

Pyridazine Studies

II. 3-Chloro-6-hydrazino-4- and 5-methyl-pyridazine and Some Tetrazolo[1,5-b]- and s-Triazolo[4,3-b]pyridazines

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The structures of the two isomeric products 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II) from the reaction of 3,6-dichloro-4-methyl-pyridazine with hydrazine were established by reduction with Raney nickel to the amino derivatives and by oxidation with hypochlorite to the corresponding 3-chloro-4- and 5-methyl-1,6-dihydro-6-oxo-pyridazines. The structures found are not in agreement with Takahayashi's results¹. The hydrazino compounds (I and II) were converted into 6-chloro-7- and 8-methyl-tetrazolo[1,5-b]pyridazine (III and IV) and 6-chloro-7- and 8-methyl-s-triazolo[4,3-b]pyridazine (V and VI). V and VI were hydrolysed to 7- and 8-methyl-5,6-dihydro-6-oxo-s-triazolo[4,3-b]pyridazine, and through comparison of the infra-red spectra it was shown that the product from the reaction between acetoacetic ester and 4-amino-1,2,4-triazole is 6-methyl-8-hydroxy-s-triazolo[4,3-b]pyridazine as postulated by Bülow² and not 8-methyl-5,6-dihydro-6-oxo-s-triazolo[4,3-b]pyridazine as suggested by Kost and Gents³.

As part of our investigations on 3- and/or 6-substituted 4-methyl-pyridazines⁴, 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine were prepared from 3,6-dichloro-4-methyl-pyridazine and 50 % aqueous hydrazine. Separation of the two isomeric compounds was achieved by several recrystallisations from water or aqueous ethanol. The melting points of the two components I and II were 158° and 199°, I being the more soluble isomer. The purity of the compounds was demonstrated through their infra-red and NMR spectra.

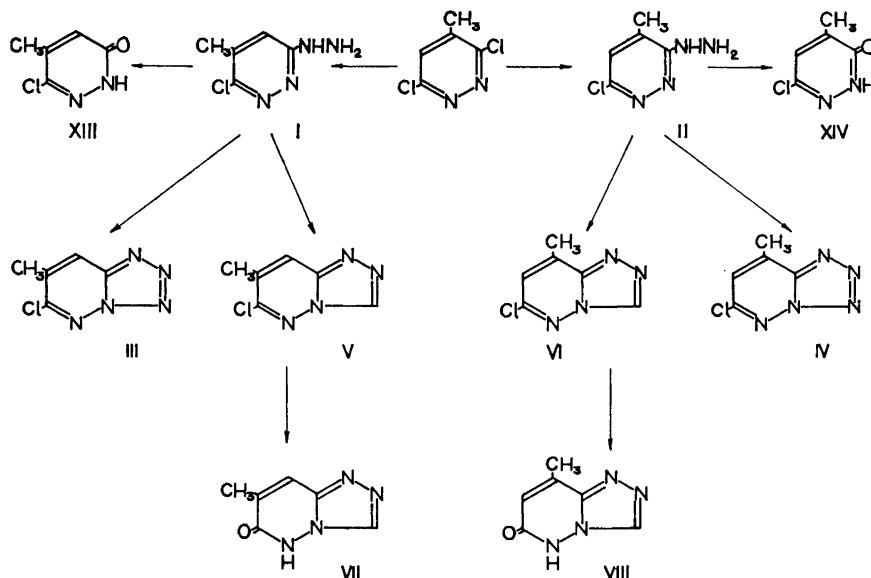
In order to establish the structures of the hydrazino derivatives, they were hydrogenated in methanolic potassium hydroxide solution at atmospheric pressure using Raney nickel as a catalyst. Cleavage of the hydrazino group and removal of the chlorine atom was expected, and from II (m.p. 199°) a compound C₅H₇N₃ with m.p. 193.5° was obtained. 6-Amino-4- and 5-methyl-pyridazine were previously unknown, but an NMR spectrum of the hydrogenation product showed the presence of two adjacent aromatic hydrogen atoms (H₃: τ = 1.85 ppm, H₄: τ = 3.62 ppm, J = 4.5 cps in aqueous solution with TMS as external reference) indicating the structure 6-amino-5-methyl-pyridazine.

