

Department of Chemistry, University of New Mexico

## *s*-Triazolo[4,3-*b*]pyridazines and Imidazo[4,5-*c*]pyridazines.

Tsukasa Kuraishi (1) and Raymond N. Castle (2)

8-Amino-*s*-triazolo[4,3-*b*]pyridazine (I), an adenine analog has been prepared by two different routes. Likewise 8-amino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (V) has been prepared. Both of these compounds have been prepared utilizing 3,4,5-trichloropyridazine and 3,4,6-trichloropyridazine as the starting materials thus interrelating the 3,4,5- and the 3,4,6-series. A variety of other transformations have been carried out.

In a previous paper (3) adenine analogs have been prepared, namely 7-aminoimidazo[4,5-*c*]pyridazine and 8-aminotetrazolo[1,5-*b*]pyridazine. This work was undertaken in order to prepare the additional adenine analogs, 8-amino-*s*-triazolo[4,3-*b*]pyridazine (I) and the 8-amino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (V) which should simulate an adenine nucleoside where the sugar moiety has been replaced by a phenyl group. A variety of other compounds in the *s*-triazolo[4,3-*b*]pyridazine series as well as the two new imidazo[4,5-*c*]pyridazines have been prepared for antitumor screening.

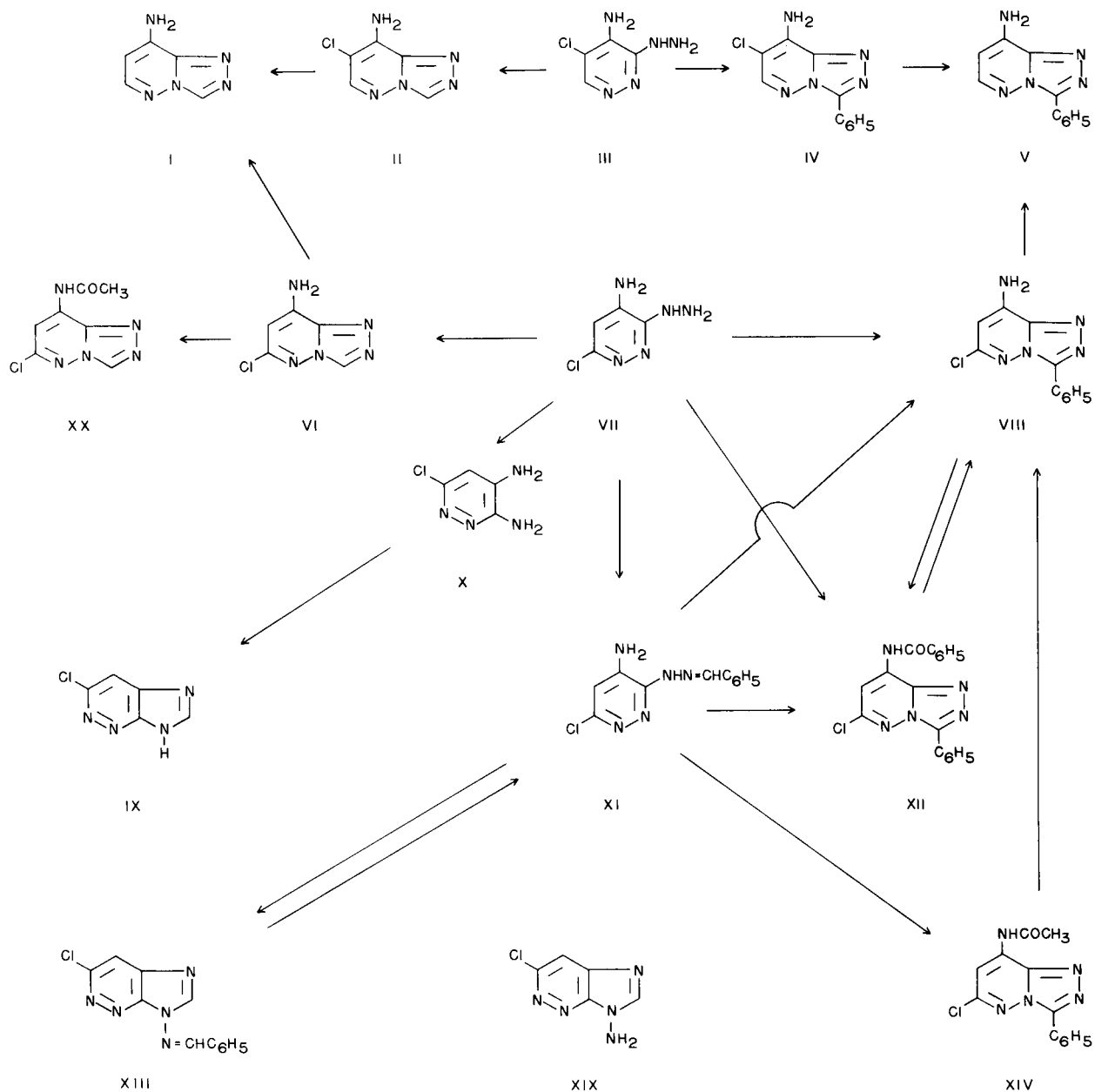
A mixture of 5-amino-3,4-dichloropyridazine (XV) and 4-amino-3,5-dichloropyridazine (XVI) was obtained from an alcoholic solution of ammonia and 3,4,5-trichloropyridazine (4). Compound XVI was readily converted into 4-amino-5-chloro-3-hydrazinopyridazine (III) (3). Compound III was allowed to react with formic acid to give the cyclized product, 8-amino-7-chloro-*s*-triazolo[4,3-*b*]pyridazine (II). Compound II was smoothly dechlorinated with palladium/charcoal and hydrogen at atmospheric pressure to give 8-amino-*s*-triazolo[4,3-*b*]pyridazine (I). Compound I was also obtained from VI as described below. Compound III was allowed to react with benzoyl chloride in pyridine solution to give 8-amino-7-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (IV). Compound IV was readily dechlorinated with palladium/charcoal and hydrogen into 8-amino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (V).

