Pyridazine Studies

I. The Preparation of Some 3,6-Disubstituted 4-Methyl-pyridazines

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The competitive monosubstitution of the individual chlorine atoms of 4-methyl-3,6-dichloro-pyridazine by alkoxide ions is studied. A preferential reaction at the 6-position by alkoxy groupings larger than methoxy is noticed. Reaction of 4-methyl-3,6-dichloro-pyridazine with ammonia at 120° results in the production of two isomeric amino-chloro-4-methyl-pyridazines, whereas dimethylamine affords only one product of as yet unestablished structure.

The structures of the various isomeric substitution products have been established by synthetic transformations and comparison with authentic compounds.

For some time we have been studying the reactivity of methyl groups present as substituents in various heterocyclic systems and the influence of other substituents on the reactivity of such methyl groups. In this connection some 3- and 6-substituted 4-methyl-pyridazines were desired, and 4-methyl-3,6-dichloro-pyridazine served as a useful starting material for the synthesis of such compounds. The latter was synthesised according to Mizzoni and Spoerri¹ from citraconic anhydride and hydrazine. Dehydration of itaconic acid by means of acetic anhydride² provided a satisfactory route to the anhydride employed. The conversion of citraconic anhydride into 4-methyl-3,6-dichloro-pyridazine was performed essentially as described¹.

Selective exchange of one halogen atom was effected by treatment of the dichloro compound with sodium alkanolate, water, ammonia and dimethylamine, as suggested by Druey *et al.*³ For each of these reagents two isomeric compounds are possible:

After separation of the reaction products it was necessary to identify each of the components separately. The difference in solubility of the isomeric mono-

methoxy and monoethoxy substitutes was sufficiently great to allow separation of the less soluble component by repeated recrystallisations. It was difficult, however, to obtain the more soluble isomerides in homogeneous form. The methoxy compounds (see Table 1) were formed in almost equal amounts, the 5-methyl-6-methoxy-3-chloro-pyridazine (I) * being the less soluble isomer.

For the ethoxy derivatives, (IX) and (X), the proportion was displaced in favour of the 4-methyl-6-ethoxy-3-chloro-pyridazine (X). We therefore undertook a preliminary investigation of the influence of the alkyl size on the proportion between the two isomers. The reaction with sodium methanolate, ethanolate, 2-propanolate, *isobutanolate* and *cyclohexanolate* was studied and a tendency to preferential 6-alkoxylation with increasing size of the alkyl group was noticed. It would be of interest to include sodium *tert.*-butanolate into this series of alkanolates, but according to Druey *et al.*³ much more vigorous conditions would be needed in this case.

As mentioned above, the methoxy compounds could be separated. For the other alkoxy derivatives, however, separation was more easily achieved after hydrolysis to the pyridazinones with constant boiling hydrochloric acid. As pointed out by Druey *et al.*³ and verified by us, the remaining chlorine atom is not attacked by this treatment. Because 4-methyl-3,6-dichloro-pyridazine is hydrolysed under these conditions, quantitative reaction of one of the chlorine atoms must be ascertained before the ratio between the two isomeric pyridazinones can be utilized for estimating the ratio between the alkoxy derivatives. Quantitative reaction was in each case established by isolating and weighing the sodium chloride separating from the solutions, before hydrolysis of the mixture of the alkoxy compounds. The two compounds, 5-methyl-3-chloro-1,6-dihydro-pyridazin-6-one (VII), (5-methyl-3-chloro-6-hydroxy-pyridazine) and 4-methyl-3-chloro-1,6-dihydro-pyridazin-6-one (VIII), (4-methyl-3-chloro-6-hydroxy-pyridazine), could be almost quantitatively separated, and the structures of the two isomeric compounds were established by unambiguous methods.

A mixture of the isomeric compounds (VII) and (VIII) was obtained in 61 % yield from 4-methyl-1,2,3,6-tetrahydro-pyridazin-3,6-dione by treating this compound with phosphoryl chloride, and, in turn, hydrolysing the crude reaction product with hydrochloric acid. Acid was found superior to alkali for the hydrolysis, giving fewer side reactions and less tar formation.

