Methylation of Aminopyridazines

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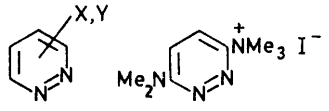
Quaternisations of mono- and di-aminopyridazines with methyl iodide in methanol have been examined and the products identified. 3- and 4-Aminopyridazine and 3,5-diaminopyridazine gave both 1- and 2-methyl derivatives. 3,4-, 3,6-, and 4,5-Diaminopyridazines each gave a single product, which in the first case was tentatively identified as 3,4-diamino-1-methylpyridazinium iodide. No ammonio-compounds were detected in these reactions. Ionization constants, u.v. and ^{1}H n.m.r. spectra are recorded and discussed.

QUATERNISATIONS of pyridazines (I) have been examined on a number of occasions.[1-6] With regard to aminopyr-



(I) (II)

idazines, Lund and Lunde [1] have studied by n.m.r. spectroscopy the mixtures obtained from the reactions of some 3-aminopyridazines with methyl iodide in acetonitrile, and observed signals due to 1- and 2-methyl derivatives; and 3,6-bis(dimethylamino)pyridazine alone underwent quaternisation in part at the exocyclic nitrogen atom, to give 6-dimethylaminopyridazin-3-yltrimethylammonium iodide (II), and in part at the ring nitrogen atom.

We describe here the reactions of the simple monoamino- and diamino-pyridazines with methyl iodide in methanol to give in most cases both 1- and 2-methylated products. The isomers formed have been separated by t.l.c. and identified by ^{1}H n.m.r. spectroscopy and/or hydrolysis to known compounds. There was no evidence of formation of ammonio-compounds in the methylations examined.

The aminopyridazines required were prepared by literature procedures except for 3,6-diaminopyridazine. This could not be prepared from 3-amino-6-chloropyridazine by treatment with ammonia,[7] nor from 3-amino-6-methylsulphonylpyridazine with ammonia or hydrazine; it was prepared by reduction of 3,6-dihydrazinopyridazine.

Methylation of 3-aminopyridazine with methyl iodide in methanol at 20 °C gave both 1- and 2-methyl derivatives (as distinct from the trimethylammonio-compound) as shown by the ^{1}H n.m.r. spectra of the individual products and by hydrolysis of 3-amino-2-methylpyridazinium iodide to the known 2-methylpyridazin-3-one.[3] 4-Aminopyridazine likewise gave the two nuclear *N*-methyl isomers, and 4-amino-1-methylpyridazinium iodide was hydrolysed to the known 1-methylpyridazin-

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[3] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 1959, 3789.
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[5] M. S. Bale, A. B. Simmonds, and W. F. Trager, *J. Chem. Soc.* (*B*), 1966, 867.
[6] G. F. Duffin, *Adv. Heterocyclic Chem.*, 1964, **3**, 1.
[7] T. V. Gortinskaya and M. N. Shchukina, *J. Gen. Chem.* (*U.S.S.R.*), 1960, **30**, 1531.

