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Studies on the Pyridazine Derivatives. XVII.[1] Structural Studies on the Product of 3-Hydrazino-4-aminopyridazine with Formic Acid (A Novel Ring Isomerization)[2]

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The reaction product of 3-hydrazino-4-amino-6-chloropyridazine (IX) with formic acid was established to 6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XII) by synthetic method and nuclear magnetic resonance spectral studies. 3-Benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (XI) was hydrolyzed to give 3-benzylidenehydrazino-4-amino-6-chloropyridazine (X), benzaldehyde and XII which was confirmed as a ring isomerization product of XI.

As one of the authors reported in a previous paper,[4] 3-benzylideneamino-6-chloroimidazo-[4,5-*c*]pyridazine (XI) was hydrolyzed with ethanolic hydrochloric acid to 3-benzylidenehydrazino-4-amino-6-chloropyridazine (X) and benzaldehyde which was identified as 2,4-dinitrophenylhydrazone. In this time the compound XI was treated with 1N hydrochloric acid and we obtained X, benzaldehyde and XII which had a melting point of 278°. The elementary analysis of XII is equivalent to $C_5H_4N_5Cl$ and identified with one of the reaction products of 3-hydrazino-4-amino-6-chloropyridazine (IX) with formic acid. The product had already been synthesized successfully by Kuraishi and Castle[4] but no definite proof had been presented for its chemical structure, although several inferences were drown from the spectral data.

Now the structure of the compound XII was established as 6-chloro-8-amino-*s*-triazolo-[4,5-*b*]pyridazine by the following synthetic method and the aid of nuclear magnetic resonance (NMR) spectral studies.

3,6-Dichloro-4-carbamoylpyridazine (I)[5] was converted to 3-hydrazino-4-carbamoyl-6-chloropyridazine (II) with hydrazine hydrate. Cyclization of II with formic acid or a mixture of ethyl orthoformate and N,N-dimethylformamide (DMF) gave compound III which was established as 6-chloro-8-carbamoyl-*s*-triazolo[4,5-*b*]pyridazine by the following methods. The NMR spectrum of dechlorinated compound VI shows two doublet signals at δ 8.80 (J=4.7 cps) and δ 7.78 (J=4.7 cps), the coupling constant indicated *ortho* coupling, therefore chloro function locates on *meta* position of carbamoyl group in compound III. Moreover the elemental analysis of dehydrated compound IV is equivalent to $C_6H_2N_5Cl$, and there are no absorptions in NH stretching vibration region in the infrared (IR) spectrum, hence, it is obvious that the compound II closes to form *s*-triazol ring.

Hofmann rearrangement of VI with potassium hypobromite afforded bromine-contained compound VII which was equivalent to $C_5H_4N_5Br$ in elementary analysis. The NMR spectrum of this compound shows two singlet peaks as ring protons at δ 9.43 and δ 8.29, these signals were assignable to 3 and 6 position, respectively. Signal of 3 position appears at

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[1] Part XVI: M. Yanai, T. Kinoshita, and S. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 166 (1972).
[2] Short communication was presented to *J. Heterocyclic Chem.*, **7**, 465 (1970).
[3] Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*
[4] T. Kuraishi and R.N. Castle, *J. Heterocyclic Chem.*, **3**, 218 (1966).
[5] M. Yanai, T. Kinoshita, H. Watanabe, and S. Iwasaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1849 (1971).

