Synthesis of Pyridazine Derivatives. XXI. Tetrazolo-Azido Transformations in Some Fused Azolopyridazines

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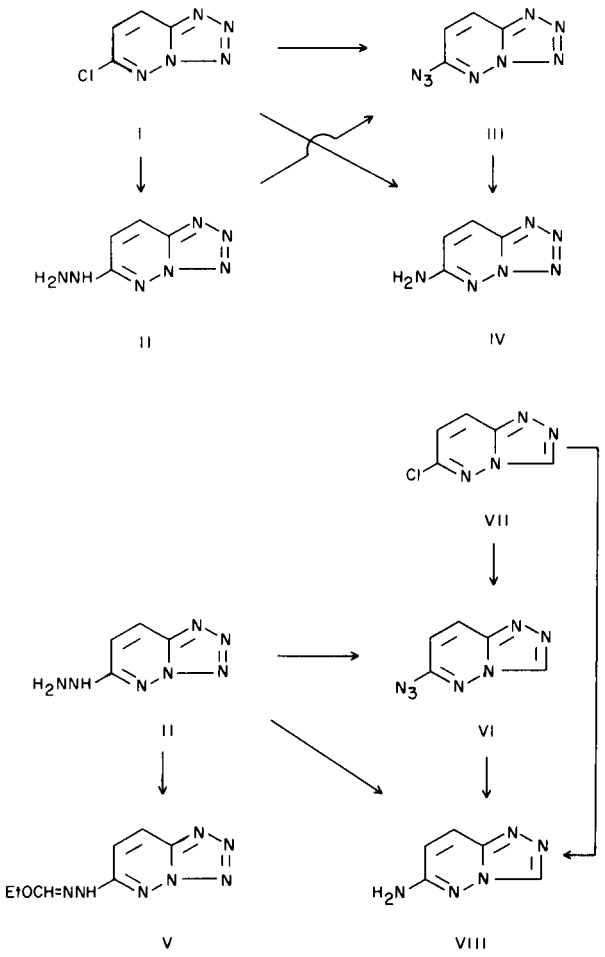
6-Azidotetrazolo[1,5-*b*]pyridazine (III) has been prepared by two different routes and is easily transformed into the 6-amino derivative (IV). The attempted cyclization of 6-hydrazinotetrazolo[1,5-*b*]pyridazine (II) into the postulated tricycle has been shown to result in the formation of 6-azido-*s*-triazolo[4,3-*b*]pyridazine (VI), obtained also in a separate experiment from VII. The azido structure of VI has been confirmed from spectroscopic data and from its conversion into 6-amino-*s*-triazolo[4,3-*b*]pyridazine (VIII), obtained in another experiment from VII. Similarly, cyclization of II with cyanogen bromide resulted in the simultaneous formation of the *s*-triazolo ring and ring opening of the fused tetrazolo ring, giving IX. For 6-azido-2-phenylimidazo[1,2-*b*]pyridazine (XII) the expected azide structure proved to be correct.

Our recent findings on the selective ring orientation in some fused polyazaheterocycles by the use of azidoazomethine-tetrazole equilibrium (1) prompted the examination of this phenomenon on some azolopyridazines.

Extensive investigations on azidoazomethine-tetrazole equilibrium on several heterocyclic systems were reported (1-6). In addition to structural features the equilibrium was found solvent and temperature dependent, likewise the presence of substituents in some systems was also not negligible (4,7). There are also some available data regarding the behaviour and structure of tetrazolo[1,5-*b*]-pyridazines or their tautomeric 3-azidopyridazines. Several derivatives of tetrazolo[1,5-*b*]pyridazines were prepared (8-13) and examination of their infrared spectra revealed the absence of the azide absorption band, excluding thus the conceivable azide structure. However, the attachment of another azide group on the ring carbon, adjacent to one of the ring nitrogens in pyridazine ring precludes its transformation into another fused tetrazolo ring. So far, in all known cases no bis-tetrazolopyridazine could be isolated since all compounds revealed a strong azide absorption band in the infrared spectra (8,11,14).