Hydrogenation of I (m.p. 158°) gave a mixture of products from which 3-chloro-6-amino-4-methyl-pyridazine^{1,4}, m.p. 187°, was isolated. This compound was identified through mixed melting point with an authentic sample, through its infra-red spectrum and its acetyl derivative⁴. It was later shown that hydrogenation of 3-chloro-6-amino-4-methyl-pyridazine under the conditions described above proceeded extremely slowly.

Consequently, I (m.p. 158°) must have the structure 3-chloro-6-hydrazino-4-methyl-pyridazine and II (m.p. 199°) the structure 3-chloro-6-hydrazino-5-methyl-pyridazine.

Takahayashi¹ reported the preparation of these hydrazino derivatives and assigned the structures as follows: 3-chloro-6-hydrazino-4-methyl-pyridazine, m.p. 193°, and 3-chloro-6-hydrazino-5-methyl-pyridazine, m.p. 149°. The structures were established by "heating strongly for 8 hrs. with conc. HCl to form the corresponding hydroxy derivatives in poor yields"¹. Thus the hydrazino compound with m.p. 193° gave 3-chloro-6-hydroxy-4-methyl-pyridazine (3-chloro-4-methyl-1,6-dihydro-6-oxo-pyridazine) m.p. 227°, and the hydrazino compound with m.p. 149° gave 3-chloro-6-hydroxy-5-methyl-pyridazine (3-chloro-5-methyl-1,6-dihydro-6-oxo-pyridazine) m.p. 148°. This hydrolysis could not be reproduced in our laboratory and was contrary to our results.

Conversion of the hydrazino derivatives into the pyridazones could be performed by oxidation with hypochlorite or hypobromite in 5 N sulfuric acid solution. From I (m.p. 158°) we obtained 3-chloro-4-methyl-1,6-dihydro-6-oxo-pyridazine (XIII), m.p. 224° subl., thus establishing the structure of I as 3-chloro-6-hydrazino-4-methyl-pyridazine. Likewise, II (m.p. 199°) yielded 3-chloro-5-methyl-1,6-dihydro-6-oxo-pyridazine (XIV), m.p. 170° subl. The identity of the oxidation products was proven through their infra-red spectra and mixed melting points with authentic samples⁴.



The application of this oxidation procedure to the preparation of hydroxy-, chloro- and bromo-substituted N-hetero-aromatics will be described in detail in a later publication.

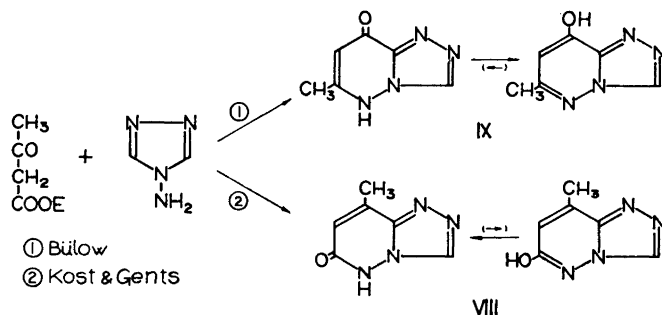
Treatment of 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II) with sodium nitrite in acetic acid solution yielded 6-chloro-7- and 8-methyl-tetrazolo[1,5-b] pyridazine (III and IV). That ring closure had occurred was seen from the infra-red spectra, which showed no azide absorption band in the region 2160—2120 cm^{-1} . The melting points were 140.5° and 107.0°, respectively. The latter (IV) has previously been reported (m.p. 97°) by Takahayashi ⁵.

