drying at 95° under high vacuum over phosphorus pentoxide for 10 hrs. m.p. >360° dec.

Anal. Calcd. for $C_5H_3ClN_4S$: C, 32.15; H, 1.61; N, 30.02. Found: C, 32.33; H, 2.03; N, 30.54.

7-Chloro-2-methylthioimidazo[4,5-c]pyridazine (VI).

To a solution containing 1.0 g. (0.00535 mole) of IX dissolved in 10 ml. of 1 N potassium hydroxide solution was added 0.8 g. (0.00563 mole) of methyl iodide. The mixture was stirred at room temperature for 3 hrs. Some crystals of unknown structure separated during the reaction. These were removed and the filtrate was acidified with acetic acid. The solid was collected and recrystallized from aqueous ethanol giving 0.3 g. (28%) of VI, m.p. >360° dec.

U.V. λ max (abs. C_2H_5OH) 207 (ε, 17,000); 227 (ε, 18,600); 297 mμ (ε, 19,600).

Infrared cm^{-1}, 2425 (m), 1733 (w), 1568 (m), 1478 (m), 1423 (s), 1358 (m), 1318 (m), 1270 (s), 1242 (s), 1214 (s), 1087 (m), 981 (m), 949 (m), 898 (m), 719 (w), 691 (s).

Anal. Calcd. for $C_6H_5ClN_4S$: C, 35.91; H, 2.49; N, 27.93; S, 15.98. Found: C, 35.34; H, 2.62; N, 27.61; S, 15.92.

8-Amino-7-chlorotetrazolo[1,5-b]pyridazine (IV).

A solution was prepared containing 1.1 g. (0.0069 mole) of V in 10 ml. of water containing 0.6 ml. of concentrated hydrochloric acid. A trace of undissolved solid was removed by filtration. To this solution was added 0.5 g. of sodium nitrite in 4 ml. of water at room temperature. The crystals which separated were collected and recrystallized from water giving 1.2 g. (93%) of product, m.p. 292-293°.

U.V. λ max (95% C_2H_5OH) 205 (ε, 15,500); 273 (ε, 9,130); 299 mμ (ε, 10,900).

Infrared cm^{-1}, 3355 (m), 3325 (m), 3230 (w), 3180 (s), 3050 (m), 1653 (s), 1593 (w), 1578 (s), 1503 (m), 1383 (m), 1333 (s), 1313 (m), 1290 (m), 1251 (w), 1218 (m), 1150 (m), 1101 (m), 1072 (s), 1003 (s), 969 (w), 919 (m), 909 (m), 754 (m), 720 (w), 715 (w).

Anal. Calcd. for $C_4H_3ClN_6$: C, 28.15; H, 1.76; N, 49.25; Cl, 20.85. Found: C, 28.51; H, 2.72; N, 49.65; Cl, 21.01.

8-Aminotetrazolo[1,5-b]pyridazine (I).

To a solution containing 0.3 g. (0.00176 mole) of IV and 0.1 g. (0.0025 mole) of NaOH in 100 ml. of 95% ethanol was added approximately 1.0 g. of 5% palladium on charcoal. The mixture was hydrogenated at atmospheric pressure and at 27° until about 50 ml. of hydrogen was absorbed. After removal of catalyst, the filtrate was evaporated to dryness under reduced pressure and the residue was extracted with hot absolute ethanol. After cooling the extract, 0.15 g. (63%) of white crystals separated, m.p. 275-277° dec. The analytical sample was further recrystallized from water with no change in melting point.

U.V. λ max (95% C_2H_5OH); 209 (ε, 11,250); 294 mμ (ε, 19,600).

Infrared cm^{-1}, 3380 (s), 3335 (s), 3190 (s), 3070 (m), 1948 (w), 1658 (s),

1578 (s), 1493 (s), 1403 (w), 1383 (m), 1353 (m), 1328 (w), 1301 (s), 1258 (m), 1221 (m), 1149 (w), 1088 (m), 1022 (w), 1008 (m), 892 (m), 850 (m), 844 (m), 765 (w), 722 (w), 711 (w).

Anal. Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.94; N, 61.76. Found: C, 35.17; H, 3.02; N. 61.67.

5-Amino-3,4-pyridazinedithiol (XVII).

Method 1.

A mixture of 3.2 g. (0.0195 mole) of XVI and 3.1 g. (0.0408 mole) of thiourea in 60 ml. of absolute ethanol was heated under reflux for 2 hrs. After cooling, the solid which separated was warmed with 50 ml. of 10% sodium hydroxide solution on a steam bath for 5 min. and filtered. The filtrate was acidified with glacial acetic acid to about *p*H 3-4, and chilled in the refrigerator. The crystals were collected and recrystallized from water, 0.5 g. (16%), m.p. >350° dec.