TABLE 1

pK_a Values and u.v. spectra

Pyridazine	Ionization (in water at 20 °C) Species [a]	pK_a	Spread (±)	Concn. (M)	Analyt. λ/nm [b]	Spectroscopy (in water) [c] $\lambda_{max.}$/nm	log ε	pH [d]
Unsubstituted		2.33 [e]						
3-NH_2	0					231, 294	3.86, 3.31	8.0
	+	5.19 [e]				227, 289	3.76, 3.42	2.0
4-NH_2	0					249, *280* [g]	4.07, *3.57*	
	+	6.69 [f]				272 [g]	4.12	
3,4-$(NH_2)_2$ [h]	0					214, 254, 291	4.13, 3.72, 3.77	10.0
	+	7.64	0.03	0.000 1	300	226, 299	4.06, 3.98	5.0
	2+	0.02	0.05	0.000 15	350	226, 299	3.97, 3.93	−2.10
3,5-$(NH_2)_2$ [h]	0					218, 257, 278	4.49, 3.54, 3.54	10.0
	+	7.84	0.04	0.000 1	280	225, 277	4.46, 3.74	5.5
	2+							
3,6-$(NH_2)_2$	0					235, 326	4.06, 3.29	9.0
	+	6.72	0.02	0.000 1	280	233, 332	4.26, 3.27	2.0
	2+	−1.82	0.04	0.000 02	273	229, 296	4.10, 3.34	−3.9
4,5-$(NH_2)_2$ [h]	0					214, 281	4.38, 3.94	9.0
	+	6.74	0.02	0.000 06	315	219, *286*, 314	4.24, *3.79*, 3.97	4.0
3-NH_2-6-Cl	0					(213,) 239, 312	(3.67), 3.76, 2.95	6.0
	+	3.53	0.05	0.000 2	250	213, 232, 301	4.07, 3.68, 2.99	1.0
6-CO_2H-3-OH	0					247, 281	3.87, 3.38	0.5
	−	2.75	0.05	0.000 2	255	237, 285	3.84, 3.27	6.0
	2−	10.55	0.03	0.000 2	260	253, 295	4.06, 3.55	12.5
3-OH-4,5-H_2-6-Me	0					241	3.80	5.0
4-NH_2-2-Me-3=O	0					*287*, 292, *309*	*4.035*, 4.045, *3.71*	4.0
	+	−0.28	0.04	0.000 01	283	*222*, 226, *235*, 311	*3.88*, 3.93, *3.74*, 4.24	−2.35
5-NH_2-2-Me-3=O	0					276	3.78	4.0
	+	0.40	0.07	0.000 02	260	220, 259, 263, 281	4.14, 3.82, 3.84, 3.87	−2.35
5-NH_2-4-Cl-3-NH·NH_2	0					259, *295*	3.91, *3.56*	11.0
	+	8.96	0.06	0.000 5	265	227	4.36	7.9
	2+	6.82	0.03	0.000 5	305	232, 285	4.36, 3.75	4.0
4,5-Cl_2-3-OH	0					*210*, 214, *238*, 289	*4.20*, 4.22, *3.15*, 3.47	6.0
	−	8.49	0.04	0.000 3	315	218, *236*, 305	4.26, *3.48*, 3.51	11.0
4-NH_2-3,6-Cl_2	0					217, 256, 292	4.12, 3.96, 3.66	5.0
	+	1.32	0.03	0.000 025	257	*222*, 281	*3.96*, 4.10	−1.0
3,4-$(NH_2)_2$-6-Cl	0					208, 221, 259, 297	4.27, 4.15, 3.75, 3.76	7.0
	+	4.49	0.03	0.000 07	305	204, 232, *275*, 302	4.29, 4.00, *3.77*, 3.98	2.0
5-NH_2-6-Cl-2-Me-3=O	0					282	3.73	4.0
	+	−0.30	0.05	0.000 04	295	223, 287	4.18, 3.85	−2.35
4-Cl-3,6-$(OH)_2$	0					211, *232*, 308	4.31, *3.62*, 3.47	2.0
	−	4.70	0.02	0.000 3	345	223, *241*, 337	4.30, *3.87*, 3.39	8.0
	2−	12.59	0.05	0.000 07	345	*241*, 341	*3.87*, 3.50	14.7
4-Cl-6-OH-2-Me-3=O	0					211, *230*, 314	4.29, *3.66*, 3.56	3.0
	−	5.14	0.05	0.000 3	350	222, 340	4.28, 3.48	8.0
5-Cl-6-OH-2-Me-3=O	0					214, 312	4.22, 3.36	2.0
	−	4.19 [f]	0.02	0.001		221, *240*, 339	3.69, *3.21*, 2.89	7.0
5,6-Cl_2-2-Me-3=O	0					217, *235*, 303	4.45, *3.67*, 3.41	5.0
Pyridazinium iodide								
3-NH_2-1-Me [j]	+	>14 [k]				(213), 243, 320	(4.26), 3.82, 3.31	10.0
3-NH_2-2-Me [j]	+	>10 [k]				228, 289	3.63, 3.45	8.0
4-NH_2-1-Me [j]	0	13.59	0.05	0.000 03	320	287	4.21	14.7
	+					277	4.18	11.0
4-NH_2-2-Me [j]	+	>14 [k]				(212), 260, 312	(4.22), 3.98, 3.56	10.0
3,4-$(NH_2)_2$-1-Me [j]	0	13.68	0.04	0.000 03	310	317	4.13	15.0
	+					(204), 229, 305	(4.15), 3.91, 4.05	7.0
3,5-$(NH_2)_2$-1-Me [j]	+	>13 [k]				229, 300	4.57, 3.57	9.0
3,5-$(NH_2)_2$-2-Me [j]	+					226, 278	4.45, 3.78	7.0
3,6-$(NH_2)_2$-1-Me [j]	+	>11 [k]				231, 331	4.23, 3.32	7.0
4,5-$(NH_2)_2$-1-Me [j]	+	>13 [k]				224, *290*, 319	4.39, *3.79*, 4.02	7.0