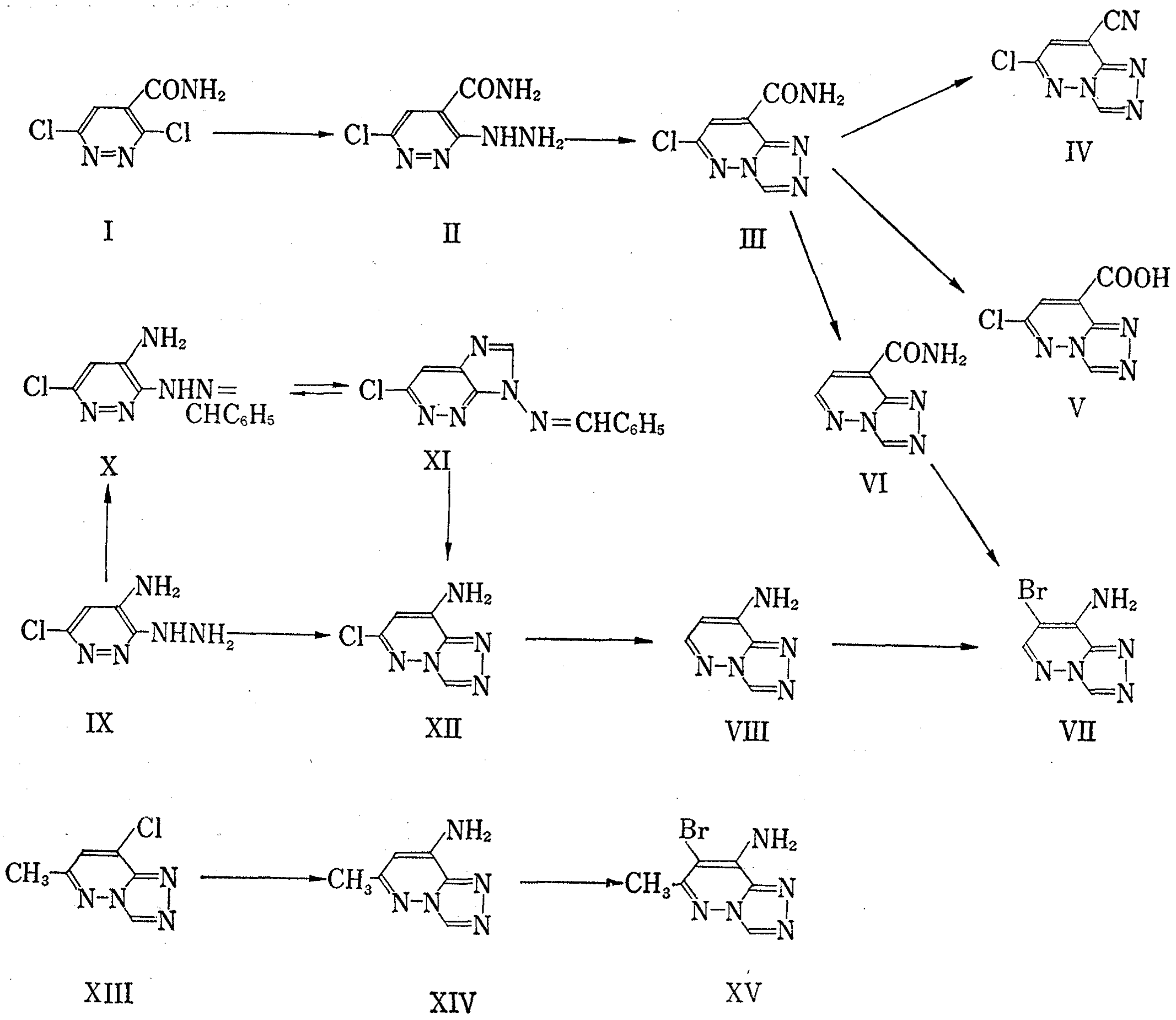

Chart 1

very low magnetic field, therefore this is useful characteristic absorption for analysis of *s*-tirazolo[4,5-*b*]pyridazine ring system. Furthermore, the ultraviolet (UV) spectrum was similar to that of 6-methyl-7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XV). The product VII was concluded to be 7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine from these observations. On the other hand, compound VIII was brominated in glacial acetic acid at room temperature and the resultant product was identified with VII by the testing of mixed melting point, and by comparison of NMR and IR spectra. Therefore the cyclization product (XII) of compound IX with formic acid was established to 6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine and at the same time a novel ring isomerization, from 3-benzylideneamino-6-chloroimidazo-

TABLE I. NMR Spectra of *s*-Triazolo[4,5-*b*]pyridazine[a]

Comp.	3H	6H	7H	$8NH_2$
VI	9.80 s	8.80 d (J=4.7 cps)	7.78 d (J=4.7 cps)	8.5 b
VII	9.43 s	8.29 s	—	7.7 b
VIII	9.39 s	8.06 d (J=6.0 cps)	6.13 d (J=6.0 cps)	7.4 b
XII	9.40 s	—	6.19 s	7.9 b
XIV	9.26 s	—	5.99 s	7.3 b
XV	9.36 s	—	—	7.6 b

[a] Spectra were measured in DMSO-d_6, signals were shown by δ value and TMS was used as the internal standard. s,singlet; d, doublet; b, broad

[4,5-*c*]pyridazine (XI) to 6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XII), was found. This ring isomerization will be discussed in the following paper.

