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Dimethylamination of Chloropyridazines

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3,6-Dichloropyridazine, 4-methyl-3,6-dichloropyridazine, the two trichloropyridazines, and tetrachloropyridazine are treated with aqueous dimethylamine in ethanol at reflux temperature. In no case is more than one dimethylamino group introduced, the 4- (or 5-) position being substituted in the tri- and tetra-chlorinated pyridazines. The reaction products are reductively dehalogenated and subsequently identified by NMR analysis. The chlorine atoms *ortho* to the dimethylamino group are preferentially eliminated by hydrogenolysis.

Only a few dimethylaminopyridazines have hitherto been reported.[1–4] For further investigations a number of dimethylaminopyridazines were prepared by reaction of the corresponding chloropyridazines with dimethylamine in aqueous ethanol at reflux temperature. The dimethylaminopyridazines (Chart 1) were identified by reductive dehalogenation (H_2, 1 atm., Raney nickel, KOH) and subsequent NMR analysis, *cf.* Chart 1 and the Tables 1 and 2.

3-Chloro-6-dimethylaminopyridazine (IIa) is prepared by the above procedure in 90 % yield, considerably higher than the 60 % yield obtained by the method of Nyeberg and Cheng.[3] Hydrogenolysis of (IIa) afforded 3-dimethylaminopyridazine (IVa), the coupling constants of which (*ortho* and *meta* aromatic hydrogen, see Table 1) were utilized for the identification of the dimethylaminopyridazines (Vb), (XIII), and (XIV), (see below and Chart 1). Reaction of 3,6-dichloro-4-methylpyridazine (Ib) with dimethylamine gave, in quantitative yield, a mixture of the isomers (IIb) and (IIIb) (ratio *ca.* 3:1 by gas chromatography). This was in contrast to the results of Linholter *et al.*[1,5] who carried out the reaction at 120° and isolated solely (IIb), (*cf.* also Mori [6]). The reaction may also be carried out at 0° (3 months, 100 % conversion) without the ratio between the two isomers being altered. The previous identification of (IIb) [5] was confirmed by dehalogenation of the isomer (IIIb) to yield (Vb). NMR analysis of the latter showed that the coupling constant of the two aromatic protons was 4.8 cps (Table 1), *cf.* $J_{56} = 4$ to 5 cps as previously predicted.[5] The structure assigned to the isomers (IIb) and (IIIb) were also in accordance with their reactivity towards ethanolic-aqueous dimethylamine (at 120° for 24 h), the less hindered chlorine of (IIIb)