Compound I and V have also been prepared from 3,4,6-trichloropyridazine (XVII) via 4-amino-3,6-dichloropyridazine (XVIII) (5). 4-Amino-6-chloro-3-hydrazinopyridazine (VII) (3) was prepared from XVIII and hydrazine (6). When VII was allowed to react with formic acid, 8-amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (VI) was obtained. Compound VI was catalytically dechlorinated (palladium/charcoal) into the adenine analog (I). When VI was allowed to react with acetic anhydride, 8-acetylamino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (XX) was obtained.

Compound VII was readily converted into 8-amino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (VIII) by allowing VII to react with benzoyl chloride in pyridine solution. Compound VIII was converted into V by catalytic dechlorination (palladium/charcoal). Thus I and V have been prepared from both the 3,4,5- and the 3,4,6-substituted pyridazines thus relating these two series.

Compound VIII was benzoylated to give 8-benzoylamino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (XII). Compound XII was hydrolyzed to regenerate VIII. Compound XII was cyclized directly from VII by allowing VII to react with benzoyl chloride under reflux without any other solvent. In order to establish that the above cyclizations gave the *s*-triazolo[4,3-*b*]pyridazines rather than cyclizing in another way, VII was allowed to react with benzaldehyde to give benzaldehyde 4-amino-6-chloro-3-pyridazinylhydrazone (XI). Compound XI was cyclized by heating it in aqueous acetic acid to give VIII. Furthermore, when XI was heated with benzoyl chloride, XII was obtained. Compound XI was also converted into VIII via XIV by allowing XI to react under reflux with acetic anhydride to give 8-acetylamino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (XIV) which was hydrolyzed into VIII. When XI was heated under reflux with ethyl orthoformate, 3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (XIII) was obtained. The ring opening of XIII with 10% hydrogen chloride in absolute ethanol gave XI. From this reaction mixture benzaldehyde was also isolated as the 2,4-dinitrophenylhydrazone, however, the 3-amino-6-chloroimidazo[4,5-*c*]pyridazine (XIX) could not be recovered. Compound VII was cleaved into 6-chloro-3,4-diaminopyridazine (X) with Raney nickel (7). When X was allowed to react with ethyl orthoformate, 6-chloroimidazo[4,5-*c*]pyridazine (IX) was obtained. In addition to the interrelated reactions described above, the constitution of the above compounds was confirmed by their ultraviolet and infrared spectra.

## FLOW SHEET



## EXPERIMENTAL (8)

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

4-Amino-5-chloro-3-hydrazinopyridazine (III) (2 g., 12.5 mmoles) was allowed to react under reflux with 20 ml. of formic acid for 1.5 hours. After removal of the excess formic acid under reduced pressure, the residue was recrystallized from a mixture of ethanol and water. There was obtained 1.78 g. (84%) of product, m.p. 315-317°.