Also the same ring closure was observed[6] in pyrimidine ring system, for example 7-chloro-8-amino-*s*-triazolo[4,5-*c*]pyrimidine was obtained[6a] when 4-hydrazino-5-amino-6-chloropyrimidine was treated with excess diethoxymethylacetate. However, in general, pyrimidine analogues[7] were cyclized to form N-aminoimidazo[4,5-*c*]pyrimidines and/or 1,2-dihydro-*as*-triazino[6,5-*d*]pyrimidines by reaction with formic acid or ethyl orthoformate, even 4-hydrazino-5-amino-6-chloropyrimidine was converted to 9-aminohypoxanthine.[6a]

Amination of XIII[8] with 28% aqueous ammonia gave 6-methyl-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XIV), which by bromination afforded 6-methyl-7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XV).

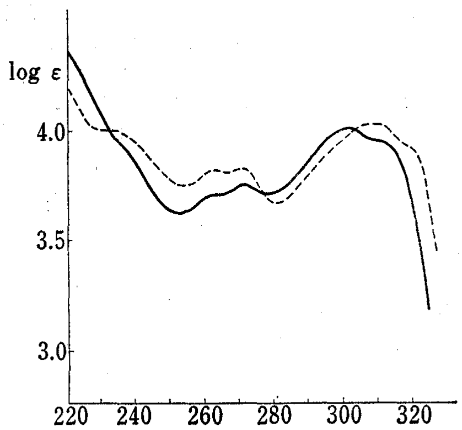

Fig. 1. Ultraveilet Spectra of VII (------) and XV (——)

Experimental

3-Hydrazino-4-carbamoyl-6-chloropyridazine (II)——A mixture of 0.5 g of I, 0.21 g of hydrazine hydrate and 20 ml of EtOH was refluxed for 45 min. After cooling, crystalline mass was collected and recrystallized from EtOH to give 0.31 g (63%) of orange needles, mp 184°. *Anal.* Calcd. for $C_5H_6ON_5Cl$: C, 32.01; H, 3.22; N, 37.34. Found: C, 31.95; H, 3.04; N, 37.06.

6-Chloro-8-carbamoyl-*s*-triazolo[4,5-*b*]pyridazine (III)——*a*) A mixture of 0.5 g of II and 0.5 ml of 95% formic acid was heated on a boiling water bath for 30 min. After cooling, crystalline mass was collected and recrystallized from MeOH to give 0.39 g (74%) of pale yellow prisms, mp 247° (decomp.). *Anal.* Calcd. for $C_6H_4ON_5Cl$: C, 36.42; H, 2.04; N, 35.39. Found: C, 36.78; H, 2.05; N, 35.31.

b) A mixture of 0.5 g of II, 0.4 g of ethyl orthoformate and 10 ml of DMF was refluxed for 5 hr. The reaction mixture was evaporated to dryness *in vacuo*, the residue was washed with MeOH and recrystallized from MeOH to give 0.4 g (76%) of pale yellow prisms, mp 247° (decomp.). *Anal.* Found: C, 36.42; H, 1.96; N, 35.14. This compound was identified with above a) product by comparison of IR spectrum.

6-Chloro-8-cyano-*s*-triazolo[4,5-*b*]pyridazine (IV)——A mixture of 0.35 g of III and 10 ml of $POCl_3$ was refluxed for 1.5 hr. After removal of excess $POCl_3$, the residue was poured onto crushed ice. The mixture was alkalized by addition of $NaHCO_3$ with ice cooling, and extracted with ether. The ethereal solution was dried over $MgSO_4$, then evaporated to dryness. The residue was recrystallized from a mixture of acetone and isopropyl ether to give 0.27 g (59%) of pale yellow needles, mp 159°. *Anal.* Calcd. for $C_6H_2N_5Cl$: C, 40.13; H, 1.12; N, 38.10. Found: C, 40.26; H, 1.20; N, 38.11.

6-Chloro-8-carboxy-*s*-triazolo[4,5-*b*]pyridazine (V)——To a solution of 0.3 g of III and 8 ml of concd. HCl, a solution of 0.23 g of $NaNO_2$ and 5 ml of water was added portionwise. As crystalline mass separated, 4 ml of 40% H_2SO_4 was added to dissolve. After stirring for 2 hr at room temperature, the solution was diluted with water. The separated crystalline mass was collected and recrystallized from MeOH to give 0.17 g (55%) of pale violet needles, mp 208°. *Anal.* Calcd. for $C_6H_3O_2N_4Cl \cdot H_2O$: C, 33.28; H, 2.33; N, 25.87. Found: C, 33.49; H, 2.43; N, 26.00.