The structures of these compounds were established as outlined in the formula scheme. The methoxy-chloro compounds (I) and (II) were dehalogenated by reduction with hydrogen and Raney nickel in methanolic potassium hydroxide solution according to Kämmerer *et al.*⁴ Both methyl-methoxy-pyridazines (III) and (IV) had a smell similar to that of anisole and formed addition products with picric acid. The picrates were used for analysis, because the parent compounds, one of which is liquid at room temperature, are rapidly discoloured. The methoxy compounds were hydrolysed with hydrochloric acid, and the m.p.'s of the two methyl-pyridazinones (V) and (VI) were compared with the m.p. of authentic 5-methyl-1,6-dihydro-pyridazin-6-one prepared

* In a recent publication, Steck⁹ reports the preparation of a methoxy substitute with m.p. 118°, yet without structural assignment.

Table 1.

Substituents	M.p. * °C	Formula	C		H		N		Cl	
			Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
I 5-methyl-6-methoxy-3-chloro	113	C ₈ H ₉ N ₂ ClO	45.95	45.45	4.68	4.43	17.20	17.66	22.53	22.35
II 4-methyl-6-methoxy-3-chloro	66	C ₈ H ₉ N ₂ ClO	45.30	45.45	4.37	4.43	17.24	17.66	22.30	22.35
III 5-methyl-6-methoxy **	34	C ₁₂ H ₁₁ N ₂ O ₈	40.70	40.79	3.14	3.11	19.97	19.83		
IV 4-methyl-6-methoxy **	15	C ₁₂ H ₁₁ N ₂ O ₈	40.80	40.79	3.21	3.11	19.99	19.83		
V 5-methyl-6-hydroxy	156	C ₈ H ₉ N ₂ O								
VI 4-methyl-6-hydroxy	162	C ₈ H ₉ N ₂ O								
VII 5-methyl-6-hydroxy-3-chloro	170	C ₈ H ₉ N ₂ ClO	41.45	41.51	3.39	3.49	19.48	19.39	24.35	24.53
VIII 4-methyl-6-hydroxy-3-chloro	220	C ₈ H ₉ N ₂ ClO	41.40	41.51	3.49	3.49	19.57	19.39	24.46	24.53
IX 5-methyl-6-ethoxy-3-chloro	78	C ₇ H ₉ N ₂ ClO	48.65	48.72	5.13	5.36	15.80	16.24	20.51	20.94
X 4-methyl-6-ethoxy-3-chloro	49	C ₇ H ₉ N ₂ ClO	48.75	48.72	5.24	5.36	15.52	16.24	20.44	20.94
XI 5-methyl-6-amino-3-chloro	137	C ₈ H ₉ N ₃ Cl	41.90	41.83	4.26	4.21	29.42	29.26	24.67	24.69
XII 4-methyl-6-amino-3-chloro	187	C ₈ H ₉ N ₃ Cl	41.40	41.83	4.34	4.21	29.03	29.26	24.59	24.69
XIII 4-methyl-6-dimethylamino-3-chloro ***	122	C ₇ H ₁₀ N ₃ Cl	48.92	49.01	5.87	5.65	24.28	24.12		
XIV 4-methyl-6-dimethylamino **	90	C ₇ H ₁₁ N ₃	61.00	61.28	8.00	8.08	30.77	30.63		

Analyses by P. Hansen, The Chemical Laboratory of the University of Copenhagen.

* All the m.p.'s are uncorrected.

** Analyses on the picrates.

*** The position of the methyl group is unknown.

according to McMillan *et al.*⁵ from α -keto- γ -methyl-glutaric acid⁶ as indicated in the scheme. The identity of one of the isomeric hydrolysis products with the authentic specimen was thus established. The structure of the other isomer is therefore indirectly ascertained.