U. V.  $\lambda$  max (95% ethanol), 203 ( $\epsilon$ , 20,200), 227 ( $\epsilon$ , 8,750), 255 ( $\epsilon$ , 5,500), 263 ( $\epsilon$ , 5,380), 300 m $\mu$  ( $\epsilon$ , 9,750).

Infrared  $\text{cm}^{-1}$ , 3350(m), 3150(s), 2700(w), 1655(s), 1565(s), 1500(m), 1400(w), 1350(m), 1340(m), 1315(m), 1165(m), 1080(m), 1015(m), 970(w), 925(m), 910(m), 810(s), 755(m), 745(m), 720(m), (Nujol mull).  
 Anal. Calcd. for  $\text{C}_5\text{H}_4\text{ClN}_5$ : C, 35.39; H, 2.36; N, 41.29. Found: C, 35.19; H, 2.24; N, 41.37.

## 8-Amino-s-triazolo[4,3-b]pyridazine (I).

(a) A mixture containing 1 g. (5.88 mmoles) of 8-amino-7-chloro-s-triazolo[4,3-b]pyridazine (II), 1 g. of 5% palladium on charcoal and 0.24 g. (6.0 mmoles) of sodium hydroxide in 400 ml. of aqueous ethanol (80%) was hydrogenated at atmospheric pressure and at room

temperature. The catalyst was removed by filtration and the filtrate was neutralized with acetic acid. The solution was evaporated to dryness on the steam bath and the residue was extracted on the steam bath. There was obtained 0.25 g. (32%) of crystalline solid, m.p. 224-228° upon chilling the acetic acid solution.

U. V.  $\lambda$  max (95% ethanol), 205 ( $\epsilon$ , 19,500), 232 ( $\epsilon$ , 14,100), 300  $\mu$  ( $\epsilon$ , 16,000).

Infrared  $\text{cm}^{-1}$ , 3330(s), 3175(s), 2665(w), 1665(s), 1640(s), 1595(m), 1565(s), 1400(w), 1340(m), 1300(m), 1175(m), 1155(m), 1105(w), 1090(w), 1015(m), 1005(m), 960(m), 890(s), 840(s), 825(m), 800(w), 755(m), 720(m), (Nujol mull).

Anal. Calcd. for  $\text{C}_7\text{H}_6\text{ClN}_5$ : C, 44.44; H, 3.73; N, 51.83. Found: C, 44.70; H, 3.69; N, 51.43.

(b) Compound I was also prepared from 8-amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (VI) as follows: VI (2.6 g., 15.3 mmoles), 0.62 g. (15.5 mmoles) of sodium hydroxide and 1 g. of palladium on charcoal (5%) in 300 ml. of aqueous ethanol (80%) were hydrogenated and worked up as described above under (a). There was obtained 1.30 g. (63%) of rhombic crystals, m.p. 225°. A mixture melting point with the product prepared by method (a) above showed no depression.

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

4-Amino-5-chloro-3-hydrazinopyridazine (III) (4) (3.2 g., 20 mmoles) was dissolved in 100 ml. of pyridine and 2.5 ml. (21.5 mmoles) of benzoyl chloride was added to the solution and the reaction mixture was allowed to stand at room temperature for 4 hours. After removal of the solvent, the residue was washed with methanol, collected and recrystallized from ethanol, yield 3.6 g. (73%), m.p. 248-249°.

U. V.  $\lambda$  max (95% ethanol), 203 ( $\epsilon$ , 28,000), 240 ( $\epsilon$ , 17,500), 280 ( $\epsilon$ , 14,500), 310  $\mu$  ( $\epsilon$ , 9,250).

Infrared  $\text{cm}^{-1}$ , 3460(m), 3320(m), 2670(w), 1640(s), 1560(s), 1490(s), 1400(w), 1340(w), 1315(m), 1250(m), 1110(w), 1055(m), 1030(w), 980(m), 945(w), 925(m), 915(m), 775(s), 745(m), 720(m), (Nujol mull).

Anal. Calcd. for  $\text{C}_{11}\text{H}_8\text{ClN}_5$ : C, 53.76; H, 3.28; N, 28.51. Found: C, 53.80; H, 3.16; N, 28.17.

