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Pyridazine Studies

III. The Oxidation of 3-Hydrazino Substituted Pyridazines with Sodium Hypohalite. The Preparation of 3-Chloro-6-bromo-pyridazine and Its 4- and 5-Methyl Derivatives

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The oxidation of some 3-hydrazino substituted pyridazines in strong acidic solution with sodium hypohalite proceeds through a four electron change reaction, probably through the very unstable diazonium intermediate. The reaction of the diazonium intermediate with the anions of the solution has been applied to the preparation of 3-chloro-6-bromo-pyridazine and its 4- and 5-methyl derivatives (V and VI). The reaction of V and VI with dimethylamine showed that this reagent under the conditions applied only attacks the position *meta* to the methyl group. This was used to establish the structure of the previously described [1] product from the reaction of 3,6-dichloro-4-methylpyridazine with dimethylamine. 3,6-Dibromo-4-methyl-pyridazine and hydrazine gave a mixture of the two isomeric 3-hydrazino-6-bromo-4- and 5-methyl-pyridazines (IX and X). The structure of the 4-methyl derivative (IX) was established by conversion into 3-chloro-6-bromo-4-methyl-pyridazine (V).

Most of the methods applied for the estimation of organic derivatives of hydrazine are based on the strong reductive properties of the hydrazino function. Various oxidants have been recommended in the literature, and this subject was recently reviewed by Singh and Sahota [2].

Oxidation of hydrazino derivatives can proceed through several reaction paths depending on the oxidant used, the degree of substitution on the hydrazino group, and the acidity of the reaction medium. Monosubstituted hydrazines are generally oxidised through a four electron change reaction, and for most practical purposes halogens in higher oxidation states are recommended for the estimation of hydrazines [2,3]. Some limitations in the versatility of these oxidation procedures may arise from reactions involving other reactive centers in the molecule [3], *e.g.* halogenation, addition of halogens to double bonds, and oxidation of other functional groups.

Singh *et al.*[4] published a convenient method for the estimation of a wide variety of hydrazine derivatives. These authors recommended potentiometrical titration in strong acidic solution using a standard solution of chloramine T. The chloramine T was employed in place of sodium hypochlorite because of its stability.

For a long time a need for a convenient method for the estimation of hydrazine derivatives has been recognized in this laboratory. Therefore, a preliminary investigation of the scope and limitations of the method of Singh *et al.*[4] was undertaken. Among several compounds some hydrazino substituted pyridazines were titrated potentiometrically with chloramine T essentially as described by Singh *et al.*[4] The compounds in question are listed in Table 1.

The method was useful for these types of compounds. The reaction involves a four electron change reaction and the endpoint is sharp. The potential changes about 450 mV by the addition of 0.05 ml of a 0.05 M solution of chloramine T. No side reactions were observed and the only inconvenience was the relatively long reaction time towards the endpoint of the titration. The reproducibility was satisfactory for our purposes, and the greatest deviation (3 %) from the theoretical value of the molecular weight was found in a sample of 3-hydrazino-6-phenyl-pyridazine which was not analytically pure.

Miller and Furman [5] demonstrated the presence of a diazonium ion in the reaction mixture by coupling with β-naphthol, when phenylhydrazine was titrated with iodine or potassium iodate solution. Since nitrogen was evolved during the oxidation of the hydrazino-pyridazines, it was assumed, that a diazonium ion was the primary oxidation product in this instance. We were not able to demonstrate the presence of this intermediate in the acidic reaction mixture due to the rapid liberation of nitrogen from this α-diazo substituted N-heteroaromatic system. However, when the oxidant (chloramine T, sodium hypochlorite or hypobromite) was added to a suspension of the hydrazino derivative in alkaline β-naphthol solution a dark red dye was immediately

Table 1. Estimation of the molecular weight of hydrazino-pyridazines.