Without isolation of the intermediately formed β -formylhydrazino-derivatives 6-chloro-7- and 8-methyl-*s*-triazolo[4,3-*b*]pyridazine (V and VI, m.p.'s 157.5—158.0° and 134.0—134.5°) were obtained when the hydrazino compounds were heated under reflux with 80 or 100 % formic acid. For these compounds Takahayashi ¹ reported the melting points 158° and 107°. Hydrolysis of V and VI in potassium hydroxide solution yielded 7- and 8-methyl-5,6-dihydro-6-oxo-*s*-triazolo[4,3-*b*]pyridazine (VII and VIII), melting points above 265°.

In 1909 Bülow ² allowed various β -keto-esters to react with 4-amino-1,2,4-triazole. He formulated the reaction products as derivatives of 8-hydroxy-*s*-triazolo[4,3-*b*]pyridazine without any proof of structures. Thus acetoacetic ester gave 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine (IX).

In 1959 Steck and Brundage ⁵ reported the preparation of some 8-substituted 6-methyl-*s*-triazolo[4,3-*b*]pyridazines based on acetoacetic ester and 4-amino-1,2,4-triazole, yet without any proof of structures.

In 1958 Kost and Gents ³ reported the preparation of a series of 7- and/or 8-substituted 5,6-dihydro-6-oxo-*s*-triazolo[4,3-*b*]pyridazines from β -keto-esters and 4-amino-1,2,4-triazole considering these alternative structures of the reaction products more probable than the ones postulated by Bülow ².



If the reaction between acetoacetic ester and 4-amino-1,2,4-triazole followed the route proposed by Kost and Gents, the product should be identical with VIII, 8-methyl-5,6-dihydro-6-oxo-*s*-triazolo[4,3-*b*]pyridazine. The melting points of these substances are far too high to allow any comparison by mixed melting points, but the infra-red spectra clearly showed that the reaction product IX was different from VIII. The spectra of VII and VIII (in KBr discs) contained carbonyl absorption bands at 1634 and 1624 cm^{-1} , respectively, whereas the spectrum of IX only showed an extremely weak band in

this region. This indicated that IX in the solid state exists as 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine and not in the tautomeric vinyllog lactam form 6-methyl-5,8-dihydro-8-oxo-*s*-triazolo[4,3-*b*]pyridazine. The infra-red spectra were consistent with the fact, that only IX gave a positive, intense red colour reaction with ferric chloride solution. The spectra of all three compounds contained two broad bands between 2600 and 1700 cm^{-1} , showing the presence of strong hydrogen bonding. This may in the case of VII and VIII explain why the intensity of the carbonyl bands is less than usual for this kind of lactams.

As a further control the reaction product was treated with phosphoryl chloride as described by Steck and Brundage⁵, and this reaction yielded 8-chloro-6-methyl-*s*-triazolo[4,3-*b*]pyridazine^{5,6}, which was not identical with VI, the product from the reaction between 3-chloro-6-hydrazino-5-methylpyridazine and formic acid. Thus, Bülow's original formula for the product formed from acetoacetic ester and 4-amino-1,2,4-triazole is correct.

Treatment of 6-chloro-7-methyl-*s*-triazolo[4,3-*b*]pyridazine with hydrazine gave as described by Takahayashi¹ the corresponding 6-hydrazino derivative. When this compound was treated with formic acid under conditions similar to those applied for the preparation of the triazolo-pyridazines, only the 6-formylhydrazino derivative was obtained. Ring closure to a bis-*s*-triazolo [4,3-*b*:3',4'-*f*]pyridazine could not be performed.

EXPERIMENTAL

All melting points are uncorrected. The infra-red spectra were recorded on a Perkin-Elmer Model 21 Spectrometer in KBr discs. The microanalyses were carried out by P. Hansen, The Chemical Laboratory of the University of Copenhagen.