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

(a) 8-Amino-7-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (IV) (1.35 g., 5.5 mmoles), 0.24 g. (6.0 mmoles) of sodium hydroxide and 0.6 g. of palladium on charcoal (5%) were suspended in 200 ml. of aqueous ethanol (80%) and the mixture hydrogenated at atmospheric pressure and at room temperature. After removal of the catalyst the filtrate was evaporated to dryness and the residue was extracted with acetone. The acetone was evaporated and the dry residue was dissolved in chloroform and the chloroform solution was chromatographed on alumina, additional chloroform being used as the eluent. The chloroform eluate was evaporated to dryness and the residue was recrystallized from hot water. There was obtained 0.7 g. (60%) of product, m.p. 210-212°.

U. V.  $\lambda$  max (95% ethanol), 205 ( $\epsilon$ , 22,500), 252 ( $\epsilon$ , 19,700), 294 ( $\epsilon$ , 16,400), 306  $\mu$  (sh) ( $\epsilon$ , 14,400).

Infrared  $\text{cm}^{-1}$ , 3510(m), 3340(w), 3155(s), 3095(w), 1650(s), 1570(s), 1495(s), 1410(m), 1325(m), 1315(m), 1225(w), 1135(m), 1070(m), 1015(w), 975(m), 930(w), 905(m), 845(w), 800(m), 775(s), 750(s), 720(w), 710(m), 705(m), (Nujol mull).

Anal. Calcd. for  $\text{C}_{11}\text{H}_8\text{N}_5$ : C, 62.54; H, 4.29; N, 33.16. Found: C, 62.93; H, 4.68; N, 32.89.

(b) Compound V was also prepared from VIII as follows: 8-amino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (VIII) (1 g., 4.07 mmoles), 0.2 g. (5.0 mmoles) of sodium hydroxide and 0.5 g. of palladium on charcoal (5%) were suspended in 200 ml. of aqueous ethanol (80%) and hydrogenated, isolated and purified as described above under (a). There was obtained 0.6 g. of product, m.p. 209-212°, which did not depress the melting point of V as prepared under method (a). The infrared spectrum was identical.

#### 8-Amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (VI).

4-Amino-6-chloro-3-hydrazinopyridazine (VII) (6) (3.2 g., 20.0 mmoles) was heated under reflux with 50 ml. (excess) of formic acid (98%) for 4 hours. After cooling a small quantity of water was added to the reaction mixture and the cooled solution was allowed to stand. The solid which separated was filtered and recrystallized from hot water, yield 3.2 g. (94%), m.p. 278°.

U. V.  $\lambda$  max (95% ethanol), 212 ( $\epsilon$ , 17,300), 230 (sh) ( $\epsilon$ , 7,000), 298  $\mu$  ( $\epsilon$ , 10,400).

Infrared  $\text{cm}^{-1}$ , 3350(s), 3100(s), 2700(w), 1670(s), 1575(s), 1345(m), 1170(w), 1120(m), 1070(w), 1015(m), 970(m), 950(s), 850(w), 825(w), 805(w), 770(m), 745(m) (Nujol mull).

Anal. Calcd. for  $\text{C}_8\text{H}_6\text{ClN}_5$ : C, 35.39; H, 2.36; N, 41.29. Found: C, 35.32; H, 2.32; N, 41.20.

#### 8-Acetylamino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (XX).

Compound VI (1 g.) and 30 ml. of acetic anhydride were heated under reflux for 8 hours. The excess solvent was evaporated and the residue was recrystallized from hot water, yield 0.9 g. (80%), m.p. 259°.

Anal. Calcd. for  $\text{C}_7\text{H}_6\text{ClN}_5\text{O}$ : C, 39.71; H, 2.83; N, 33.09; Cl, 16.77. Found: C, 39.85; H, 2.96; N, 32.85; Cl, 16.40.

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

(a) From 4-Amino-6-chloro-3-hydrazinopyridazine (VII).

Compound VII (1.6 g., 10 mmoles) was suspended in 50 ml. of pyridine and 2.3 ml. (20 mmoles) of benzoyl chloride was added with stirring. After the exothermic reaction subsided, the reaction mixture was heated on the steam bath for 1 hour, then evaporated to dryness under reduced pressure. The residue was washed with methanol and then with water, dried, and recrystallized from ethanol, yield 1.55 g. (63%), m.p. 274°.