	Found	Theoretical
3-Chloro-6-hydrazino [6]	144.9 145.3	144.6
3-Chloro-6-hydrazino-4-methyl [7]	159.8 159.6	158.6
3-Chloro-6-hydrazino-5-methyl [7]	159.0 159.4	158.6
3-Phenyl-6-hydrazino [9]	192.3 190.2	186.2
1,4-Dimethyl-3-hydrazino-1,6-dihydro-6-oxo *	151.7 152.0	154.2
1,5-Dimethyl-3-hydrazino-1,6-dihydro-6-oxo *	151.6 152.2	154.2

* See footnote p. 962.

formed. Consequently we expected that the reaction product from the oxidation would entirely depend on the composition of the solution.

$$R-\overset{+}{N}HNH_3 + 2\,HOX \longrightarrow R-\overset{+}{N}\equiv N + 2\,X^- + 2\,H^+ + 2\,H_2O$$

$$R-\overset{+}{N}\equiv N + X^- \longrightarrow RX + N_2$$

The analytical oxidation procedure was adopted for preparative purposes. The hydrazino-pyridazines were dissolved in 5 N hydrochloric acid and a 3 M solution of sodium hypochlorite was used as oxidant. From 3-chloro-6-hydrazino-pyridazine [6] an 84 % yield of 3,6-dichloro-pyridazine [6] was obtained, and 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II) [7] were converted into 3,6-dichloro-4-methyl-pyridazine [6] in a 92 % and 74 % yield, respectively.

An attempt to convert 1,4- and 1,5-dimethyl-3-hydrazino-1,6-dihydro-6-oxo-pyridazine into the corresponding 3-chloro-derivatives * failed. The expected products could not be isolated from the reaction mixture, even though the titrations of these hydrazino derivatives with chloramine T indicated that a four electron change reaction had occurred. The absence of a diazonium intermediate after the addition of the sodium hypochlorite solution was indicated by the evolution of nitrogen and demonstrated by the negative reaction with alkaline β-naphthol. Instead, 3-hydroxy derivatives could have been formed, but no attempts were made to isolate these products.

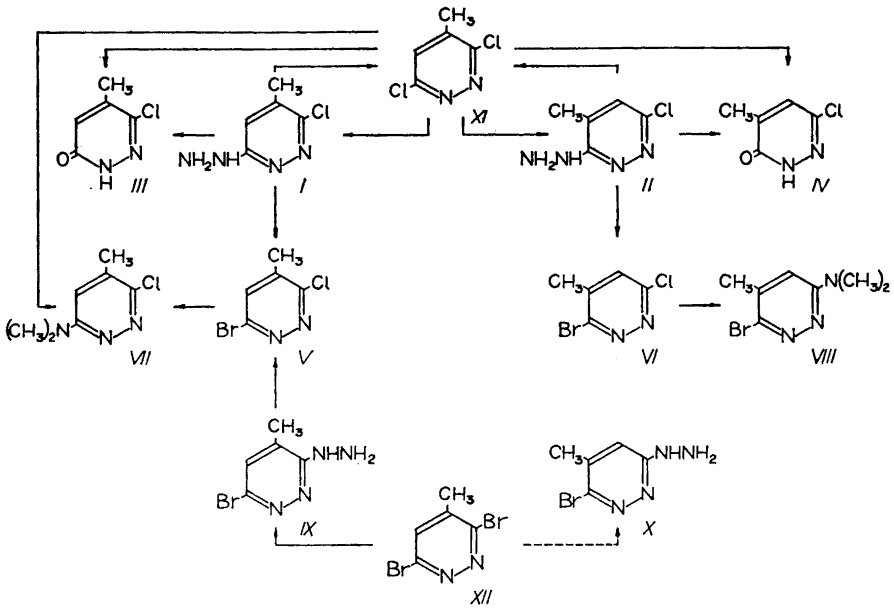
When 5 N sulfuric acid was used as a solvent instead of hydrochloric acid 3-chloro-6-hydrazino-pyridazine and its 4- and 5-methyl derivatives (I and II) were converted into the corresponding hydroxy derivatives, 3-chloro-1,6-dihydro-6-oxo-pyridazine [6] and its 4- and 5-methyl derivatives (III and IV) [1]. The yields were widely different due to the different solubility of the products, 4-methyl-3-chloro-1,6-dihydro-6-oxo-pyridazine[1] (IV) being by far the most insoluble isomer in aqueous solutions. The aqueous solution could not be evaporated due to the risk of hydrolysis of the 3,6-dichloro-4-methyl-pyridazine formed from the reaction of the diazonium intermediate with added chlorine ion. This would in the case of the methyl derivatives result in the formation of a mixture of 4- and 5-methyl-3-chloro-1,6-dihydro-6-oxo-pyridazine. The application of this reaction in the establishment of the structures of 4- and 5-methyl-3-chloro-6-hydrazino-pyridazine (I and II) was described in a previous paper [7].