In view of the above observations, it appeared plausible that azolopyridazinyl azides might assume also the open chain structure instead of the cyclic tetrazolo form. When the fused azolo ring is represented by a tetrazolo ring, the simplest compound appears to be 6-azidotetrazolo[1,5-b]-pyridazine (III). This was obtained according to the known procedure (14) and in addition as follows. Nitrosation of 6-hydrazinotetrazolo[1,5-*b*]pyridazine (II) gave the desired azido compound (III) in a far better yield than the direct nucleophilic displacement of the chlorine atom of 6-chlorotetrazolo[1,5-*b*]pyridazine (I) by means of sodium azide. The structure of the product as having an azido group and not two fused tetrazolo rings has been confirmed by examination of its infrared spectrum which revealed a strong asymmetric stretching absorption at 2151 cm^{-1}, characteristic for azide (15,16). Compound III was easily reduced to IV, obtainable on the other hand from I through an amination procedure.

In an attempt to generate a fused triazolo ring, 6-hydrazinotetrazolo[1,5-*b*]pyridazine (II) was allowed to react with diethoxymethyl acetate, a reagent used previously with success for the formation of such rings (2,17,18). A short reaction time caused only the formation of the corresponding ethoxymethylene derivative (V), whereas longer heating afforded the cyclic product (VI) with a simultaneous opening of the tetrazolo ring. The product was, however, not isolated pure, but its presence is evident from its reduction into the 6-amino derivative (VIII). A pure 6-azido compound (VI) could be obtained from 6-chloro-*s*-triazolo[4,3-*b*]pyridazine (VII), which was also transformed into the authentic 6-amino compound (VIII). For compound VI two structures are conceivable, VIa and VIb. From its infrared spectrum, which exhibits a strong azide absorption band at 2128 cm^{-1} and no

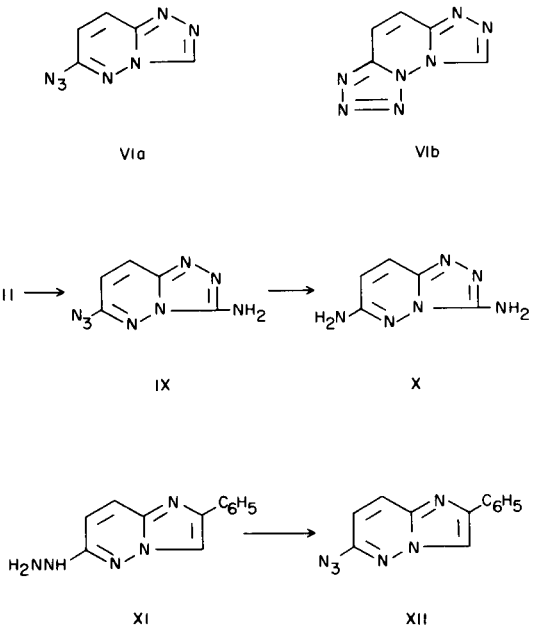


bands which could be assigned for the tetrazole ring (19,20), it can be concluded that the azido form is present in the solid state (VIa). This is also in accordance with the easy conversion of VI into the corresponding amino derivative (VIII).

Furthermore, in another cyclization reaction, starting from 6-hydrazinotetrazolo[1,5-*b*]pyridazine and cyanogen bromide, the formation of the new fused *s*-triazolo ring caused in a similar way the opening of the tetrazolo ring giving thus rise to 3-amino-6-azido-*s*-triazolo[4,3-*b*]pyridazine (IX). This can be further easily reduced to the 3,6-diamino derivative (X).

The above mentioned method of simultaneous formation of a fused azolo ring and opening of the originally present tetrazolo ring with subsequent formation of an azido group was not successful when applied to the imidazole ring formation. Thus, 6-aminotetrazolo[1,5-*b*]-pyridazine did not react with phenacyl bromide, a reaction used successfully for the synthesis of imidazo[1,2-*b*]-pyridazines, and the unchanged starting material was isolated. The desired compound was obtained, however, by nitrosation of 6-hydrazino-2-phenylimidazo[1,2-*b*]-pyridazine (XI) and the new product (XII) had the expected azido structure as evident from its infrared spectrum.