U. V.  $\lambda$  max (95% ethanol), 203 ( $\epsilon$ , 21,500), 253 ( $\epsilon$ , 21,700), 288 ( $\epsilon$ , 13,600), 300 (sh)  $\mu$  ( $\epsilon$ , 10,700).

Infrared  $\text{cm}^{-1}$ , 3480(m), 3325(w), 3075(m), 2665(w), 1645(s), 1600(m), 1575(s), 1410(m), 1250(m), 1140(m), 1110(m), 1095(m), 1070(w), 1030(w), 985(m), 950(s), 940(s), 920(w), 840(s), 770(m), 765(s), 745(m), 715(m), 695(m), (Nujol mull).

Anal. Calcd. for  $\text{C}_{11}\text{H}_8\text{ClN}_5$ : C, 53.79; H, 3.28; N, 28.51. Found: C, 53.99; H, 3.32; N, 28.90.

(b) From Benzaldehyde 4-Amino-6-chloro-3-pyridazinylhydrazone (XI).

Compound XI (1 g., 6.72 mmoles) was suspended in 150 ml. of aqueous acetic acid (20%) and the mixture was heated on the steam bath for 25 hours. After allowing the solution to cool, 0.6 g. (40%) of crystals, m.p. 270-272°, was obtained. The compound melted at 273° after recrystallization from ethanol. This sample did not depress the melting point of a sample prepared by method (a) above.

(c) From 8-Acetylamino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (XIV).

Compound XIV (1 g., 3.4 mmoles) was heated with a mixture of 30 ml. of concentrated hydrochloric acid and 80 ml. of ethanol on a steam bath for 1 hour. After evaporation of the solvent the residue was washed with dilute potassium carbonate solution. The residue was recrystallized from ethanol, yield 0.7 g. (82%), m.p. 272°. Compound VIII prepared by this method did not depress the melting point of VIII as prepared by method (a).

(d) From 8-Benzoylamino-6-phenyl-*s*-triazolo[4,3-*b*]pyridazine (XII).

Compound XII (1 g., 2.86 mmoles) was heated under reflux with 190 ml. of 5% sodium hydroxide solution in ethanol for 1 hour. After evaporation of the solvent, the residue was washed with water, filtered and recrystallized from ethanol, yield 0.4 g. (57%), m.p. 272°. This sample of VIII did not depress the melting point of VIII as prepared by methods described under (a,b,c) above.

#### 8-Benzoylamino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (XII).

(a) From 4-Amino-6-chloro-3-hydrazinopyridazine (VII).

Compound VII (2.0 g., 12.5 mmoles) was heated with 25 ml. (215 mmoles) of benzoyl chloride without any additional solvent under reflux for 40 minutes. The reaction mixture was allowed to cool and after standing at room temperature, crystals separated which were filtered and washed with methanol and recrystallized from ethanol, yield 2.25 g. (51%), m.p. 216-223°.

U. V.  $\lambda$  max (95% ethanol), 207 ( $\epsilon$ , 23,900), 273 ( $\epsilon$ , 24,200), 321  $\mu$  ( $\epsilon$ , 11,500).

Infrared  $\text{cm}^{-1}$ , 3450(w), 2700(w), 1695(s), 1620(m), 1600(w), 1580(w), 1555(s), 1530(m), 1515(s), 1490(m), 1425(w), 1405(m), 1330(w), 1315(w), 1280(w), 1250(s), 1230(m), 1130(m), 1105(s), 1070(w), 1040(w), 1025(s), 980(m), 945(m), 930(w), 855(s), 780(m), 775(s), 745(w), 705(s), (Nujol mull).

Anal. Calcd. for  $\text{C}_{18}\text{H}_{12}\text{ClN}_5\text{O}$ : C, 61.80; H, 3.46; N, 20.03; Cl, 10.14. Found: C, 61.79; H, 3.34; N, 19.69; Cl, 10.62.

(b) From Benzaldehyde 4-Amino-6-chloro-3-pyridazinylhydrazone (XI).

Compound XI (1.0 g., 6.72 mmoles) was heated with 14 ml. (120 mmoles) of benzoyl chloride under gentle reflux for 30 minutes. The reaction mixture was allowed to stand overnight in the refrigerator, whereupon 0.3 g. (14%) of crystals, m.p. 218-222°, was obtained. This sample of XII did not depress the melting point of the sample of XII prepared by method (a).

(c) From 8-Amino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (VIII).