By a similar procedure 3-chloro-6-hydrazino-pyridazine was converted into 3-chloro-6-bromo-pyridazine, m.p. 93.5—94.0°, by oxidation with either sodium hypobromite or bromine in hydrobromic acid solution. This compound was prepared earlier ** by the action of bromine and sodium nitrite on 3-chloro-6-amino-pyridazine [6] according to the method of Craig [8].

Analogously 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II) yielded 3-chloro-6-bromo-4- and 5-methyl-pyridazine (V and VI), m.p.'s 97.0° and 98.5°, respectively. However, the yields were not good compared to the oxidations in hydrochloric acid. This was partly due to the formation of oxida-

* The method of preparation of these compounds will be described in the next paper of this series.

** Unpublished results.



tion products resulting from a different oxidation mechanism and partly due to the formation of pyridazine-6-ones (III and IV) from the reaction of the diazonium intermediate with water.

The infra-red spectra of the 3,6-dihalogeno-pyridazines were only slightly different. Usually only one band appeared from the four principal ring stretching vibrations of the pyridazine ring, and the most characteristic feature of the spectra was the frequency variation of this band. The wavenumber decreased from 1557 cm^{-1} to 1525 cm^{-1}, with increasing atomic weight of the substituents, the lowest wave number being 1525 cm^{-1} for 3,6-diiodo-pyridazine *. Introduction of a methyl group in the 4-and-5-position increased the wave number in agreement with the electron donor properties of this substituent [10].

3,6-Dibromo-4-methyl-pyridazine (XII), m.p. 103.5°, was prepared from cyclic citraconic hydrazide and phosphoryl bromide similar to the preparation of 3,6-dichloro-4-methyl-pyridazine in a 41 % yield. Treatment of XII with aqueous hydrazine gave a mixture of the two isomeric 6-bromo-3-hydrazino-4- and 5-methyl-pyridazines from which the higher melting isomer (IX), m.p. 180°, was isolated in pure condition. Attempts to isolate the lower melting isomer free from IX by recrystallisations from water or water/ethanol failed. Conversion of IX into 3-chloro-6-bromo-4-methyl-pyridazine (V) by oxidation with sodium hypochlorite in hydrochloric acid solution established the structure of IX as 3-hydrazino-6-bromo-4-methyl-pyridazine.

We earlier described [1] the reaction between 3,6-dichloro-4-methylpyridazine and dimethylamine resulting in the formation of only one isomer, 3-dimethyl-

* A sample of this compound was kindly placed at our disposal by mag. scient. I. Crossland.

Table 2. Wave numbers (cm^{-1}) of the first ring stretching band of 3,6-dihalogenopyridazines.

3,6-Dichloro	1556
3-Chloro-6-bromo	1550
3,6-Dibromo	1544
3,6-Diiodo	1525
3-Chloro-6-bromo-4-methyl	1557
3-Chlorol-6-bromo-5-methyl	1560
3,6-Dichloro-4-methyl	1567
3,6-Dibromo-4-methyl	1553

amino-6-chloro-4- or 5-methyl-pyridazine, m.p. 122°. An NMR spectrum of the dehalogenated derivative [1] indicated the structure 3-dimethylamino-5-methyl-pyridazine for this compound. The signals from the two aromatic protons (in the 4 and 6 position) appeared as broad singlets at $\tau = 3.62$ and $\tau = 1.85$ ppm, respectively. (Carbon tetrachloride solution with tetramethylsilane as the internal reference.) If the remaining two aromatic protons had been adjacent, the signals should have been split into doublets with a coupling constant $J = 4-5$ cps, but the observed signals, whose fine structure arose from spin-spin coupling with the proton in the *meta* position and with the protons of the methyl group, indicated the structure given above. The structure of VII was proven by its formation from 3-bromo-6-chloro-5-methyl-pyridazine (V) and dimethylamine, and 3-dimethylamino-6-bromo-5-methyl-pyridazine (VIII) was analogously obtained from 3-chloro-6-bromo-5-methyl-pyridazine (VI). It was evident that dimethylamine under the conditions applied attacks only the halogen atom in the *meta* position to the methyl group, the *ortho* position being protected by steric hindrance.

EXPERIMENTAL

All melting points are uncorrected. The infra-red spectra were recorded on a Perkin-Elmer Model 21 Spectrometer and the NMR spectra on a Varian A-60 Spectrometer. The microanalyses were carried out by P. Hansen, The Chemical Laboratory of the University of Copenhagen.