Attempts to reproduce the preparation by Druey *et al.*³ of an aminochloro-4-methyl-pyridazine by treating 4-methyl-3,6-dichloro-pyridazine with aqueous ammonia at elevated temperature proved unsuccessful. However, reaction of the latter with anhydrous ammonia in methanol at 120° resulted in partial conversion into a mixture of amino-chloro-4-methyl-pyridazines that could be separated as N-acetyl derivatives into the two isomers (XI) and (XII). The structures of these were established by transforming them separately by diazotation into the above described hydroxy-chloro-pyridazines. On treating the dichloro derivative with aqueous or alcoholic dimethylamine at 120° only one isomer was obtained, representing 4- or 5-methyl-substituted 3-dimethylamino-6-chloro-pyridazine, of which the latter seems more likely for steric reasons. No bis-amination, as reported by Druey *et al.*³ in the case of 3,6-dichloro-pyridazine, was observed. Reductive dehalogenation with Raney nickel proceeded smoothly to give 4-(or 5-) methyl-6-dimethylamino-pyridazine. The more facile reduction of the chloro-substituted pyridazines containing methoxy- or dimethylamino-substituents, compared to the chloro-pyridazinones, can probably be attributed to the diminished aromatic character of the latter, resulting from the lactam-lactim-tautomerism.

EXPERIMENTAL

All melting points are uncorrected.

*Citraconic anhydride.*² 43 g (1/3 mole) of itaconic acid was suspended in 68 g (2/3 moles) of acetic anhydride. After standing for about 20 h, the mixture was heated to 80° for 2 h. Acetic acid and excess acetic anhydride were removed *in vacuo*. Itaconic anhydride distilled at 12 mm and 110–115° and crystallised in the receiver as long, beautiful columns, though some of the solid was already transformed into liquid citraconic anhydride. Distillation at atmospheric pressure gave 24 g (65 %) of citraconic anhydride, b.p. 215°.

*4-Methyl-1,2,3,6-tetrahydro-pyridazin-3,6-dione.*¹ To a boiling suspension of 260 g (2 moles) of hydrazine sulfate in 600 ml of water, 224 g (2 moles) of citraconic anhydride were added. The reaction started spontaneously under vigorous boiling. After heating under reflux for 2 h the mixture was cooled to 0°, and the 4-methyl-1,2,3,6-tetrahydro-pyridazine-3,6-dione was filtered off, washed with ice-cold water and dried at 100°. Yield 99–100 %.

*4-Methyl-3,6-dichloro-pyridazine.*¹ To 126 g (1 mole) of 4-methyl-1,2,3,6-tetrahydro-pyridazine-3,6-dione, 400 ml of phosphoryl chloride were added, and the mixture heated gently under reflux for 0.5 h. Excess reagent was distilled off *in vacuo*, and the residue was poured onto a mixture of water and crushed ice. The light yellow precipitate was filtered off and dried. The filtrate was extracted with chloroform giving 7 g of the dichloro compound. The crude 4-methyl-3,6-dichloro-pyridazine was distilled at 1 mm, b.p. 130–135°. The molten distillate was poured into petroleum ether and the crystals collected after cooling in the ice-box. Yield 147 g (90 %). m.p. 86°.

5-Methyl-6-methoxy-3-chloro-pyridazine (I) and 4-methyl-6-methoxy-3-chloro-pyridazine (II). To a solution of 1 mole of sodium methoxide in 750 ml of methanol, 163 g (1 mole) of 4-methyl-3,6-dichloro-pyridazine were added. A vigorous reaction started quickly with separation of sodium chloride. After cooling to room temperature the salt was filtered off, and the methanolic solution was kept at –10° overnight. The almost pure crystals were recrystallised from methanol or ether, by far the greatest part of (I) formed being isolated in this way. The yield of 5-methyl-6-methoxy-3-chloro-pyridazine (I) was 62 g, m.p. 113°.

The filtrate was evaporated to dryness *in vacuo* and the residue extracted with 250 ml of boiling ether. The inorganic material was removed — a little (I) separated here — and 250 ml of petroleum ether were added. To complete the crystallisation, the mixture was kept at –10° overnight. The product was recrystallised from petroleum ether giving 17 g of (II), m.p. 66°. From the combined filtrates, 36 g of (II) was obtained by repeated recrystallisations from petroleum ether. The yield of 4-methyl-6-methoxy-3-chloro-pyridazine (II) was 53 g, m.p. 66°. Total yield 115 g (73 %).