Thus, we could show that irrespective of the nature of the fused azolo ring, this causes destabilization of the tetrazolo ring of the corresponding tetrazolo[1,5-*b*]-pyridazine system, assuming hence the azido form. It is most probable that the driving force for the observed tetrazole destabilization originates from the strain of the ring fusion and simultaneous stabilization of the electron donating azido group through the azolopyridazine moiety. This method can be therefore used for the elimination of a tetrazole ring in polyazaheterocycles of the above type. All azido compounds appeared to be photochromic.



EXPERIMENTAL (21)

6-Chlorotetrazolo[1,5-*b*]pyridazine and 6-chloro-*s*-triazolo-[4,3-*b*]pyridazine were obtained according to the procedures described by Takahayashi (12). The first mentioned compound was converted with hydrazine into 6-hydrazinotetrazolo[1,5-*b*]-pyridazine, m.p. 230-235° (Lit. (13,14) gives m.p. 230.5° and 238-240°). 6-Azidotetrazolo[1,5-*b*]pyridazine was synthesized from 3,6-dichloropyridazine and sodium azide, m.p. 120-131° dec., (Lit. (14) gives m.p. 128-129°). 6-Hydrazino-2-phenylimidazo-[1,2-*b*]pyridazine was prepared as described previously (22).

6-Azidotetrazolo[1,5-*b*]pyridazine (III).

Method 1.

A solution containing 1 g. of 6-hydrazinotetrazolo[1,5-*b*]-pyridazine (II) in 10 ml. of 12% acetic acid was cooled in ice. To the stirred solution a solution of 0.45 g. of sodium nitrite in 1

ml. of water was added dropwise. After the addition was complete, the reaction mixture was left standing in ice for 15 minutes. The separated solid was collected and crystallized from water giving 0.7 g. of the pure product, m.p. 130-131°. Infrared: strong absorption at 2151 cm^{-1} (azide group); bands at 1081, 999 and 757 cm^{-1} characteristic for the tetrazolo ring (19,20).

Anal. Calcd. for $C_4H_2N_8$: C, 29.63; H, 1.24; N, 69.12. Found: C, 29.38; H, 1.52; N, 69.02.

Method 2.

A solution of 1 g. of 6-chlorotetrazolo[1,5-*b*]pyridazine (I) in 25 ml. of ethanol was treated with 0.43 g. of sodium azide and the mixture heated under reflux for 3 hours. The solvent was evaporated to dryness and the residue crystallized from water yielding 0.45 g. of the pure product, m.p. 131-132°. Mixed melting point with the compound prepared as described under Method 1. was undepressed and both infrared spectra were identical.

6-Aminotetrazolo[1,5-*b*]pyridazine (IV).

Method 1.

Into a hot solution containing 1 g. of 6-azidotetrazolo[1,5-*b*]-pyridazine (III) in 10 ml. of ethanol a stream of hydrogen sulfide was introduced for about 40 minutes. The separated product was filtered and the contaminating sulfur extracted with tetrahydrofurane. The residue was crystallized from *N,N*-dimethylformamide, yield 83%, m.p. 313-315° (The Japanese authors who obtained this compound after catalytic reduction, gave m.p. 293-295° (14)).

Anal. Calcd. for $C_4H_4N_6$: C, 35.29; H, 2.96; N, 61.75. Found: C, 35.03; H, 3.01; N, 61.48.

Method 2.

Two g. of 6-chlorotetrazolo[1,5-*b*]pyridazine (I) was dissolved in 50 ml. of liquid ammonia and the mixture heated in a stainless steel vessel at 100° for 4 hours. Upon cooling the vessel was vented and the residue treated with 10 ml. of water. The crude product was filtered and purified by crystallization from *N,N*-dimethylformamide, yield 91%, m.p. 293° dec. The compound was found to be identical with that obtained as described in Method 1.

6-Ethoxymethylenehydrazinotetrazolo[1,5-*b*]pyridazine (V).