[a] 0, neutral species; +, cation; 2+, dication; −, anion; 2−, dianion. [b] Analytical wavelength for spectroscopic determination of pK_a. [c] Shoulders and inflections in italics. [d] pH Values below 0 obtained in solutions of hydrochloric or sulphuric acid to which Hammett acidity functions (*cf.* M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1) were assigned. [e] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240. [f] A. Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 124. [g] S. F. Mason, *J. Chem. Soc.*, 1960, 219. [h] As the picrate; reference cell compensated with picric acid for the determination of spectra. [i] Determined by potentiometric titration. [j] For the determination of the spectra the reference cell was compensated with potassium iodide. [k] Relative instability in solutions of high pH precluded determination of the pK_a value.

4-one.[2] 3,4-Diaminopyridazine with methyl iodide in methanol gave one product only, which with N-sodium hydroxide gave no 4-amino-2-methylpyridazin-3-one.[8]

3,5-Diaminopyridazine gave two nuclear *N*-methyl derivatives whose orientation was established by hydrolysis of the 3,5-diamino-2-methylpyridazinium iodide to 5-amino-2-methylpyridazin-3-one.[8] Methylation of 3,6-diaminopyridazine with methyl iodide in methanol gave 3,6-diamino-1-methylpyridazinium iodide only, which was hydrolysed in N-sodium hydroxide at 100 °C to 6-amino-2-methylpyridazin-3-one; [8] and 4,5-diaminopyridazine with methyl iodide in methanol at 20 °C gave the only possible nuclear methiodide.

TABLE 2

^{1}H N.m.r. spectra (δ values) [a]

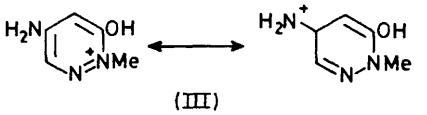
Compound									
Pyridine methiodide	Solvent	1-Me	2-Me	NH_2	2-H	3-H	4-H	5-H	6-H
2-NH_2 [b]	D_2O [c]	3.81				7.01	7.76	6.78	7.76
	$(CD_3)_2SO$	3.80		8.18		7.01	7.93	6.72	7.93
3-NH_2 [d]	D_2O	4.17			7.91		7.55	7.55	7.91
	$(CD_3)_2SO$	4.16		6.50	7.98		7.55	7.55	7.98
4-NH_2 [e]	D_2O	3.93			7.85	6.77		6.77	7.85
	$(CD_3)_2SO$	3.86		7.88	8.06	6.73		6.73	8.06
Pyridazine									
3-NH_2-1-MeI	D_2O	4.24					7.44	7.83	8.60
	$(CD_3)_2SO$	4.19		7.68			7.51	7.86	9.00
3-NH_2-2-MeI	D_2O		3.92				7.58	7.52	8.25
	$(CD_3)_2SO$		3.81	5.22			7.52	7.44	8.21
4-NH_2-1-MeI	D_2O	4.07				8.42		6.96	8.42
	$(CD_3)_2SO$	4.04		8.47		8.40		7.02	8.65
4-NH_2-2-MeI	D_2O		4.33			8.77		8.55	7.14
3,4-$(NH_2)_2$-1-MeI	$(CD_3)_2SO$	3.91		6.99, 7.78				6.70	8.32
3,5-$(NH_2)_2$-1-MeI	D_2O	4.09					6.28		8.20
	$(CD_3)_2SO$	4.04		6.90(3), 7.19(5)			6.14		8.21
3,5-$(NH_2)_2$-2-MeI	D_2O		3.76				6.16		7.76
	$(CD_3)_2SO$		3.74	7.54(5), 7.78(3)			6.11		7.80
3,6-$(NH_2)_2$-1-MeI	$(CD_3)_2SO$	3.61		6.60(6), 7.98(3)			7.14	7.14	
4,5-$(NH_2)_2$-1-MeI	$(CD_3)_2SO$	4.13		6.50(4), 7.39(5)		8.05			8.16