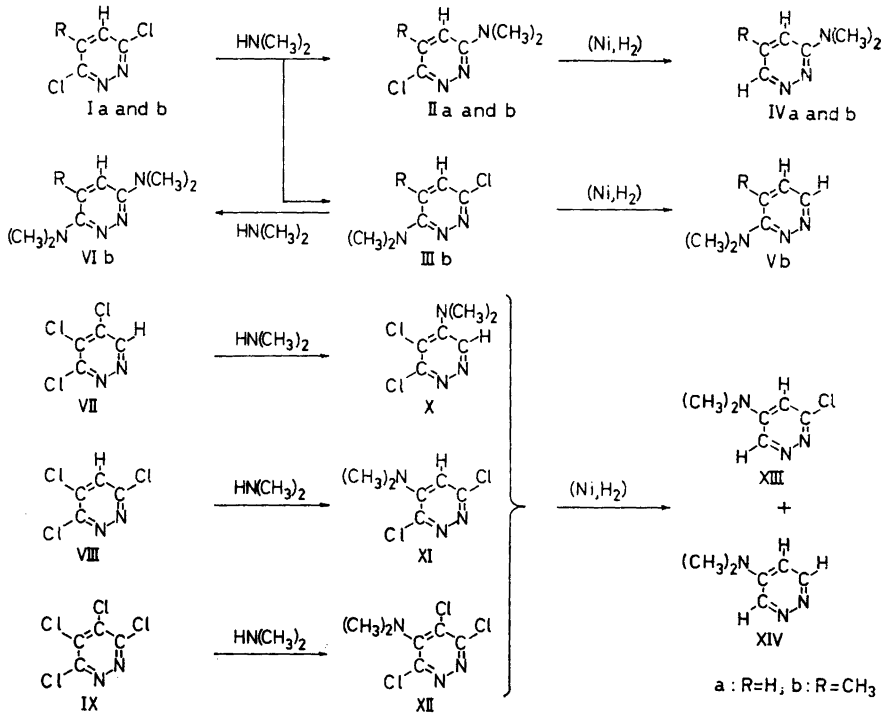

Chart 1

being more susceptible to displacement than that of (IIb). Under anhydrous conditions, 3,6-bis(dimethylamino)-4-methylpyridazine (VIb) may be obtained in 80 % yield from 3,6-dichloro-4-methylpyridazine (Ib) (see Experimental). The former gives a very intense, blue colour with bromine, of diagnostic value in the chromatographic separations.

Halogen positioned at 4- (or 5-) in the pyridazine nucleus is generally considered to be more reactive towards anionic (*e.g.* methoxide) and neutral (*e.g.* ammonia) nucleophiles than halogen in the 3- (or 6-) position.[7] This apparently applies also to the reaction with dimethylamine of the three chloropyridazines (VII), (VIII), and (IX), as illustrated in the Chart. The trichloropyridazine (VII) gave only (X), probably due to steric hindrance of the chlorine atom in 4-position. According to Kuraishi,[8] ammonia attacks both the 4- and the 5-position of (VII). Again, the dimethylaminopyridazines (X), (XI), and (XII) were identified by reductive dehalogenation (*cf.* above) and subsequent NMR analysis. In all three cases hydrogenolysis led to a mixture of 3-chloro-5-dimethylaminopyridazine (XIII) and 4-dimethylaminopyridazine (XIV). The NMR spectrum of the former (Table 1) disclosed the presence of one proton in 3- (or 6-) position and one proton in 4- (or 5-) position. The coupling constant (J = 2.8 cps) further indicated their *meta* position. The identity of (XIV) may be similarly ascertained from the data of Table 1.

Table 1. Proton magnetic resonance data of pyridazine derivatives.[a]

	Substituent	Chemical shift in ppm (δ)						Coupling constants (cps)		
		δ_3	δ_4	δ_5	δ_6	δ_{CH_3}	$\delta_{N(CH_3)_2}$	$J_{4\,5}$	$J_{4\,6}$	$J_{5\,6}$
(IIa)	3-$N(CH_3)_2$, 6-Cl	—	6.8	7.2	—	—	3.15	9.6	—	—
(IVa)	3-$N(CH_3)_2$	—	6.8	7.2	8.5	—	3.15	9.5	1.4	4.2
(IIb)	3-$N(CH_3)_2$, 5-CH_3, 6-Cl	—	6.7	—	—	2.3	3.15	1.0[b]	—	—
(IIIb)	3-$N(CH_3)_2$, 4-CH_3, 6-Cl	—	—	7.1	—	2.31	2.95	1.0[b]	—	—
(IVb)	3-$N(CH_3)_2$, 5-CH_3	—	6.59	—	8.35	2.24	3.15	1.0[b]	1.8	0[b]
(Vb)	3-$N(CH_3)_3$, 4-CH_2	—	—	7.1	8.62	2.34	3.0	1.0[b]	0[b]	4.8
(VIb)	3,6-$(N(CH_3)_2)_2$, 5-CH_3	—	6.68	—	—	2.28	3.1 2.84	1.0[b]	—	—
(X)	3,4-$(Cl)_2$, 5-$N(CH_3)_2$	—	—	—	8.62	—	3.2	—	—	—
(XI)	3,6-$(Cl)_2$, 5-$N(CH_3)_2$	—	6.65	—	—	—	3.1	—	—	—
(XII)	3,4,6-$(Cl)_3$, 5-$N(CH_3)_2$	—	—	—	—	—	3.15	—	—	—
(XIII)	3-Cl, 5-$N(CH_3)_2$	—	6.5	—	8.57	—	3.1	—	2.8	—
								$J_{3\,4}$	$J_{4\,6}$	$J_{3\,6}$
(XIV)	5-$N(CH_3)_2$	8.63	6.51	—	8.68	—	3.05	6.4	3.4	0.8