U.V. λ max (5N NaOH); 227 (ε, 20,800); 262 (ε, 21,900); 319 mμ (ε, 13,250).

U.V. λ max (95% C_2H_5OH) 212 (ε, 20,250); 255 (ε, 18,200); 278 (ε, 20,000); 314 mμ (ε, 12,200).

Infrared cm^{-1}, 3385 (m), 3320 (m), 3200 (m), 2300 (m), 1658 (s), 1588 (m), 1543 (s), 1463 (m), 1433 (m), 1338 (s), 1313 (m), 1233 (s), 1079 (w), 1044 (w), 972 (m), 888 (m), 842 (m), 779 (s), 722 (m).

Anal. Calcd. for $C_4H_5N_3S_2 \cdot 1/2H_2O$: C, 28.55; H, 3.56; N, 24.97; S, 38.12. Found: C, 28.76; H, 3.34; N, 25.24; S, 38.02.

Method 2.

A solution containing 2.5 g. (0.0152 mole) of XVI and 20 g. (0.09 mole) of phosphorus pentasulfide in 100 ml. of dry pyridine was protected from moisture and heated under reflux for 8 hrs. After removal of the pyridine under reduced pressure, the residue was poured on ice and stirred. The mixture was heated on the steam bath for 2 hrs., filtered while still warm and acidified with glacial acetic acid to about *p*H 4 and chilled. The crystals were collected and recrystallized from water giving 1.6 g. (64%), m.p. >350° dec. The infrared spectrum was identical with that from the sample prepared as described in Method 1.

Method 3.

In 100 ml. of pyridine, 2.91 g. (0.002 mole) of XIV and 20 g. (0.009 mole) of phosphorus pentasulfide was heated for 8 hrs. The product was treated and isolated as described in Method 2 above; yield 0.7 g. (20%). The infrared spectrum of this compound was identical with those prepared by methods 1 and 2.

4-Amino-5-chloropyridazine (XXIII).

A suspension of 2.4 g. (0.014 mole) of XVI in 12 ml. of hydrazine was heated on a steam bath for 3 hrs. During the heating period XVI dissolved in the hydrazine. After cooling, water was added and 1.9 g. of crude 5-amino-4-chloro-3-hydrazinopyridazine (XIX) was collected which had a m.p. of 205-208° after crystallization from water. In 50 ml. of hot water was dissolved 1.6 g. (0.00627 mole) of (XIX) and to this a solution (45 ml.) containing 5.5 g. (0.022 mole) of copper sulfate pentahydrate was added and heated for 1.5 hrs. The solution was made basic with 10% sodium hydroxide solution and it was again heated for 5 min. The precipitated copper oxide was removed by filtration, the filtrate was acidified with acetic acid and evaporated to dryness under reduced pressure. The residue was extracted with acetone, the acetone extract evaporated and the residue recrystallized from water or from benzene; yield 0.5 g., m.p. 70-73°.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.06; H, 3.09. Found: C, 36.59; H, 3.84.

Picrate of XXIII, m.p. 210-212° from water.

Anal. Calcd. for $C_{10}H_7ClN_6O_7$: C, 33.48; H, 1.95; N, 23.43. Found: C, 33.71; H, 2.06; N, 23.69.

7-Amino-8-chlorotriazolo[4,3-b]pyridazine (XXI).

In 50 ml. of formic acid, 3.2 g. (0.02 mole) of XIX was heated for 3 hrs. After removal of the excess formic acid under reduced pressure, the residue was washed with water. After recrystallization from water, there was obtained 2.8 g. (82%) yield of XXI, m.p. 285° dec.

U.V. λ max (95% C_2H_5OH) 208 (ε, 18,400); 225 (sh) (ε, 17,250); 247-248 (ε, 7,000); 334-336 mμ (ε, 4,100).

Infrared cm^{-1}, 3430 (s), 3325 (s), 3210 (s), 3140 (m), 3040 (w), 3015 (w), 2950 (w), 1648 (s), 1628 (s), 1542 (w), 1518 (s), 1468 (w), 1428 (s), 1358 (m), 1333 (s), 1240 (m), 1192 (s), 1147 (w), 1025 (m), 1019 (m), 974 (w), 949 (w), 919 (m), 797 (s), 733 (m), 721 (w).

Anal. Calcd. for $C_5H_4ClN_5$: C, 35.39; H, 2.36; N, 41.29. Found: C, 35.71; H, 2.55; N, 40.96.