8-Carbamoyl-*s*-triazolo[4,5-*b*]pyridazine (VI)——III (0.5 g) in 50 ml of pyridine was hydrogenated over 0.2 g of 5% Pd-$BaSO_4$. After filtration of catalyst, the filtrate was evaporated to dryness *in vacuo*. The residue was washed with water and recrystallized from MeOH to give 0.29 g (70%) of colorless needles, mp 259°. *Anal.* Calcd. for $C_6H_5ON_5$: C, 44.17; H, 3.09; N, 42.93. Found: C, 43.97; H, 3.12; N, 42.89.

7-Bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (VII)——a) Hofmann Rearrangement of VI: A hypobromite solution was prepared by dissolving 1.38 g of KOH in 200 ml of water and to the cold solution was added slowly 0.98 g of bromine with stirring and ice cooling. To this solution was added portionwise 0.5 g

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6) *a*) C. Temple, Jr., R.L. McKee, and J.A. Montgomery, *J. Org. Chem.*, **28**, 2257 (1963); *b*) M.E.C. Biffin, D.J. Brown, and T. Sugimoto, *J. Chem. Soc.* (*C*), **1970**, 139.

7) J.A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960); E.C. Taylor, J.W. Barton, and W.W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961); C. Temple, Jr., R.L. McKee, and J.A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

8) D. Liebermann and R. Jacquier, *Bull. Soc. Chim. France*, **1962** 355; *Chem. Abstr.*, **57**, 813 (1962).

of VI with stirring and ice cooling. After cooling for one hour, temperature was elevated slowly until 95° and heated on a boiling water bath for one hour. The separated crystalline mass was collected and recrystallized from MeOH to give 0.295 g (45%) of colorless needles, mp 281—282°. *Anal.* Calcd. for $C_5H_4N_5Br$: C, 28.06; H, 1.88; N, 32.77. Found: C, 28.38; H, 2.16; N, 32.98.

b) Bromination of VIII: To a solution of 0.3 g of VIII and 4 ml of glacial acetic acid was added a solution of 0.43 g of bromine and 1 ml of glacial acetic acid with stirring at room temperature. After one hour, 15 ml of water was added to the reaction mixture. The separated crystalline mass was collected and recrystallized from MeOH to give 0.38 g (80%) of colorless needles, mp 281—282°. This compound was identified with above obtained compound by mixed melting point test and IR comparison.

6-Methyl-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XIV)——A mixture of 1.5 g of XIII and 20 ml of 28% aq. ammonia was heated in a sealed tube for 5 hr. After removal of excess ammonia gas and ice cooling, the crystalline mass was collected. The product was recrystallized from MeOH to give 1.07 g (88%) of colorless needles, mp 218—219°. *Anal.* Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.96. Found: C, 48.03; H, 4.95; N, 46.64.

6-Methyl-7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XV)——To a solution of 0.2 g of XIV and 4 ml of glacial acetic acid was added a solution of 0.28 g of bromine and 1 ml of glacial acetic acid with stirring at room temperature. After one hour, 10 ml of water was added and separated crystalline mass was collected. The product was recrystallized from MeOH to give 0.23 g (75%) of colorless needles, mp 258—259°. *Anal.* Calcd. for $C_6H_6N_5Br$: C, 31.60; H, 2.65; N, 30.71. Found: C, 31.73; H, 2.86; N, 30.63.

Hydrolysis of XI with 1N Hydrochloric Acid——A mixture of 0.5 g of XI and 15 ml of 1N HCl was refluxed for 2 hr. After cool, the separated crystalline mass was collected and recrystallized from MeOH to give 0.35 g (64%) of pale yellow needles, mp 263—264° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}N_5Cl \cdot HCl$ (hydrochloride of X): C, 46.49; H, 3.90; N, 24.64. Found: C, 46.67; H, 4.09; N, 24.32. The filtrate was evaporated to dryness *in vacuo* and residue was recrystallized from MeOH to give 0.1 g (30%) of colorless needles, mp 275—276°. This compound was identified with an authentic specimen of XII by IR comparison. To the evaporated product was added 2,4-dinitrophenylhydrazine reagent and the separated reddish yellow crystalline mass was collected, mp 234—235°, yielding 0.06 g (11% as benzaldehyde). This compound was identified with an authentic specimen of 2,4-dinitrophenylhydrazone of benzaldehyde by mixed melting point test.

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