Estimation of the hydrazino-pyridazines. The titrations were carried out by the method of Singh *et al.*[4] The course of the reaction was followed on a Radiometer Potentiometer Model 22. The equivalence point appeared as a sharp change in potential (about 450 mV). Towards the endpoint of the titration equilibrium was first restored after 5—10 min. About 0.0005 moles of the hydrazino compound was titrated with a 0.05 M solution of chloramine T, standardised against hydrazine sulfate.

Oxidations with sodium hypochlorite solution. A 3 M solution of sodium hypochlorite was prepared by the addition of 21.4 g (0.3 moles) of chlorine to a solution of 20 g (0.5 moles) of sodium hydroxide in water at 0° followed by dilution to 100 ml. The hydrazino-chloro-pyridazine (0.005 moles) was dissolved in 10 ml of 5 N hydrochloric acid. The solution was efficiently stirred and cooled in an ice-bath, and the hypochlorite solution (3.5 ml) was added dropwise. A voluminous white precipitate separated from the solution with the evolution of nitrogen. The precipitate was filtered off, washed with icecold water, and dried over potassium hydroxide *in vacuo*. The product was recrystallised from petroleum ether.

From 3-chloro-6-hydrazino-pyridazine was obtained 0.63 g (84 %) of 3,6-dichloro-pyridazine, m.p. 68°. 3-Chloro-6-hydrazino-4- and 5-methyl-pyridazine (I and II) yielded 0.75 g (92 %) and 0.60 g (74 %), respectively, of 3,6-dichloro-4-methyl-pyridazine, m.p. 87°. The products were identified by mixed melting points with authentic samples [6].

The oxidations of 3-chloro-6-hydrazino-4- and 5-methyl-pyridazine in sulfuric acid solution with sodium hypochlorite are described in detail in a previous paper [7]. Only a small amount of 3-chloro-1,6-dihydro-6-oxo-pyridazine was obtained from the oxidation of 3-chloro-6-hydrazino-pyridazine after extraction of the reaction mixture with chloroform. It was identified by a mixed melting point (138°) with an authentic sample and by its infra-red spectrum.

Oxidations with sodium hypobromite solution. A 2 M solution of sodium hypobromite was prepared by the addition of 16.0 g (0.1 moles) of bromine to a solution of 10 g (0.25 moles) of sodium hydroxide in water followed by dilution to 50 ml.

3-Chloro-6-bromo-pyridazine. 3-Chloro-6-hydrazino-pyridazine (0.72 g, 0.005 moles) was dissolved in 12 ml of constant boiling hydrobromic acid. A vigorous evolution of nitrogen was observed during the addition of 3.5 ml of sodium hypobromite solution. Addition of a few drops of a 25 % solution of sodium hydroxide resulted in the separation of a yellowish product, which was filtered off, washed with water, and dried over potassium hydroxide *in vacuo*. No residue was obtained when the filtrate was neutralised with sodium hydroxide solution, extracted with chloroform and the chloroform solution evaporated. Yield of 3-chloro-6-bromo-pyridazine after recrystallisation from petroleum ether 0.40 g (41 %), m.p. 93.5 – 94.0°. (Found: C 25.07; H 1.40; N 14.75; Cl 18.02; Br 40.90. Calc. for $C_4H_2BrClN_2$: C 24.85; H 1.03; N 14.51; Cl 18.34; Br 41.33.

3-Chloro-6-bromo-4-methyl-pyridazine (V). 3-Chloro-6-hydrazino-4-methyl-pyridazine (I, 0.40 g, 0.0025 moles) was dissolved in 6 ml of constant boiling hydrobromic acid. After the addition of sodium hypobromite solution an excess of a 25 % solution of sodium hydroxide was added, and the precipitate was filtered off, washed with water and dried *in vacuo* over potassium hydroxide. The compound was recrystallised from petroleum ether, yielding 0.27 g (52 %) of 3-chloro-6-bromo-4-methyl-pyridazine (V), m.p. 97.0°. (Found: C 29.65; H 1.98; N 13.04; Cl 16.82; Br 38.60. Calc. for $C_5H_4BrClN_2$: C 28.95; H 1.94; N 13.50; Cl 17.10; Br 38.50).