3-Chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II). 3,6-Dichloro-4-methylpyridazine (81.0 g, 0.5 mole) was heated with 250 ml of a 50 % aqueous solution of hydrazine hydrate. As the reaction mixture was heated above the melting point of 3,6-dichloro-4-methylpyridazine (87°) a vigorous reaction started with the separation of the hydrazino derivatives. The suspension was boiled under reflux for $\frac{1}{2}$ h to complete the reaction, and 250 ml of water were added. The reflux was continued for further 20 min and insoluble material was removed from the hot suspension by filtration. Recrystallisation of the collected material from 400 ml of water gave 12.7 g of 3-chloro-6-hydrazino-5-methylpyridazine (II), m.p. 199–200°.

From the filtrate was isolated 3.0 g of II and 34.0 g of the more soluble component 3-chloro-6-hydrazino-4-methylpyridazine (I), m.p. 158° after numerous recrystallisations from water or ethanol-water. The yield of I was significantly lower than the amount of I formed due to heavy losses during the separation procedure. (Found for I: C 37.70; H 4.54; N 35.36; Cl 22.27. Found for II: C 37.55; H 4.46; N 34.81; Cl 22.20. Calc. for $\text{C}_5\text{H}_7\text{N}_4\text{Cl}$: C 37.87; H 4.45; N 35.34; Cl 22.36).

Characteristic infra-red absorption bands:

	I	II
NH ₂ deformation	1610 *	1627
Ring stretching	1610 *, 1495	1598, 1560, 1495
C—CH ₃ deformation	1382	1378
γ CH (out-of-plane) deformation	898	880, 917
β CH (in-plane) deformation, ring breathing, etc.	{ 1225, 1145, 1066, 985, 763	{ 1314, 1129, 1086 1002, 974, 797

* Absorption considered to be the superimposition of two peaks.

Hydrogenation of 3-chloro-6-hydrazino-4-methyl-pyridazine. To a solution of 6.3 g (0.04 mole) of 3-chloro-6-hydrazino-4-methyl-pyridazine (I) in 200 ml of methanol were added 8 g of Raney nickel. Addition of hydrogen was carried out at atmospheric pressure, but no hydrogen was absorbed. 2.2 g of potassium hydroxide were added and absorption of hydrogen proceeded slowly. After 36 h 0.04 mole of hydrogen was absorbed, and the Raney nickel was filtered off. The alkaline, black filtrate was acidified with acetic acid and evaporated to dryness *in vacuo*. The residue was dissolved in 25 ml of water and after filtration a dark coloured material crystallised on cooling, m.p. 186–187°. It was purified by recrystallisation from water and charcoal. A mixed melting point with an authentic sample⁴ and an infra-red spectrum established the structure as 3-chloro-6-amino-4-methyl-pyridazine. Yield: 0.9 g (16 %).

Concentration of the filtrate and crystallisation yielded 0.5 g of dark coloured material with m.p. 140–150° (decomp.), which was considered to be a mixture of various hydrogenation products.

The isolated amino-chloro compound (0.2 g) was heated to boiling with a few milliliters of acetic anhydride and the acetyl derivative crystallised on cooling, m.p. 216°. Mixed melting point with an authentic sample⁴ showed no depression.

Hydrogenation of 3-chloro-6-hydrazino-5-methyl-pyridazine. 6-Amino-5-methyl-pyridazine. To a solution of 3.2 g (0.02 mole) of 3-chloro-6-hydrazino-5-methyl-pyridazine (II) in 60 ml of methanol were added 5 g of Raney nickel and 40 ml of a 1 N methanolic solution of potassium hydroxide (0.04 mole). Hydrogenation was carried out at atmospheric pressure, and the theoretical amount of hydrogen was absorbed within 24 h. The Raney nickel was filtered off and the methanol evaporated off *in vacuo*. The residue was dissolved in boiling water, and the solution was filtered and cooled to 0°. Yellowish crystals (needles, 1.2 g) could be isolated, m.p. 192–193°. Concentration of the filtrate yielded another 0.4 g, m.p. 190–192°. Recrystallisation from water raised the m.p. to 193.5°. The Beilstein test for halogen was negative. The analysis showed the empirical formula $C_5H_7N_3 \cdot \frac{1}{2}H_2O$. Recrystallisation from chloroform gave 1.4 g (64 %) of anhydrous 5-methyl-6-amino-pyridazine, m.p. 193.5°. (Found: C 54.80; H 6.28; N 38.42. Calc. for $C_5H_7N_3$: C 55.03; H 6.47; N 38.51).