[a] Sodium 3-trimethylsilylpropane-1-sulphonate and tetramethylsilane were used as internal standards. [b] P. Karrer, T. Ishii, F. W. Kahnt, and J. van Bergen, *Helv. Chim. Acta*, 1938, **21**, 1174. [c] T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171, also record this spectrum. [d] B. M. Anderson, C. J. Ciotti, and N. O. Kaplan, *J. Biol. Chem.*, 1959, **234**, 1219. [e] E. J. Poziomek, *J. Org. Chem.*, 1963, **28**, 590.

Ionization Constants and Ultraviolet Spectra (*Table* 1).—The diaminopyridazines have their first basic pK_a values in the range 6.72—7.84 and are 0.09—1.53 units stronger bases than the most basic relevant monoaminopyridazines. The difference between the first and second basic pK_a values is 7.62 and 8.54 units for 3,4- and 3,6-diaminopyridazines, respectively; *cf.* 7.01 and 8.65 in the diaminopyridines.[9]

Base weakening by chloro-substituents at the 3- and 6-positions varied from 1.66 in 3-amino-6-chloropyridazine to 5.33 units in 4-amino-3,6-dichloropyridazine.

5-Amino-2-methylpyridazin-3-one is a stronger base than 4-amino-2-methylpyridazin-3-one by 0.68 units; this may be due to *O*-protonation to give a cation of type (III) which is stabilised by resonance, a situation not shared by the 4-amino-compound.



(III)

Because of the nearness of the electron-withdrawing substituent, 5-chloro-6-hydroxy-2-methylpyridazin-3-one is a stronger acid by 0.95 pH units than its 4-chloro-isomer.

All the iminopyridazines are strong bases.

Comparison of the u.v. spectra of the aminopyridazine cations with their *N*-methyl derivatives revealed that 3-aminopyridazine cation resembled its 2-methyl derivative and 4-aminopyridazine cation its 1-methyl derivative; hence protonation involves N-2 and N-1, respectively.

Inspection of the spectra of the cations from the symmetrical 3,6- and 4,5-diaminopyridazines and of 3,5-diaminopyridazine revealed a close similarity with their methiodides but there was some divergence between the cation of 3,4-diaminopyridazine and its methiodide.

As expected, 3-amino-6-chloropyridazine on protonation showed spectral changes similar to 3-aminopyridazine, also indicating protonation at N-2; 3,4-diamino-6-chloropyridazine behaved like 3,4-diaminopyridazine; and 4-amino-3,6-dichloropyridazine like 4-aminopyridazine. A close similarity existed between the neutral species (and monoanions) from 4-chloro-3,6-dihydroxypyridazine and its 2-methyl derivative; but there was a significant divergence in intensity in the spectra of their anions from that of the anion of 5-chloro-6-hydroxy-2-methylpyridazin-3-one.

^{1}H *N.m.r. Spectra* (*Table* 2).—These were determined where possible in D_2O and $(CD_3)_2SO$ for the aminopyridazine methiodides and aminopyridine methiodides (for comparison).

The data are consistent with the structures established by conversions into known compounds. On the evidence

[8] T. Nakagone, A. Misaki, and T. Komatsu, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1082.
[9] G. B. Barlin, *J. Chem. Soc.*, 1964, 2150.

of the signals due to the methyl group and H-6 from 3,5- and 4,5-diaminopyridazine methiodides, 3,4-diaminopyridazine methiodide appears to be the 1-methyl compound.