5-Methyl-6-methoxy-pyridazine (III) and 4-methyl-6-methoxy-pyridazine (IV). 11.5 g of 5-methyl-6-methoxy-3-chloro-pyridazine (I) was partly dissolved in a mixture of 75 ml of 1 N methanolic potassium hydroxide and 50 ml of methanol⁴. 90 ml of Raney nickel suspension⁷ (500 ml contained 75 g of Raney nickel) were added and the dehalogenation was carried out at atmospheric pressure. The hydrogenation proceeded rapidly during the first 30 min, and after 1 h the reaction was complete. The catalyst was filtered off — the last part, which was difficult to remove, was filtered off with sodium sulfate as filter-aid — and the solvent was removed, the last part of it *in vacuo*. The residue was extracted with dry ether, and the ethereal solution filtered and evaporated. The residue was distilled at 12 mm, b.p. about 100°. The yield of 5-methyl-6-methoxy-pyridazine (III) was 6.3 g (75 %), m.p. 34°.

The dehalogenation of (II) was carried out analogously, giving a 67 % yield of 4-methyl-6-methoxy-pyridazine (IV), m.p. 15°, b.p. about 105° at 12 mm.

5-Methyl-1,6-dihydro-pyridazin-6-one (V) and 4-methyl-1,6-dihydro-pyridazin-6-one (VI). 0.5 g of 5-methyl-6-methoxy-pyridazine (III) was dissolved in 10 ml of conc. hydrochloric acid and the solution was refluxed for about 0.5 h and then evaporated to dryness *in vacuo*. The dry residue was extracted with chloroform, the extract dried over anhydrous magnesium sulfate and concentrated to a small volume, from which 5-methyl-pyridazinone-6 (V) separated on addition of petroleum ether. The hydrolysis of 4-methyl-6-methoxy-pyridazine (IV) was carried out in the same way. The yields were about 100 %.

The m.p.'s found were:

m.p. of (VI)	156°
m.p. of (VI)	162°
m.p. of authentic 5-methyl-pyridazone-6 ⁵	155°
m.p. of authentic 5-methyl-pyridazone-6 + (V)	156°
m.p. of authentic 5-methyl-pyridazone-6 + (VI)	110–120°

The depression of 40–50° obtained when (VI) is mixed with 5-methyl-pyridazone-6 and the lack of depression when (V) is mixed with the same substance clearly shows, that (V) is 5-methyl-pyridazone-6. For this substance McMillan *et al.*⁵ indicate the m.p. 158–9°, whereas Schmidt and Druey⁸ report the m.p. 151–3° for the isomeric 4-methyl-pyridazone-6.

5-Methyl-3-chloro-1,6-dihydro-pyridazin-6-one (VII) and 4-methyl-3-chloro-1,6-dihydro-pyridazin-6-one (VIII). 50 g of 4-methyl-3,6-dichloro-pyridazine was dissolved in 250 ml of conc. hydrochloric acid and the solution was heated under reflux for 1 h. The acid was removed *in vacuo* and the residue was dissolved in a minimum of boiling ethanol. After cooling to about 30° crystals of (VIII) were filtered off at this temperature, m.p. 220° (subl.). The filtrate was kept a 0° for some hours and almost pure (VII) crystallised, m.p. 167–9°. On concentrating the mother liquor, a less pure crop of (VII) separated, m.p. 140–155°, but it was impossible to obtain the pure components from this mixture.

The first two products were recrystallised from ethanol, and further recrystallisations did not raise the m.p.'s. Yield of 5-methyl-3-chloro-1,6-dihydro-pyridazin-6-one, (VII): 20 g, m.p. 170°. Yield of 4-methyl-3-chloro-1,6-dihydro-pyridazin-6-one, (VIII): 15 g, m.p. 222°. The preparation of (VII) and (VIII) from (I) and (II) was effected analogously to the hydrolysis of 5-methyl-6-methoxy-pyridazine. The yields were about 100 %.

5-Methyl-6-ethoxy-3-chloro-pyridazine (IX) and 4-methyl-6-ethoxy-3-chloro-pyridazine (X). To a solution of 0.1 mole of sodium ethoxide in 100 ml of ethanol, 16.3 g (0.1 mole) of 4-methyl-3,6-dichloro-pyridazine was added. A vigorous reaction started with separation of sodium chloride. The mixture was heated under reflux for 0.5 h, and the sodium chloride was filtered off at room temperature. The filtrate was evaporated to dryness and the residue was extracted with boiling petroleum ether. Inorganic material was filtered off and on slow cooling of the filtrate the main part of (IX) could be isolated before crystallisation of (X) started. Both components crystallised from petroleum ether as needles, but of quite different appearance. The first crop, (IX), crystallised from ether as plates with m.p. 78°, unchanged by further recrystallisations. The purification of (X) was more difficult and was achieved by several recrystallisations from ether, giving needles with m.p. 49°. Due to losses during the purification the yields were rather poor.