Compound VIII (0.8 g., 3.25 mmoles) was allowed to react with 8 ml. (70 mmoles) of benzoyl chloride as described in method (b) above. There was obtained 0.65 g. (57%) of crystals, m.p. 218-222°. This sample of XII did not depress the melting point of XII prepared by either methods (a) or (b).

Benzaldehyde 4-Amino-6-chloro-3-pyridazinylhydrazone (XI).

4-Amino-6-chloro-3-hydrazinopyridazine (VII) (1 g., 6.27 mmoles) was dissolved in 200 ml. of ethanol (95%) by heating on a steam bath. To this solution was added gradually 1 ml. (9.85 mmoles) of benzaldehyde. The reaction mixture was allowed to stand at room temperature overnight. The crystalline mass was collected and recrystallized from ethanol, yield 1.2 g. (77%), m.p. 234°.

U. V.  $\lambda$  max (95% ethanol), 203 ( $\epsilon$ , 20,500), 237 ( $\epsilon$ , 21,900), 344  $\mu$  ( $\epsilon$ , 20,800).

Infrared  $\text{cm}^{-1}$ , 3355(s), 3185(m), 1600(s), 1570(s), 1535(s), 1360(s), 1315(m), 1300(m), 1225(w), 1190(s), 1060(s), 965(s), 955(s), 895(w), 850(m), 840(m), 755(m), 710(w), (Nujol mull).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{ClN}_5$ : C, 53.33; H, 4.06; N, 28.28. Found: C, 52.99; H, 4.32; N, 27.90.

Acetate of XI.

Compound XI (1.78 g., 7.2 mmoles) was heated under gentle reflux with 9 ml. (95.5 mmoles) of acetic anhydride for 1 hour. After removal of the excess anhydride, the residue was treated with methanol, then recrystallized from ethanol, yield 0.9 g. (43%), m.p. 244°.

Anal. Calcd. for  $\text{C}_{13}\text{H}_{12}\text{ClN}_5\text{O}$ : C, 53.88; H, 4.18; N, 24.17. Found: C, 54.12; H, 4.56; N, 23.67.

Benzoate of XI.

Compound XI (1.23 g., 5.0 mmoles) was dissolved in 40 ml. of pyridine and 1.2 ml. (10.3 mmoles) of benzoyl chloride was added. The reaction mixture was heated under reflux for 2 hours. After removal of the solvent under reduced pressure, the residue was washed with methanol, collected and recrystallized from a pyridine-water mixture, yield 1.0 g. (57%), m.p. 260° dec.

Anal. Calcd. for  $\text{C}_{18}\text{H}_{14}\text{ClN}_5\text{O}$ : C, 61.45; H, 4.01; N, 19.91. Found: C, 61.75; H, 4.13; N, 19.81.

8-Acetylamino-6-chloro-3-phenyl-s-triazolo[4,3-b]pyridazine (XIV).

Benzaldehyde 4-amino-6-chloro-3-pyridazinylhydrazone (XI) (0.8 g., 15.3 mmoles) was heated under reflux with 35 ml. (375 mmoles) of acetic anhydride for 6 hours. The excess acetic anhydride was removed under reduced pressure and the residue was washed with methanol, collected and recrystallized from absolute ethanol, yield 2.5 g. (58%), m.p. 277°.

U. V.  $\lambda$  max (95% ethanol), 207 ( $\epsilon$ , 23,200), 264 ( $\epsilon$ , 23,900), 290 (sh) ( $\epsilon$ , 15,400), 315  $\mu$  ( $\epsilon$ , 8,750).

Infrared  $\text{cm}^{-1}$ , 1710(s), 1610(m), 1535(s), 1320(m), 1275(w), 1225(s), 1125(w), 1100(s), 1075(w), 1045(w), 1030(w), 1005(s), 995(m), 980(w), 945(m), 925(w), 845(s), 790(m), 775(s), 740(m), 720(m), 705(m), (Nujol mull).

Anal. Calcd. for  $\text{C}_{13}\text{H}_{10}\text{ClN}_5\text{O}$ : C, 54.26; H, 3.50; N, 24.35. Found: C, 54.69; H, 3.84; N, 24.14.

3-Benzylideneamino-6-chloroimidazo[4,5-c]pyridazine (XIII).