EXPERIMENTAL

All compounds were examined for the presence of isomers and impurities by paper chromatography on Whatman no. 1 paper [with (*a*) aqueous 3% ammonium chloride, and (*b*) butan-1-ol–5M-acetic acid (7 : 3) as solvents], t.l.c., and ^{1}H n.m.r. spectroscopy, and were recrystallised to constant m.p. Analyses were performed by the Australian National University Analytical Services Unit. Solids for analysis were dried at 100 °C unless otherwise stated and each m.p. was taken in a Pyrex capillary. ^{1}H N.m.r. spectra were recorded at 60 MHz and 35 °C with a Varian T-60A spectrometer. Where required, portions of the spectra were expanded, and all signals were integrated. Ionization constants were generally determined spectroscopically [10] but in one case by potentiometric titration by I. Hawkins. U.v. spectra were measured with a Perkin-Elmer 450 recording spectrophotometer and $\lambda_{max.}$ and ε values were checked with an Optica CF4 manual instrument (by D. T. Light).

3-Aminopyridazine Methiodides.—A mixture of 3-aminopyridazine [11] (0.5 g), methyl iodide (1.0 ml), and methanol (5.0 ml) was kept at 20 °C overnight. The precipitate (0.55 g) was filtered off and the filtrate evaporated to give a yellow solid (0.7 g). [N.m.r. spectroscopy (solvent D_2O) of the yellow solid showed methyl signals at δ 4.24 and 3.92 of approximately equal intensity, but the precipitate showed one only, at δ 4.24.] The precipitate was recrystallised from ethanol to give *3-amino-1-methylpyridazinium iodide*, m.p. 182—183° (Found: C, 25.8; H, 3.9; N, 17.7. $C_5H_8IN_3$ requires C, 25.3; H, 3.4; N, 17.7%). The *picrate*, prepared in and recrystallised from isopropyl alcohol, had m.p. 162—163° (Found: C, 39.15; H, 3.05; N, 25.1. $C_{11}H_{10}N_6O_7$ requires C, 39.1; H, 3.1; N, 24.85%). The yellow solid (0.7 g) was subjected to t.l.c. (silica; acetone) and gave, after recrystallisation from isopropyl alcohol, *3-amino-2-methylpyridazinium iodide* (0.15 g), m.p. 223—224° (Found: C, 25.65; H, 3.65; N, 18.1%). The *picrate*, prepared in and recrystallised from water, had m.p. 231—232° (Found: C, 38.8; H, 3.5; N, 24.5. $C_{11}H_{10}N_6O_7$ requires C, 39.1; H, 3.0; N, 24.85%).

Hydrolysis of 3-Amino-2-methylpyridazinium Iodide.—A mixture of 3-amino-2-methylpyridazinium iodide (0.010 g) and 0.1N-sodium hydroxide (5 ml) was kept at 20 °C for 14 days. The product, extracted with chloroform, was identical (paper chromatography, t.l.c., and u.v. spectrum) with authentic 2-methylpyridazin-3-one.[3]

4-Aminopyridazine Methiodides.—A mixture of 4-aminopyridazine [12,13] (0.5 g) and methyl iodide (1.0 ml) in methanol (2 ml) was kept at 20 °C for 12 h. The mixture was then evaporated to dryness and the residue recrystallised from isopropyl alcohol to give a crystalline solid (1.04 g). [The ^{1}H n.m.r. spectrum of this product in D_2O showed methyl signals at δ 4.33 and 4.07 (*ca.* 1 : 2).] A portion (0.94 g) was subjected to t.l.c. (alumina; ethanol) and gave in the upper band *4-amino-1-methylpyridazinium iodide* (0.358 g), m.p. 123—124° (from isopropyl alcohol–benzene) (Found: C, 25.65; H, 3.6; N, 17.4. $C_5H_8IN_3$ requires C, 25.3; H, 3.4; N, 17.7%), and in the lower band *4-amino-2-methylpyridazinium iodide* (0.060 g), m.p. 186—187° (from isopropyl alcohol) (Found: C, 25.5; H, 3.5; N, 18.0%).

Hydrolysis of 4-Amino-1-methylpyridazinium Iodide.—4-Amino-1-methylpyridazinium iodide (0.050 g) in N-sodium hydroxide (5 ml) was kept at 20 °C for 22 h. The mixture was then extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated to leave an oil which solidified. This product was identical (paper chromatography, t.l.c., and u.v. spectrum) with authentic 1-methylpyridazin-4-one.[2]

3,4-Diaminopyridazine monohydrochloride was prepared from 6-chloro-3,4-diaminopyridazine [14] as described by Guither *et al.*[15] The *picrate*, prepared in and recrystallised from water, had m.p. 253—254° (Found: C, 35.7; H, 2.6; N, 29.4. $C_4H_6N_4,C_6H_3N_3O_7$ requires C, 35.4; H, 2.7; N 28.9%).