The benzoate was obtained by heating XXI with excess benzoyl chloride for 30 min. The crude product was recrystallized from aqueous methanol, m.p. 220-222°.

Anal. Calcd. for $C_{12}H_8ClN_5O \cdot H_2O$: C, 49.39; H, 3.43; N, 24.01. Found: C, 49.47; H, 3.47; N, 23.83.

3-Amino-4-chloro-10H-pyridazino[3,2-b]quinazol-10-one (XV).

To 50 ml. of water containing 2 ml. of concentrated hydrochloric acid was added 1.64 g. (0.01 mole) of XVI and 1.37 g. (0.01 mole) of anthranilic acid. The mixture was heated for 7 hrs. After cooling, the solution was neutralized with 10% sodium hydroxide solution. The solid was collected and washed with water giving 1.1 g. (45%) of crude XV which when recrystallized from absolute ethanol had a m.p. of 348-350° dec.

U.V. λ max (95% C_2H_5OH) 226-230 (ε, 18,600); 329 (ε, 13,750); 343 (ε, 15,100); 381-396 mμ (ε, 5,830).

Infrared cm^{-1}, 3460 (m), 3280 (m), 3185 (m), 3045 (w), 1698 (s), 1648 (s), 1603 (m), 1558 (m), 1528 (s), 1463 (m), 1458 (s), 1418 (s), 1338 (m), 1328 (m), 1286 (m), 1254 (m), 1177 (m), 1164 (m), 1149 (m), 1004 (w), 929 (w), 896 (m), 862 (w), 796 (m), 757 (s), 720 (w).

Anal. Calcd. for $C_{11}H_7ClN_4O$: C, 53.54; H, 2.84; N, 22.71. Found: C, 53.55; H, 3.19; N, 22.94.

7-Amino-s-triazolo[4,3-b]pyridazine (XXIV).

A mixture containing 5 g. (0.295 mole) of XXI and approximately 1 g. of 5% palladium on charcoal in 1 l. of 95% ethanol was hydrogenated (980 ml. of hydrogen was absorbed at 27°). The catalyst was removed and the filtrate neutralized with ammonium hydroxide, evaporated under reduced pressure and the residue was recrystallized from water, giving 2.6 g. (66%) of yellow prisms, m.p. 272-275° dec.

U.V. λ max (95% C_2H_5OH) 214 (ε, 19,500); 234 (ε, 19,750); 252 (sh) (ε, 13,600); 343 mμ (ε, 6,880).

Infrared cm^{-1}, 3335 (m), 3150 (m), 3130 (m), 1638 (s), 1533 (s), 1448 (m), 1403 (s), 1239 (s), 1187 (m), 994 (s), 971 (m), 954 (m), 916 (m), 840 (w), 820 (m), 797 (s), 740 (s), 720 (w).

Anal. Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.70; N, 51.85. Found: C, 44.35; H, 3.86; N, 51.40.

7-Amino-8-chlorotetrazolo[1,5-b]pyridazine (XXII).

To a solution of 5.0 g. (0.0314 mole) of crude XIX in 30 ml. of 1.2 N hydrochloric acid was added portionwise at room temperature 2.5 g. (0.036 mole) of sodium nitrite in 10 ml. of water. The separated solid was collected and recrystallized from aqueous ethanol yielding 2.7 g. (51%) of XXII, m.p. 270° dec.

U.V. λ max (95% C_2H_5OH) 214 (ε, 23,750); 264 (ε, 15,200); 332 mμ (ε, 10,250).

Infrared cm^{-1}, 3330 (m), 3310 (m), 3190 (s), 1643 (s), 1623 (s), 1508 (s), 1478 (w), 1433 (s), 1358 (s), 1293 (m), 1246 (m), 1186 (m), 1151 (m), 1088 (s), 984 (m), 950 (s), 927 (m), 804 (m), 744 (w), 720 (w).

Anal. Calcd. for $C_4H_3ClN_6$: C, 28.15; H, 1.76; N, 49.25. Found: C, 28.39; H, 2.04; N, 49.11.

7-Aminotetrazolo[1,5-b]pyridazine (XXV).

A mixture containing 0.3 g. (0.00176 mole) of XXII, 0.1 g. (0.0025 mole) of sodium hydroxide and approximately 1 g. of 5% palladium charcoal in 100 ml. of 95% ethanol was hydrogenated. After removal of the catalyst and evaporation of the solvent under reduced pressure, the residue was extracted with hot absolute ethanol giving after recrystallization from water 0.18 g. (76%) of XIX, m.p. 248° dec.

U.V. λ max (95% C_2H_5OH) 218 (ε, 19,900); 262 (ε, 15,000); 334 mμ (ε, 7,500).