Benzaldehyde 4-amino-6-chloro-3-pyridazinylhydrazone (XI) (1.3 g., 4.04 mmoles) was heated under reflux with 20 ml. (127 mmoles) of freshly distilled ethyl orthoformate for 2 hours. The excess ethyl orthoformate was removed under reduced pressure and the residue was recrystallized from methanol, yield 0.7 g. (52%), m.p. 184°.

U. V.  $\lambda$  max (95% ethanol), 216 ( $\epsilon$ , 24,100), 286 ( $\epsilon$ , 23,300), 320 (sh) ( $\epsilon$ , 19,600), 286  $\mu$  (sh) ( $\epsilon$ , 2,500).

Infrared  $\text{cm}^{-1}$ , 3085(w), 3060(w), 1618(w), 1598(m), 1578(m), 1548(w), 1488(s), 1448(w), 1423(w), 1403(s), 1348(w), 1328(m),

1314(m), 1299(w), 1276(w), 1227(s), 1200(m), 1144(w), 1136(w), 1115(w), 1098(s), 1059(m), 1049(s), 987(w), 980(m), 971(w), 954(w), 944(s), 874(s), 817(s), 776(w), 756(s), 722(w), 694(s). Fluorolube mull was used in the region 4000-1300  $\text{cm}^{-1}$ ; Nujol mull was used in the region 1300-700  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_9\text{ClN}_5$ : C, 55.92; H, 3.12; N, 27.18. Found: C, 55.86; H, 3.42; N, 26.66.

Benzaldehyde 4-Amino-6-chloro-3-pyridazinylhydrazone (XI) from the Hydrolytic Cleavage of XIII.

3-Benzylideneamino-6-chloroimidazo[4,5-c]pyridazine (XIII) (1.0 g., 3.88 mmoles) was heated on a steam bath with 10% hydrogen chloride in absolute ethanol under reflux for 30 minutes. The reaction mixture was allowed to cool and the resulting crystals were collected. The product was treated with dilute sodium hydroxide solution, washed with water and recrystallized from methanol, yield 0.6 g. (62%), m.p. 231-232°. A mixture melting point with XI prepared from VII showed no depression. A small amount of benzaldehyde was isolated from the reaction mixture as the 2,4-dinitrophenylhydrazone (0.1 g.), m.p. 236°, undepressed on admixture with an authentic specimen. Attempts to isolate 3-amino-6-chloroimidazo[4,5-c]pyridazine (XIX) from the reaction mixture were unsuccessful.

6-Chloro-3,4-diaminopyridazine (X).

This compound was prepared from VII by the method previously reported (7).

6-Chloroimidazo[4,5-c]pyridazine (IX).

6-Chloro-3,4-diaminopyridazine (X), (4.6 g., 31.8 mmoles) was heated under reflux with 100 ml. of freshly distilled ethyl orthoformate for 2 hours. The reaction mixture was allowed to cool and a crystalline mass separated. The product was collected and washed with ether, yield 4.6 g. (93%), m.p. 254-255° dec. The product was recrystallized from hot water with no change in melting point.

U. V.  $\lambda$  max (95% ethanol), 210 ( $\epsilon$ , 22,750), 261 ( $\epsilon$ , 8,180), 284-286 ( $\epsilon$ , 7,750), 315  $\mu$  (sh) ( $\epsilon$ , 1,870).

Anal. Calcd. for  $\text{C}_5\text{H}_3\text{ClN}_4$ : C, 38.84; H, 1.94; N, 36.24. Found: C, 39.19; H, 2.03; N, 36.65.

Acknowledgment.

This investigation was supported by a PHS 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.
- (2) Communications concerning this paper should be directed to Professor Raymond N. Castle.
- (3) T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, **1**, 42 (1964).
- (4) T. Kuraishi, *Pharm. Bull. (Tokyo)*, **4**, 497 (1956).
- (5) T. Kuraishi, *ibid.*, **4**, 137 (1956).
- (6) M. Yanai and T. Kinoshita, *Yakugaku Zasshi*, **82**, 857 (1962).
- (7) G. A. Gerhardt and R. N. Castle, *J. Heterocyclic Chem.*, **2**, 247 (1964).
- (8) All melting points are uncorrected. The ultraviolet spectra were recorded with a Bausch and Lomb Spectronic 505 spectrophotometer in the solvent indicated. The infrared spectra were recorded with a Perkin-Elmer 337 spectrophotometer.

Received April 29, 1966

Albuquerque, New Mexico 87106