The filtrate was acidified with hydrobromic acid and the precipitate was filtered off. This compound was identified as 4-methyl-3-chloro-1,6-dihydro-6-oxo-pyridazine (III), m.p. 224°.[1]

3-Chloro-6-bromo-5-methyl-pyridazine (VI). 3-Chloro-6-hydrazino-5-methyl-pyridazine (II, 1.58 g, 0.01 moles) was dissolved in 20 ml of constant boiling hydrobromic acid. After the addition of the sodium hypobromite solution an excess of a 25 % solution of sodium hydroxide was added. The precipitate was filtered off, washed with water, dried over potassium hydroxide *in vacuo*, and recrystallised from petroleum ether. Yield of 3-chloro-6-bromo-5-methyl-pyridazine (VI) 1.35 g (65 %), m.p. 98.5°. (Found: C 29.10; H 2.03; N 13.48; Cl 16.58; Br 38.35. Calc. for $C_5H_4BrClN_2$: C 28.95; H 1.94; N 13.50, Cl 17.10; Br 38.50).

3-Dimethylamino-6-bromo-5-methyl-pyridazine (VIII). 3-Chloro-6-bromo-5-methyl-pyridazine (V, 2.08 g 0.01 moles) was heated for 20 h in an autoclave with 100 ml of a 30 % aqueous solution of dimethylamine. On cooling white crystals was filtered off in an almost quantitative yield. Recrystallisation from water gave 1.90 g (88 %) of 3-dimethylamino-6-bromo-5-methyl-pyridazine (VIII), m.p. 118.5°. (Found: C 39.10; H 4.54; N 19.36; Br 36.90. Calc. for $C_7H_{10}BrN_3$: C 38.90; H 4.66; N 19.44; Br 36.98).

3-Dimethylamino-6-chloro-5-methyl-pyridazine (VII). 3-Bromo-6-chloro-5-methyl-pyridazine (VI, 2.08 g 0.01 moles) was by a similar procedure converted into 3-dimethylamino-6-chloro-5-methyl-pyridazine, m.p. 122.0°, in a 90 % yield. An infra-red spectrum demonstrated the identity with the previously described 3-dimethylamino-6-chloro-4- or 5-methyl-pyridazine [1] from the reaction of 3,6-dichloro-4-methyl-pyridazine with dimethylamine.

3,6-Dibromo-4-methyl-pyridazine (XII). Cyclic citraconic hydrazide — 4-methyl-3-hydroxy-1,6-dihydro-6-oxo-pyridazine — (25.2 g, 0.2 moles) was boiled under reflux with 170 g (0.6 moles) of phosphoryl bromide for 10 h. The reaction mixture was still colourless, but the evaporation of the excess phosphoryl bromide *in vacuo* left a dark brown residue. The residue was poured onto a mixture of crushed ice and concentrated ammonia. The almost black precipitate was filtered off at pH 9 – 10 and dried *in vacuo* over potassium hydroxide. The filtrate was extracted with methylene chloride, but evaporation of the solvent from the extract left no residue. The black precipitate was recrystallised with activated charcoal from ethanol-water. Yield of 3,6-dibromo-4-methyl-pyridazine (XII),

20.5 g (41 %), m.p. 103.5°. (Found: C 23.51; H 1.57; N 11.20; Br 63.41. Calc. for $C_5H_4Br_2N_2$: C 24.04; H 1.60; N 11.13; Br 63.45).

3-Bromo-6-hydrazino-5-methyl-pyridazine (IX). 3,6-Dibromo-4-methyl-pyridazine (XII, 5.0 g, 0.02 moles) was heated with 20 ml of a 85 % solution of hydrazine hydrate. At about 80° a vigorous reaction started with the separation of a mixture of the two isomeric reaction products. Heating was continued for 20 min, the mixture was cooled to room temperature and the precipitate was filtered off. After several recrystallisations from water or water/ethanol a pure fraction with m.p. 179.5—180.0° was obtained. Attempts to purify the lower melting isomer (m.p. 140—145°) failed. The purity of the higher melting isomer (IX), 3-bromo-6-hydrazino-5-methyl-pyridazine, was demonstrated by an infra-red spectrum. The structure was established by oxidation with sodium hypochlorite in hydrochloric acid as described above. (Found: C 30.00; H 3.58; N 27.50; Br 38.90. Calc. for $C_5H_7BrN_4$: C 29.57; H 3.56; N 27.58; Br 39.34).

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