3,4-Diaminopyridazine Methiodide.—A mixture of 3,4-diaminopyridazine (liberated from 0.50 g of its bishydrochloride [15] with alkali in methanol), methyl iodide (3.0 ml), and methanol (10 ml) was kept at 20 °C for 3 days. (Paper chromatography indicated that the reaction was complete in 2.5 h.) The mixture was evaporated to dryness and the product recrystallised from isopropyl alcohol with concentration to give *3,4-diamino-1-methylpyridazinium iodide* (0.627 g), m.p. 213—214° (Found: C, 24.0; H, 3.8; N, 21.8. $C_5H_9IN_4$ requires C, 23.9; H, 3.6; N, 22.2%).

3,5-Diaminopyridazine Hydrochloride.—5-Amino-4-chloro-3-hydrazinopyridazine [16] was reduced to 4-chloro-3,5-diaminopyridazine [15] and 3,5-diaminopyridazine hydrochloride.[15] The *picrate* (of the latter), prepared in and recrystallised from water, had m.p. 303—305° (Found: C, 35.3; H, 2.7; N, 28.7. $C_4H_6N_4,C_6H_3N_3O_7$ requires C, 35.4; H, 2.7; N, 28.9%).

3,5-Diaminopyridazine Methiodides.—A mixture of 3,5-diaminopyridazine (liberated from 0.5 g of its monohydrochloride [15] with alkali), methyl iodide (5.0 ml), and methanol (10 ml) was kept at 20 °C for 4 days. The mixture was then evaporated to dryness and the product recrystallised from t-butyl alcohol–methanol to give a crystalline solid (0.645 g), which after further crystallisations from t-butyl alcohol–methanol gave *3,5-diamino-1-methylpyridazinium iodide* (0.254 g), m.p. 208—210° (Found: C, 24.0; H, 3.8; N, 21.8. $C_5H_9IN_4$ requires C, 23.9; H, 3.6; N, 22.2%). The *picrate*, prepared in and recrystallised from water, had m.p. 205°, depressed on admixture with the picrate of m.p. 228° (Found: C, 37.5; H, 3.4; N, 27.7. $C_{11}H_{11}N_7O_7$ requires C, 37.4; H, 3.1; N, 27.8%).

The filtrates from recrystallisation of the isomer described above were evaporated and the product was dissolved in methanol and applied to three alumina plates (20 × 40 cm). These were developed with ethanol and the upper portion of the dark band was removed and extracted with boiling ethanol. The product was recrystallised from t-butyl alcohol–methanol to give 3,5-diamino-2-methylpyridazinium iodide (0.014 g), m.p. 254—256°, characterised as its *picrate* (prepared in and recrystallised from water), m.p. 228°,

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[15] W. D. Guither, D. G. Clark, and R. N. Castle, *J. Heterocyclic Chem.*, 1965, **2**, 67.

[16] T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, 1964, **1**, 42.

depressed on admixture with the picrate of m.p. 205° (Found: C, 37.9; H, 3.4; N, 27.6. $C_{11}H_{11}N_7O_7$ requires C, 37.4; H, 3.1; N, 27.8%).

Attempted Hydrolysis of 3,5-*Diamino*-1-*methylpyridazinium Iodide with* N-*Sodium Hydroxide*.—3,5-Diamino-1-methylpyridazinium iodide (0.006 g) and N-sodium hydroxide (1.0 ml) were kept at room temperature for 4 days. Paper chromatography showed that some reaction had taken place after 3 days but the product was not 5-amino-2-methylpyridazin-3-one.[8] The mixture was adjusted to pH 8 and extracted with chloroform, and the aqueous solution was evaporated to dryness and the residue extracted with boiling ethyl acetate, but neither extract gave a significant product.