Infrared cm^{-1}, 3435 (m), 3310 (m), 3190 (m), 3065 (m), 1673 (w), 1643 (s), 1613 (s), 1568 (m), 1518 (m), 1503 (m), 1458 (w), 1428 (s), 1398 (m), 1368 (s), 1348 (s), 1288 (s), 1262 (s), 1233 (s), 1166 (w), 1080 (s), 996 (s), 970 (s), 946 (m), 855 (s), 841 (s), 757 (s), 724 (w), 699 (m).

Anal. Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.94; N, 61.76. Found: C, 35.21; H, 3.16; N, 61.45.

7-Amino-8-chloro-3-phenyl-s-triazolo[4,3-b]pyridazine (XVIII).

A mixture of 1.6 g. (0.01 mole) of crude XIX, 2.3 ml. (0.02 mole) of benzoyl chloride in 50 ml. of dry pyridine was heated on the steam bath for 1 hr. After removal of the solvent under reduced pressure, the residue was washed with a small amount of methanol. There was obtained 1.0 g. (41%) of XVIII, m.p. 295-296° dec. after recrystallization from methanol.

U.V. λ max (95% C_2H_5OH) 221 (ε, 23,200); 294 (ε, 19,700); 355 mμ (ε, 7,750).

Infrared cm^{-1}, 3465 (m), 3305 (s), 3175 (s), 3030 (m), 2950 (w), 1638 (s), 1603 (m), 1528 (w), 1505 (m), 1468 (m), 1443 (w), 1418 (m), 1378 (m), 1340 (w), 1323 (s), 1284 (w), 1246 (w), 1192 (w), 1079 (w), 1064 (m), 988 (w), 954 (w), 924 (m), 812 (w), 771 (s), 766 (s), 735 (s), 723 (w), 703 (m), 692 (s).

Anal. Calcd. for $C_{11}H_8ClN_5$: C, 53.76; H, 3.26; N, 28.51. Found: C, 53.96; H, 3.46; N, 28.17.

2-Aminothiazolo[4,5-d]pyridazine-7-thiol (XX).

To a solution of 1.3 g. (0.0077 mole) of XVII hydrate in sodium hydroxide (0.62 g. of sodium hydroxide in 20 ml. of water) cooled to below 10° was added 0.83 g. (0.0078 mole) of cyanogen bromide in 10 ml. of 95% ethanol. The temperature of the stirred solution was allowed to rise to room temperature after the addition was complete. After acidification of the solution with acetic acid, 1.6 g. of solid m.p. >350° dec. was collected. The analytical sample was recrystallized from a large amount of water.

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.60; H, 2.17; N, 30.43. Found: C, 32.99; H, 2.44; N, 30.16.

Acknowledgment.

This investigation was supported by a PHS research grant No. CA-02653 from the National Cancer Institute, Public Health Service. The authors are grateful to Mrs. Ruby Ju for the analytical data reported and acknowledge the assistance of Mrs. Miriam Malm, Miss Celia Weber and Mrs. R. R. Shoup in determining the ultraviolet absorption spectra.

REFERENCES

(1) Present address: University of Nagasaki, Ohashi-machi, Nagasaki, Japan.

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(3) T. Kuraishi, *Pharm. Bull.* (Tokyo), 4, 497 (1956).

(4) R. N. Castle and W. S. Seese, *J. Org. Chem.*, 23, 1534 (1958).

(5) J. A. Carbon, *J. Am. Chem. Soc.*, 80, 6083 (1958).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules.", Methuen and Co., Ltd., London, 2nd Edition, 1958, p. 274.

(7) E. Lieber, D. R. Levering and L. J. Patterson, *Anal. Chem.*, 23, 1594 (1951).

(8) T. Kuraishi, *Chem. Pharm. Bull.*, 6, 641 (1958).
(9) M. Yanai and T. Kinoshita, *J. Pharm. Soc. Japan*, 82, 857 (1962).
(10) Ernst Späth und Friedrich Kuffner, *Ber.*, 71, 1657 (1938).
O. A. Zeide and G. V. Chelintsev, *J. Gen. Chem.*, (U.S.S.R.) 7, 2318 (1937).
(11) G. S. Castle and K. Isaji, *Tetrahedron Letters*, 393 (1962).

(12) All melting points are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 Spectrophotometer. The range from 4000 to 1300 cm^{-1} were determined in fluorolube suspension and those from 1300 to 700 cm^{-1} were determined in Nujol suspension. The ultraviolet spectra were taken in the solvent indicated with a Bausch and Lomb Spectronic 505 Spectrophotometer.

Received January 14, 1964 Albuquerque, New Mexico