[a] NMR spectra were determined on a Varian A-60 spectrometer, with tetramethylsilane as an internal reference. [b] CH_3—H coupling

Table 2. Analyses.[a]

Compound	M.p.	Formula	C		H		N		Hal.	
			Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
(IIIb)	39—40°	$C_7H_{10}ClN_3$	48.89	49.01	5.98	5.87	24.30	25.41	20.66	20.67
(IVa)	b.p. 115—120°/7 mm	$C_6H_9N_3$	58.35	58.52	7.54	7.37	34.55	34.11		
(IVa), as methiodide	193—194°	$C_7H_{12}N_3I$	31.89	31.71	4.61	4.56	15.57	15.85	47.44	47.87
(IVa), as picrate	178—181°	$C_{12}H_{12}N_6O_7$	41.38	40.91	3.63	3.44	24.05	23.86		
(Vb), as picrate	136—137°	$C_{13}H_{14}N_6O_7$	42.61	42.62	3.90	3.86	22.80	22.94		
(VIb)	52—53°	$C_9H_{16}N_4$	59.15	59.95	8.93	8.95	31.09	31.10		
(X)	89—90°	$C_6H_7Cl_2N_3$	37.42	37.51	3.66	3.68	21.60	21.88	36.70	36.91
(XI)	70—71°	$C_6H_7Cl_2N_3$	37.29	37.51	3.50	3.68	21.88	21.88	37.05	36.91
(XII)	86—87°	$C_6H_6Cl_3N_3$	31.89	31.77	2.54	2.62	18.40	18.51	47.30	47.15
(XIII)	115—116°	$C_6H_8ClN_3$	45.74	45.80	5.36	5.08	26.67	26.64		
(XIV), as hydrate	47—48°	$C_6H_9N_3$, $3H_2O$	40.73	40.66	8.58	8.53				

[a] Performed by Mr. Preben Hansen, The Chemical Laboratory of the University of Copenhagen.

EXPERIMENTAL

All melting points are uncorrected.

3-Chloro-6-dimethylaminopyridazine (IIa).[3] 3,6-Dichloropyridazine (Ia)[9] (14.8 g), dissolved in ethanol (100 ml) and aqueous dimethylamine (40 %, 25 ml), was refluxed for 45 min. Excess ethanol and dimethylamine were removed *in vacuo* and the product extracted with chloroform. The organic phase was dried ($MgSO_4$), the solvents removed *in vacuo*, and the product was recrystallized from toluene-ligroin 110—140°. Yield 14.2 g (90 %), m.p. 101—102° (lit.[3] 100—101°).

3-Dimethylaminopyridazine (IVa). 3-Chloro-6-dimethylaminopyridazine (1.57 g), dissolved in a mixture of methanolic potassium hydroxide (10 mmoles in 10 ml methanol), 10 ml suspended Raney nickel,[10] and methanol (10 ml), was treated with hydrogen at 1 atm for 12 h. The flow rate was 1 bubble/sec. The Raney nickel was filtered off on sodium sulfate as a filter aid. The solvent was removed, the residue extracted with chloroform, and the suspended salts removed by filtration. The dried chloroform phase was evaporated *in vacuo* and the residue from two runs was distilled to give a colourless oil (IVa, 1.95 g, 80 %) (Table 2).

Methylation of IVa was carried out in ether with methyl iodide, and the yellow methiodide was crystallized from chloroform by adding ether; see Table 2. The picrate of IVa was recrystallized from ethanol; see Table 2.