Hydrolysis of a Mixture of 3,5-*Diamino*-1- *and* -2-*methylpyridazinium Iodides with* N-*Sodium Hydroxide*.—A mixture of 3,5-diamino-1-(and 2-)methylpyridazinium iodide (0.050 g; ^{1}H n.m.r. evidence) and N-sodium hydroxide (3.0 ml) were heated on a steam bath for 1 h. The mixture was adjusted to pH 9.0 and evaporated to dryness, and the residue was extracted with boiling ethyl acetate. This extract was subjected to t.l.c. (alumina; isopropyl alcohol) and gave a small quantity of 5-amino-2-methylpyridazin-3-one, identical (paper chromatography and t.l.c.) with an authentic specimen.[8]

3,6-*Diaminopyridazine*.— 3,6-Dihydrazinopyridazine [17,18] (4.0 g) in water (150 ml) was shaken with hydrogen and Raney nickel at atmospheric pressure for 5 h. The catalyst was filtered off and washed with water, and the combined filtrates were evaporated to dryness. The residue crystallised from ethanol to give 3,6-diaminopyridazine (2.1 g), m.p. 235—237° (lit.,[7] 235°) (Found: C, 43.9; H, 5.8; N, 51.1. Calc. for $C_4H_6N_4$: C, 43.6; H, 5.5; N, 50.9%); *picrate* (from ethanol), m.p. 277—279° (Found: C, 35.5; H. 3.1; N, 28.7. $C_{10}H_9N_7O_7$ requires C, 35.4; H, 2.7; N, 28.9%).

3,6-*Diamino*-1-*methylpyridazinium Iodide*.—3,6-Diaminopyridazine (0.2 g), methyl iodide (0.5 ml), and methanol (8 ml) were kept standing at room temperature for 2 days. The solvent was then removed and the residue recrystallised from isopropyl alcohol–methanol to give 3,6-*diamino*-1-*methylpyridazinium iodide* (0.28 g), m.p. 271—272° (Found: C, 24.1; H, 3.9; N, 21.8. $C_5H_9IN_4$ requires C, 23.9; H, 3.6; N, 22.2%). The *picrate*, prepared in and recrystallised from water, had m.p. 215—216° (Found: C, 37.75; H, 3.4; N, 27.95. $C_{11}H_{11}N_7O_7$ requires C, 37.4; H, 3.1; N, 27.8%).

Hydrolysis of 3,6-*Diaminopyridazine Methiodide*. 3,6-Diaminopyridazine methiodide (0.025 g) and N-sodium hydroxide (2.0 ml) were heated on a steam-bath for 1 h. The mixture was adjusted to pH 9—10 and extracted with chloroform, and the product was recrystallised from ethyl acetate to give 6-amino-2-methylpyridazin-3-one, m.p. 222—224°, not depressed on admixture with an authentic specimen.[8]

4-*Amino*-5-*chloropyridazine*.—A mixture of 4-amino-5-chloro-3-hydrazino- and 5-amino-4-chloro-3-hydrazino-pyridazines (2.87 g), copper(II) sulphate (10 g), and water (170 ml) was refluxed for 1.5 h as described by Kuraishi and Castle [16] for the reaction of 5-amino-4-chloro-3-hydrazinopyridazine. The product was isolated by recrystallisation from benzene to give crystals (0.9 g), m.p. 120—122° (lit.,[16] 70—73°) (Found, for material dried at 20° and 20 mmHg for 2 h: C, 37.6; H, 3.3; N, 32.2. $C_4H_4ClN_3$ requires C, 37.1; H, 3.1; N, 32.4%), M^+ 129 and 131.

4,5-*Diamino*-1-*methylpyridazinium Iodide*.—4,5-Diaminopyridazine hydrochloride [15] [0.2 g; *picrate* (from water), m.p. 240—241° (Found: C, 35.5; H, 2.9; N, 29.0. $C_{10}H_9N_7O_7$ requires C, 35.4; H, 2.7; N, 28.9%)] was added to sodium methoxide (from 0.04 g of sodium) in methanol (5 ml) and the mixture was evaporated to dryness. To the residue were added methanol (4 ml) and methyl iodide (2 ml), and the mixture was kept at room temperature for 5 days to give a crystalline solid. The mixture was evaporated to dryness and the product recrystallised from isopropyl alcohol–methanol to yield 4,5-*diamino*-1-*methylpyridazinium iodide*, m.p. 229—231° (Found: C, 24.1; H, 3.75; N, 21.8. $C_5H_9IN_4$ requires C, 23.9; H, 3.6; N, 22.2%). The *picrate*, prepared in and recrystallised from water, had m.p. 225—226° (Found: C, 37.3; H, 3.2; N, 27.5. $C_{11}H_{11}N_7O_7$ requires C, 37.4; H, 3.1; N, 27.8%).