Oxidation of I and II with sodium hydrochlorite or sodium hypobromite. 3-Chloro-4- and 5-methyl-1,6-dihydro-6-oxo-pyridazine (XIII and XIV). A 3 M sodium hypochlorite solution was prepared from 70 ml of water, 20 g of sodium hydroxide, and 21 g (0.3 mole) of chlorine. The solution was chilled in ice during the addition of chlorine. Finally the solution was diluted to 100 ml with water.

0.79 g (0.005 mole) of 3-chloro-6-hydrazino-4-methyl-pyridazine (I) were dissolved in 10 ml of 5 N sulfuric acid, the solution was cooled to 0°, and 3.5 ml 3 M sodium hypochlorite solution (slight excess) were added from a dropping funnel. Evolution of nitrogen started with the immediate separation of a white precipitate. After the addition of hypochlorite solution the precipitate was filtered off and recrystallised from water. Yield: 0.39 g (54 %) of 3-chloro-4-methyl-1,6-dihydro-6-oxo-pyridazine (XIII), m.p. 224° subl., identified through mixed melting point with an authentic sample⁴ and infra-red spectra.

Oxidation of 3-chloro-6-hydrazino-5-methyl-pyridazine (II) with sodium hypochlorite was carried out analogously. The greater solubility of the product, 3-chloro-5-methyl-1,6-dihydro-6-pyridazine (XIV) necessitated the extraction with chloroform after the filtration of separated material, thus yielding 0.26 g (37 %) of XIV, m.p. 169–170° after recrystallisation from water. The product was identified through mixed melting point with an authentic sample⁴ and infra-red spectra.

The same compounds, XIII and XIV, were obtained when a 2 M solution of sodium hypobromite was used as oxidative agent.

6-Chloro-7- and 8-methyl-tetrazolo[1,5-b]pyridazine (III and IV). To a well-stirred and ice cooled solution of 7.9 g (0.05 mole) of 3-chloro-6-hydrazino-4-methyl-pyridazine (I) in 200 ml 15 % acetic acid were added 25 ml of a 3 M sodium nitrite solution (0.05 mole) from a dropping funnel. At the end of the addition the separation of a white solid started and the reaction mixture was left with stirring for $\frac{1}{2}$ h. The precipitate was filtered off and recrystallised from water. Yield: 6.1 g (72 %) of 6-chloro-7-methyl-tetrazolo[1,5-b]pyridazine (III), m.p. 140.5°. (Found: C 35.05; H 2.55; N 41.15; Cl 20.83. Calc. for $C_5H_4N_4Cl$: C 35.43; H 2.38; N 41.30; Cl 20.90).

By a similar procedure was obtained a 79 % yield of 6-chloro-8-methyl-tetrazolo[1,5-b]pyridazine (IV), m.p. 107.0°, from 3-chloro-6-hydrazino-5-methyl-pyridazine (II). (Found: C 35.35; H 2.55; N 41.30; Cl 20.65. Calc. for $C_6H_5N_4Cl$: C 35.43; H 2.38; N 41.30; Cl 20.90).

