Recyclization of 3-Amino-6-chloroimidazo[4,5-c]pyridazine.

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Sir:

As one of us reported in a previous paper (1), 3-benzylideneamino-6-chloroimidazo[4,5-c]pyridazine (XI) was hydrolyzed with ethanolic hydrochloric acid to 3-benzylidenehydrazino-4-amino-6-chloropyridazine (X). We wish now to report on a new rearrangement including a ring conversion. After heating compound XI under reflux for two hours with 1 *N* hydrochloric acid or acetic acid, we obtained colorless crystals (VII) which have a melting point of 278°, and in this process compound X was obtained as a by-product. The elemental analysis of VII shows that it is equivalent to $C_5H_4ClN_5$. By testing the melting point and comparing the infrared spectrum, the product VII was identified as 6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine.

Compound VII had already been synthesized successfully by Kuraishi and Castle in 1966 (1), but no definite proof had been presented for its chemical structure, although several inferences were drawn from the spectral data.

Now the structure of the compound obtained from VII has been established as 8-amino-*s*-triazolo[4,5-*b*]pyridazine (VIII) by the following synthetic method together with the nuclear magnetic resonance spectra.

TABLE I

Nuclear Magnetic Resonance Spectra (a)

Compound	3H	6H	7H	$8NH_2$
IV	9.80s	8.80d J=4.7 cps	7.78d J=4.7 cps	*ca.* 8.5b
VII	9.40s	---	6.19s	*ca.* 7.9b
VIII	9.39s	8.06d J=6.0 cps	6.13d J=6.0 cps	*ca.* 7.4b
IX	9.43s	8.29s	---	*ca.* 7.7b
XIII	9.26s	---	5.99s	*ca.* 7.3b
XIV	9.36s	---	---	*ca.* 7.6b

(a) Nuclear magnetic resonance spectra were measured in DMSO-d_6; TMS was used as the internal standard; s, singlet; d, doublet; b, broad.

The dechlorination of the compound VII with 5% palladium on charcoal resulted in VIII (1). This compound could be brominated in glacial acetic acid at room temperature in excellent yield and the resultant product was identified as 7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (IX, m.p. 281-282°; *Anal.* Calcd. for $C_5H_4BrN_5$: C, 28.06; H, 1.88; N, 32.77. Found: C, 28.35; H, 2.06; N, 32.91) by the testing of mixed melting points, nuclear magnetic resonance and infrared spectra. The compound IX was also obtained by Hofmann rearrangement of *s*-triazolo[4,5-*b*]pyridazine-8-carboxamide (IV, m.p. 257-258°; *Anal.* Calcd. for $C_6H_5N_5O$: C, 44.17; H, 3.09; N, 42.93. Found: C, 43.97; H, 3.12; N, 42.89). The structure of IX was determined by comparing the nuclear magnetic resonance spectrum and the ultraviolet spectrum of 6-methyl-7-bromo-8-amino-*s*-triazolo[4,5-*b*]pyridazine (XIV, m.p. 258-259°; *Anal.* Calcd. for $C_6H_6BrN_5$: C, 31.60; H, 2.65; N, 30.71. Found: C, 31.73; H, 2.86; N, 30.63) (Fig. 1). The synthesis of the compound IV is shown in the following scheme (I → IV).