5-*Chloro*-6-*hydroxy*-2-*methylpyridazin*-3-*one and* 4-*Chloro*-6-*hydroxy*-2-*methylpyridazin*-3-*one*.—These compounds were prepared from chloromaleic anhydride and methylhydrazine sulphate,[8] but the more soluble and lower melting 4-chloro-6-hydroxy-2-methylpyridazin-3-one was purified by column chromatography in acetone over silica (14 in) and recrystallised from a small volume of water, acetone, or butyl acetate. It had m.p. 193—196° (lit.,[8] 185—186°) (Found: C, 37.8; H, 3.1; N, 17.4. Calc. for $C_5H_5ClN_2O_2$: C, 37.4; H, 3.1; N, 17.45%).

5-*Amino*-2-*methylpyridazin*-3-*one*.—This compound [8] was recrystallised from ethyl acetate and had m.p. 194—196° (lit.,[8] 193.5—194.5°).

4-*Amino*-2-*methylpyridazin*-3-*one*.—This compound [8] was recrystallised from ethyl acetate and had m.p. 173—175° (lit.,[8] 175—176°).

3-*Amino*-6-*methylthiopyridazine*.—A mixture of 3-amino-6-chloropyridazine [11] (2.0 g) and aqueous sodium methanethiolate (prepared from 2 g of sodium hydroxide in 20 ml of water) was heated in a sealed tube at 120 °C for 12 h. The product, extracted into chloroform and recrystallised from benzene, gave 3-*amino*-6-*methylthiopyridazine* (1.712 g), m.p. 117—118° (Found: C, 42.7; H, 5.0; N, 30.1; S, 22.8. $C_5H_7N_3S$ requires C, 42.5; H, 5.0; N, 29.8; S, 22.7%).

3-*Amino*-6-*methylsulphonylpyridazine*.—A solution of potassium permanganate (1.0 g) in water (15 ml) was added to a stirred solution of 3-amino-6-methylthiopyridazine (0.5 g) in 8N-acetic acid (15 ml) at room temperature over 30 min, and stirring was continued for 10 min. The mixture was then decolourised by passing sulphur dioxide, and adjusted to pH 8 by addition of aqueous ammonia. The product was then extracted repeatedly into chloroform, and recrystallised from ethanol to give 3-*amino*-6-*methylsulphonylpyridazine* (0.224 g), m.p. 183—185° (Found: C, 35.1; H, 4.5; N, 23.8. $C_5H_7N_3O_2S$ requires C, 34.7; H, 4.1; N, 24.3%). The *picrate*, prepared in ethanol, had m.p. 204—206° (Found: C, 33.1; H, 2.6; N, 20.8; S, 8.1. $C_{10}H_{10}N_8O_7$ requires C, 32.8; H, 2.5; N, 20.9; S, 8.0%).

Reaction of 3-*Amino*-6-*chloropyridazine with Benzylamine*.—3-Amino-6-chloropyridazine [11] (1.0 g) and benzylamine (20 ml) were refluxed for 3 h and the excess of benzylamine was removed under reduced pressure. The residue was extracted with hot ethyl acetate and the extract was filtered and chromatographed over alumina (6 in) in ethyl acetate to give 3-*benzylamino*-6-*chloropyridazine* (0.196 g), m.p. 163—164° (from benzene) (Found: C, 60.4; H, 4.5; N, 19.1. $C_{11}H_{10}ClN_3$ requires C, 60.1; H, 4.6; N, 19.1%). Elution

[17] J. A. Elvidge and J. A. Pickett, *J.C.S. Perkin I*, 1972, 1483.
[18] J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121.

of the column with ethanol gave unchanged 3-amino-6-chloropyridazine (0.458 g).

When the reaction mixture was refluxed for 63 h, there was obtained 3,6-*bisbenzylaminopyridazine picrate* (0.3 g), m.p. 218—220° (Found: N, 18.9. $C_{24}H_{21}N_7O_7$ requires N, 18.9%).

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