6-Chloro-7- and 8-methyl-s-triazolo[4,3-b]pyridazine (V and VI). 3-Chloro-6-hydrazino-4-methyl-pyridazine (I, 7.9 g, 0.05 mole) was boiled under reflux for 2 h with 80 ml 80 % (or 100 %) formic acid. The solvent was evaporated off *in vacuo* and the residue distilled at 1 mm. The distillate could be recrystallised from either petrol or water. Yield: 7.6 g (91 %) of 6-chloro-7-methyl-s-triazolo 4,3-b pyridazine (V), m.p. 157.5–158.0°. (Found: C 42.63; H 3.13; N 33.07; Cl 21.18. Calc. for $C_6H_5N_4Cl$: C 42.75; H 3.01; N 33.25; Cl 21.02).

6-Chloro-8-methyl-s-triazolo[4,3-b]pyridazine (VI), m.p. 134.0–134.5°, was prepared in a 89 % yield from 3-chloro-6-hydrazino-5-methyl-pyridazine (II) by a similar procedure. (Found: C 42.45; H 3.16; N 33.00; Cl 20.86. Calc. for $C_6H_5N_4Cl$: C 42.75; H 3.01; N 33.25; Cl 21.02).

7- and 8-Methyl-5,6-dihydro-6-oxo-s-triazolo[4,3-b]pyridazine (VII and VIII). The chloro derivatives V and VI (1.7 g, 0.01 mole) were boiled under reflux for 1 h with a solution of 1.1 g of potassium hydroxide in 25 ml of water. On acidification with acetic acid a white solid precipitated, which was recrystallised from water acidified with a minute amount of acetic acid. Yield of 7- and 8-methyl-5,6-dihydro-6-oxo-s-triazolo[4,3-b]pyridazine 1.25 g (83 %) and 1.15 g (77 %), respectively. Melting points above 265°. (Found for VII: C 47.85; H 4.20; N 37.52. Found for VIII: 47.90; H 4.06; N 37.50. Calc. for $C_6H_6N_4O$: C 48.00; H 4.03; N 37.32).

6-Hydrazino-7-methyl-s-triazolo[4,3-b]pyridazine (XI). 6-Chloro-7-methyl-s-triazolo[4,3-b]pyridazine (V, 1.7 g, 0.01 mole) was dissolved in 10 ml of 80 % aqueous hydrazine hydrate by gentle heating. After 1–2 min the separation of a white solid started and after boiling for 10 min the mixture was cooled and filtered. The isolated material was recrystallised from water. Yield of 6-hydrazino-7-methyl-s-triazolo[4,3-b]pyridazine 1.3 g (80 %), m.p. above 265°. (Found: C 43.80; H 4.86; N 51.38. Calc. for $C_6H_8N_6$: C 43.89; H 4.91; N 51.20).

6-(β-Formylhydrazino)-7-methyl-s-triazolo[4,3-b]pyridazine (XII). A solution of 1.0 g (0.006 mole) of 6-hydrazino-7-methyl-s-triazolo[4,3-b]pyridazine (XI) in 10 ml of formic acid (100 %) was heated under reflux for 2 h. The formic acid was evaporated off *in vacuo*, and the residue was recrystallised from water, giving a quantitative yield (1.15 g) of 6-(β-formylhydrazino)-7-methyl-s-triazolo[4,3-b]pyridazine, m.p. above 265°. (Found: C 43.65; H 4.25; N 43.58. Calc. for $C_7H_8N_6O$: C 43.75; H 4.20; N 43.73).

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REFERENCES

1. Takahayashi, N. *Pharm. Bull. Japan* **5** (1957) 229.
2. Bülow, C. *Ber.* **42** (1909) 2594.
3. Kost, A. N. and Gents, F. *J. Gen. Chem. U.S.S.R.* **26** (1958) 2796.
4. Linholter, S., Kristensen, Aa. B., Rosenørn, R., Nielsen, S. E. and Kaaber, H. *Acta Chem. Scand.* **15** (1961) 1660.
5. Steck, E. A. and Brundage, R. P. *J. Am. Chem. Soc.* **81** (1959) 6289.
6. Bülow, C. and Haas, K. *Ber.* **43** (1910) 1975.

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