A mixture containing 0.2 g. of 6-hydrazinotetrazolo[1,5-*b*]-pyridazine (II) and 0.75 ml. of diethoxymethyl acetate was heated under reflux for 3 minutes and left to cool slowly to room temperature. The product which separated was collected and crystallized from ethanol yielding 54% of the pure compound, m.p. 187-188°.

Anal. Calcd. for $C_7H_9N_7O$: C, 40.58; H, 4.38; N, 47.32. Found: C, 40.30; H, 4.50; N, 47.88.

6-Azido-*s*-triazolo[4,3-*b*]pyridazine (VI).

Method 1.

A solution containing 1.43 g. of 6-chloro-*s*-triazolo[4,3-*b*]-pyridazine (VII) dissolved in 30 ml. of ethanol was treated with 0.65 g. of sodium azide. The mixture was heated under reflux on water bath for 5 hours. The solvent was then evaporated to dryness and the residue crystallized from water. The pure compound was obtained in 80% yield, m.p. 174-176° dec. Infrared spectrum: strong absorption band at 2128 cm^{-1} (azide).

Anal. Calcd. for $C_5H_3N_7$: C, 37.27; H, 1.88; N, 60.86. Found: C, 37.08; H, 2.10; N, 60.98.

Method 2.

To an ice cold stirred solution containing 1.1 g. of 6-hydrazino-*s*-triazolo[4,3-*b*]pyridazine dissolved in 10 ml. of 12% acetic acid was added dropwise a solution containing 0.5 g. of sodium nitrite dissolved in 1.5 ml. of water. The mixture was stirred on ice for further 10 minutes, filtered and the residue crystallized from water, yield 64%, m.p. 174-176°. Melting point and mixed melting point with the compound prepared as described in Method 1 was without depression and the infrared spectra were identical.

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

Method 1.

A mixture containing 0.2 g. of 6-hydrazinotetrazolo[1,5-*b*]-pyridazine and 0.75 ml. of diethoxymethyl acetate was heated under reflux for 15 minutes. The dark brown solution was allowed to cool to room temperature and diluted with 6 ml. of ethanol. The solution was heated again and when hot, hydrogen sulfide was introduced during 30 minutes. Upon cooling, the separated product was filtered off and crystallized from water, yield 3%, m.p. 283-285°. The compound was found to be identical with the product, prepared as described in Method 2, since mixed melting point showed no depression.

Method 2.

A solution containing 4.8 g. of 6-chloro-*s*-triazolo[4,3-*b*]-pyridazine (VII) dissolved in 90 ml. of ethanol, freshly saturated with ammonia gas during 1 hour, was prepared. The reaction mixture was placed in a stainless steel vessel and heated at 150° for 3 hours. The crude product which separated from the cooled reaction mixture was collected and crystallized from water yielding 83% of the pure compound, m.p. 283-286° (Lit. (13) gives m.p. 272.5°).

Anal. Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.26; H, 3.60; N, 51.83.

Method 3.

Into a hot solution containing 0.5 g. of 6-azido-*s*-triazolo-[4,3-*b*]pyridazine (VI) dissolved in 15 ml. of ethanol hydrogen sulfide was introduced until no more precipitate was formed. The collected product, purified from water, was obtained in 36% yield, m.p. 281-283°. Mixed melting point with the compound prepared as described in Method 2 showed no depression.

3-Amino-6-azido-*s*-triazolo[4,3-*b*]pyridazine (IX).

To a hot solution containing 1 g. of 6-hydrazinotetrazolo-[1,5-*b*]pyridazine (II) dissolved in 35 ml. of ethanol, 1 g. of cyanogen bromide was added and the reaction mixture was allowed to stand for a few minutes. The separated product was filtered off, dissolved in water and treated with solid sodium bicarbonate until neutralized. The free base was collected in 73% yield and decomposed when heated over 250°. Infrared spectrum: 3279 cm^{-1} (NH) and strong absorption band at 2137 cm^{-1} (azide).

Anal. Calcd. for $C_5H_4N_8$: C, 34.09; H, 2.29; N, 63.62. Found: C, 34.06; H, 2.51; N, 63.51.

3,6-Diamino-*s*-triazolo[4,3-*b*]pyridazine (X).