The hydrolysis, establishing the structure of (IX) by giving 5-methyl-3-chloro-1,6-dihydro-pyridazin-6-one (VII), m.p. 170°, was carried out analogously to the hydrolysis of (I) and (II), the corresponding methoxy compounds.

5-Methyl-6-amino-3-chloro-pyridazine (XI) and 4-methyl-6-amino-3-chloro-pyridazine (XII). 16.3 g (0.1 mole) of 4-methyl-3,6-dichloro-pyridazine was suspended in 50 ml of methanol and 150 ml liquid ammonia were added. The reaction mixture was heated at 120° in an autoclave for 5 h. After cooling to room temperature, methanol and ammonia were removed on a steam bath. The residue was dissolved in dilute hydrochloric acid, and the acid solution was extracted with chloroform to remove unchanged starting material. In this way about 50 % of the dichloro compound were recovered. To the acid solution sodium hydroxide was added until alkaline reaction. The separated crude product corresponded to about 50 % conversion. The product was dried and acetylated by dissolving it in a minimum of boiling acetic anhydride. On cooling, the acetylation product of (XII) separated, m.p. 216°. The filtrate was concentrated to about one tenth of its original volume, and on cooling the almost pure acetylation product of (XI) separated, m.p. about 140°. Without further purification, the acetylation products were hydrolysed with the equivalent amount of potassium hydroxide in aqueous-alcoholic solution. Concentration and cooling gave 4-methyl-6-amino-3-chloro-pyridazine, (XII), m.p. 187° and 5-methyl-6-amino-3-chloro-pyridazine, (XI), m.p. 137°. The ratio between the amounts of (XI) and (XII) was about 1:10.

Diazotation of the amino-chloro-pyridazines, (XI) and (XII). 100 mg of the amino compounds was dissolved in a mixture of 2 ml of water and 1 ml of conc. sulfuric acid.

A small piece of ice was added and the solution cooled to 0°. The equivalent quantity of a 10 % solution of sodium nitrite was added while the reaction flask was thoroughly shaken. The diazotized 4-methyl-6-amino-3-chloro-pyridazine (XII) gave off nitrogen spontaneously at 0°, whereas the diazotized solution of (XI) required heating to about 40–50° before evolution of nitrogen started. Then the solutions were concentrated to about half their volumes. The pyridazones, which separated on cooling, established the structures of the amino-chloro-pyridazines. From (XII), m.p. 187°, 4-methyl-3-chloro-pyridazone-6, m.p. 220°, was obtained, and from (XI), m.p. 137°, 5-methyl-3-chloro-pyridazone-6, m.p. 170°.

4- (or 5-) Methyl-6-dimethylamino-3-chloro-pyridazine (XIII). 8.15 g (0.05 moles) of 4-methyl-3,6-dichloro-pyridazine was heated in an autoclave at 120° for 20 h with 100 ml of 30 % aqueous solution of dimethylamine. After cooling, colourless needles, m.p. 122°, could be filtered off. Recrystallisation from ethanol did not raise the m.p. Yield of (XIII) 7.1 g (83 %), m.p. 122°.

4- (or 5-) Methyl-6-dimethylamino-pyridazine (XIV). 5.7 g (1/20 mole) of 4- (or 5-) methyl-6-dimethylamino-3-chloro-pyridazine (XIII) was dehalogenated with hydrogen and Raney nickel as described above for 5-methyl-6-methoxy-3-chloro-pyridazine. The theoretical amount of hydrogen was absorbed during 1 h. The Raney nickel was filtered off and the solution evaporated to dryness. The residue was extracted with chloroform and inorganic material was removed. The chloroform was evaporated off and the residue distilled at 12 mm. The distillate solidified to slightly pink crystals, but the colour disappeared on melting the crystals and pouring the melt into petroleum ether. Yield of (XIV) 3.7 g (80 %), m.p. 90°.

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