3-Chloro-4-methyl-6-dimethylaminopyridazine (IIb)[1,4] and *3-dimethylamino-4-methyl-6-chloropyridazine (IIIb).* 3,6-Dichloro-4-methylpyridazine[11] (1.62 g) was dissolved in ethanol (20 ml) and treated with dimethylamine (15 ml, 40 %). The mixture was refluxed for 30 min and the ethanol and dimethylamine removed *in vacuo*. Water (10 ml) and chloroform (25 ml) were added and the mixture of the two products, (IIb) and (IIIb), was isolated from the chloroform phase in quantitative yield. They were separated by chromatography on silica gel (Merck 0.05—0.20 mm, eluent: benzene-ether 1:3). The ratio (IIb:IIIb) in the reaction mixture was approximately 3:1 as determined by gas chromatography (5 % "degs" on celite). (IIb), m.p. 121—122° (lit.[1,4] 122°); (IIIb), colourless crystals after sublimation; see Table 2.

3-Dimethylamino-4-methylpyridazine (Vb) was prepared from 3-dimethylamino-4-methyl-6-chloropyridazine (IIIb) as above; duration of hydrogenation: 3 h. Yield: 98 %. The oily (Vb) was virtually homogeneous (NMR, Table 1) and characterized as its picrate (from ethanol; Table 2).

3,6-bis(Dimethylamino)-4-methylpyridazine (VIb). 3-Dimethylamino-4-methyl-6-chloropyridazine (IIIb) (1.71 g) in ethanol was treated with an excess of aqueous dimethylamine for 24 h at 120° in an autoclave. Ethanol and dimethylamine were removed *in vacuo* and the 3,6-bis(dimethylamino)-4-methylpyridazine extracted with chloroform. The chloroform phase was dried and evaporated, and the product was purified by chromatography on silica gel (Merck 0.05—0.20 mm), eluent: acetone. Yield 1.6 g (90 %).

Alternatively the 3,6-bis(dimethylamino)-4-methylpyridazine was prepared from (Ib)[11] (40.5 g), which was dissolved in ethanol (200 ml) and treated with an excess of pure dimethylamine (106 ml) for 48 h at 120° in an autoclave. The product was isolated as described above, but purified by distillation. The fraction, b.p. 164—165/7 mm (36 g, 80 %) was collected as a yellow oil, which crystallized from toluene-ligroin, see Table 2.

3,4-Dichloro-5-dimethylaminopyridazine (X), 3,6-dichloro-4-dimethylaminopyridazine (XI) and 3,4,6-trichloro-5-dimethylaminopyridazine (XII). To 0.01 mole each of 3,4,5-trichloropyridazine (VII),[8] 3,4,6-trichloropyridazine (VIII),[11] and tetrachloropyridazine (IX),[12] dissolved in ethanol (10 ml), were added aqueous dimethylamine (5 ml, 40 %) and the solutions were heated to 50—70° for 5—10 min. The products crystallized on cooling the reaction mixture to 0°. Recrystallization from toluene-ligroin 110—140°. Yields: (X): 61 %, colourless crystals; (XI): 78 %, colourless crystals; (XII: 73 %, yellow crystals; see Table 2.

3-Chloro-5-dimethylaminopyridazine (XIII) and 4-dimethylaminopyridazine (XIV) were prepared from the dimethylaminopyridazines (X), (XI), and (XII) in the same way as described above. From each of the three hydrogenations, both (XIII) and (XIV) could be isolated (chromatography on silica gel; elution with acetone-methanol 4:1) when the hydrogenation was continued until no unreacted material was present as determinated by thin layer chromatography. Duration of hydrogenation and amount

of base employed per mole were as follows: (X): 15 min, 2.5 moles; (XI): 9 h, 2.5 moles; (XII): 5 h, 3.5 moles. The monochloro compound, (XIII), was recrystallized from ether to give colourless crystals, see Table 2. The halogenfree compound (XIV) was recrystallized from petroleum ether-toluene to give colourless, hygroscopic crystals, and was characterized as a trihydrate (see Table 2).

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