A hot solution containing 0.5 g. of 3-amino-6-azido-*s*-triazolo-[4,3-*b*]pyridazine dissolved in 15 ml. of ethanol was treated with hydrogen sulfide for 30 minutes. The separated product was collected and crystallized from *N,N*-dimethylformamide, yield 70%, m.p. 332-335°.

Anal. Calcd. for $C_5H_6N_6$: C, 39.99; H, 4.03; N, 55.98. Found: C, 40.05; H, 4.30; N, 55.48.

6-Azido-2-phenylimidazo[1,2-*b*]pyridazine (XII).

In 20 ml. of an ice cold 12% acetic acid 1.05 g. of 6-hydrazino-2-phenylimidazo[1,2-*b*]pyridazine (XI) were dissolved and the solution was treated portionwise with an ice cold solution containing 0.35 g. of sodium nitrite in 1.5 ml. of water. After the addition was complete the separated product was filtered off, washed with a few ml. of ice cold water, dried and crystallized from ethanol, yield 91%, m.p. 200-204°. Infrared spectrum: strong absorption band at 2105 cm^{-1} (azide).

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.00; H, 3.41; N, 35.58. Found: C, 60.70; H, 3.58; N, 35.65.

REFERENCES

(1) B. Stanovnik and M. Tišler, *Chimia*, 22, 141 (1968).

(2) B. Stanovnik and M. Tišler, *Tetrahedron*, 23, 387 (1967).

(3) J. H. Boyer and F. C. Canter, *Chem. Rev.*, 54, 1 (1954).

(4) C. Temple, C. L. Kussner and J. A. Montgomery, *J. Org. Chem.*, 31, 2210 (1966) and references cited therein for previous papers.

(5) G. A. Reynolds, J. A. Van Allan and J. F. Tinker, *ibid.*, 24, 1205 (1959).

(6) S. Carboni, A. Da Settimo and P. L. Ferrarini, *Gazz. Chim. Ital.*, 97, 1061 (1967) and references cited therein for previous papers.

(7) C. Temple, M. C. Thorpe, W. C. Coburn and J. A. Montgomery, *J. Org. Chem.*, 31, 935 (1966).

(8) W. D. Guither, D. G. Clark and R. N. Castle, *J. Heterocyclic Chem.*, 2, 67 (1965).

(9) T. Kuraishi and R. N. Castle, *ibid.*, 1, 42 (1964).

(10) S. Linholter and R. Rosenørn, *Acta Chem. Scand.*, 16, 2389 (1962).

(11) I. B. Lundina, Yu. N. Sheinker and I. Ya. Postovskii, *Izv. Akad. Nauk, Ser. Khim.*, 66 (1967).

(12) N. Takahayashi, *J. Pharm. Soc. Japan*, 75, 1242 (1955); *Chem. Abstr.*, 50, 8655 (1956).

(13) N. Takahayashi, *J. Pharm. Soc. Japan*, 76, 765 (1956); *Chem. Abstr.*, 51, 1192 (1957).

(14) T. Itai, S. Kamiya, *Chem. Pharm. Bull. (Tokyo)*, 11, 348 (1963); *Chem. Abstr.*, 59, 8734 (1963).

(15) L. J. Bellamy "The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., 1960, p. 273.

(16) E. Lieber, C. N. R. Rao, T. S. Chao and C. W. W. Hoffman, *Anal. Chem.*, 29, 916 (1957).

(17) B. Stanovnik, A. Krbavčič and M. Tišler, *J. Org. Chem.*, 32, 1139 (1967).

(18) B. Stanovnik and M. Tišler, *Tetrahedron Letters*, 2403 (1966).

(19) J. H. Boyer and E. J. Miller, *J. Am. Chem. Soc.*, 81, 4671 (1959).

(20) E. Lieber, D. Levering and L. Patterson, *Anal. Chem.*, 23, 1594 (1961).

(21) All melting points were determined on a Kofler melting point apparatus. The infrared spectra were determined with Infracord Model 137 spectrophotometer as mulls in Nujol.

(22) B. Stanovnik and M. Tišler, *Tetrahedron*, 23, 2739 (1967).

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