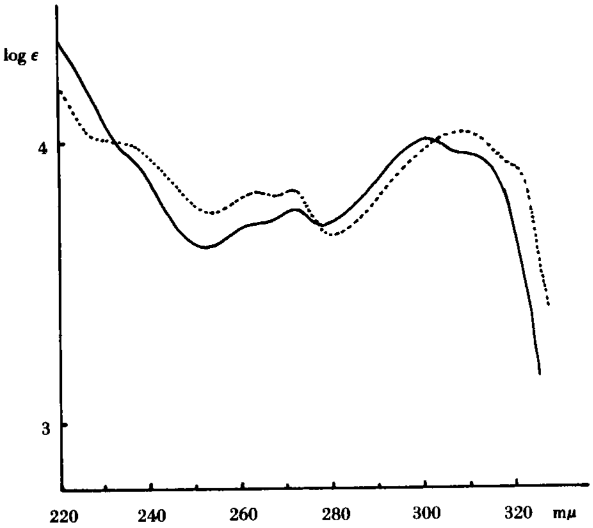
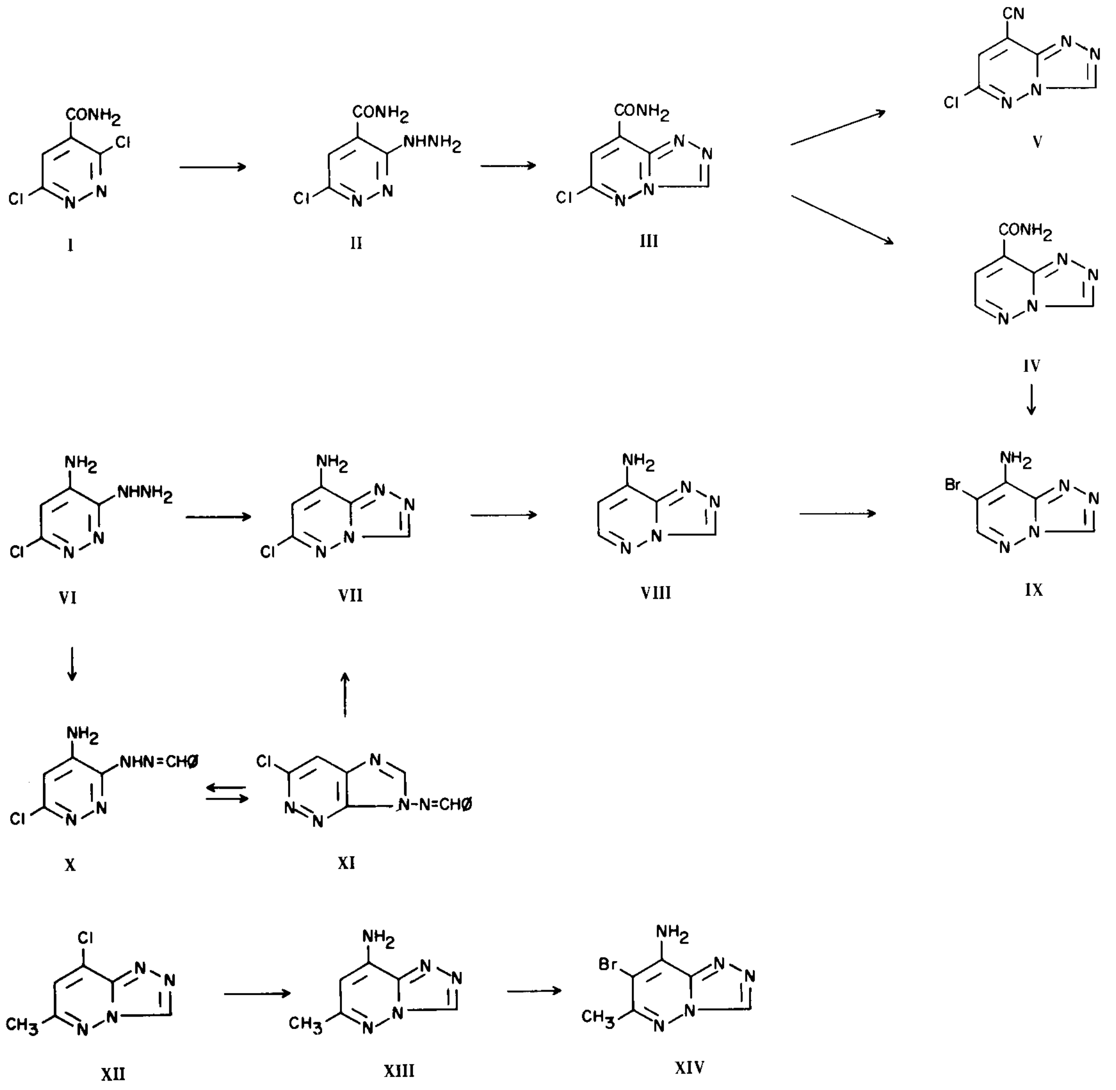


Fig. 1: Ultraviolet spectra of IX (———) and XIV (———).

FLOW SHEET I



Ethyl 3,6-dichloropyridazine-4-carboxylate was converted with 28% aqueous ammonia into 3,6-dichloropyridazine-4-carboxamide (I, m.p. 175-176°; *Anal.* Calcd. for $C_5H_3Cl_2N_3O$: C, 31.25; H, 1.56; N, 21.87. Found: C, 31.50; H, 1.42; N, 21.97). The compound I was converted to 3-hydrazino-6-chloropyridazine-4-carboxamide (II, m.p. 183-184°; *Anal.* Calcd. for $C_5H_6ClN_5O$: C, 32.01; H, 3.22; N, 37.34. Found: C, 31.95; H, 3.04; N, 37.06). Cyclization of the compound II with formic acid gave 6-chloro-*s*-triazolo[4,5-*b*]pyridazine-8-carboxamide (III, m.p. 247° dec.; *Anal.* Calcd. for $C_6H_4ClN_5O$: C, 36.42; H, 2.04; N, 35.39. Found: C, 36.78; H, 2.05; N, 35.31), which can be converted into 6-chloro-8-cyano-*s*-triazolo[4,5-*b*]pyridazine (V, m.p. 158-159°; *Anal.* Calcd. for $C_6H_2ClN_5$: C, 40.13; H, 1.12; N, 38.10. Found: C, 40.26; H, 1.20; N, 38.11) with phosphorus oxychloride.

The product IV was obtained after the dechlorination of compound III with 5% palladium on barium sulfate in pyridine solution. 6-Methyl-7-bromo-8-amino-*s*-triazolo-[4,5-*b*]pyridazine (XIV) was obtained by the bromination of XIII (m.p. 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) which is the amination product of 6-methyl-8-chloro-*s*-triazolo[4,5-*b*]pyridazine (XII) (2).

REFERENCES

(1) T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, 3, 218 (1966).

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

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