Tautomerism in *N*-Heterocycles. Part 3.[1] 3,4,5-Trimercaptopyridazine

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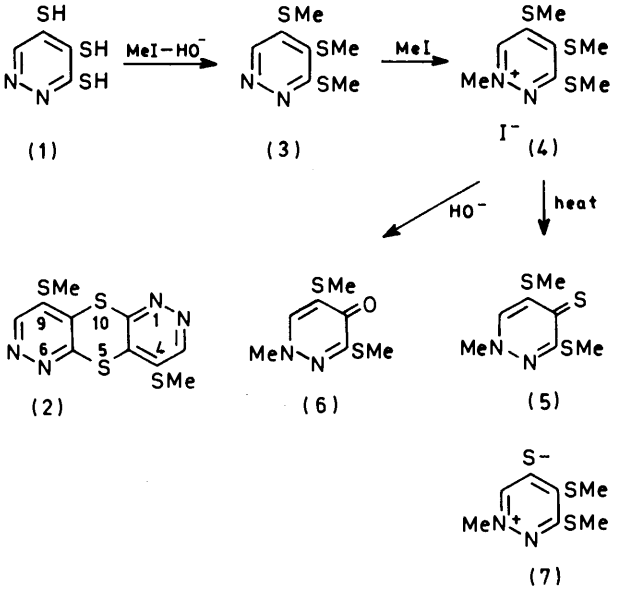
A number of *N*- and *S*-methyl derivatives of 3,4,5-trimercaptopyridazine have been prepared, and ionization constants and u.v. spectra determined. These studies reveal that 3,4,5-trimercaptopyridazine exists in an N(2)H tautomeric form. Some oxygen analogues have also been synthesised.

TAUTOMERISM in pyridazines with three potentially tautomeric groups has not been examined previously. We now report studies of 3,4,5-trimercaptopyridazine (1) and some of its *N*- and *S*-methyl derivatives and of some oxygen analogues.

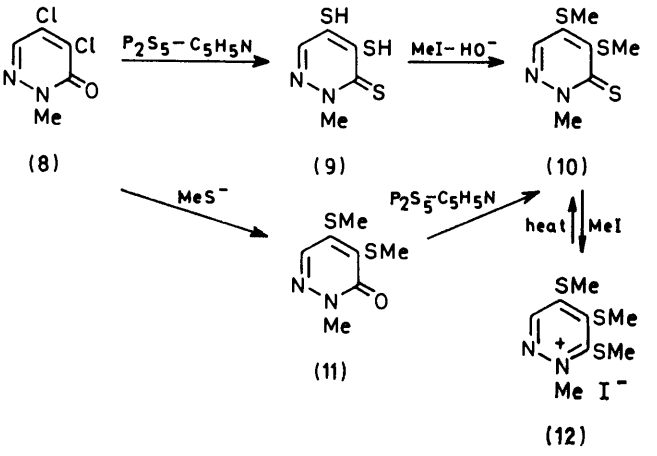
The preparation of the parent 3,4,5-trimercaptopyridazine from 4,5-dibromo- and 4,5-dichloropyridazin-3-one [2,3] {and [1,4]dithiino[2,3-*d*:5,6-*d'*]dipyridazin-1,6-(2*H*,7*H*)dione [4]} by reaction with phosphorus pentasulphide in pyridine has been claimed. The product was reported [3] to be 'insoluble in every solvent tried,' and was purified by reprecipitation from aqueous sodium hydroxide with dilute hydrochloric acid to pH 1.



SCHEME 1

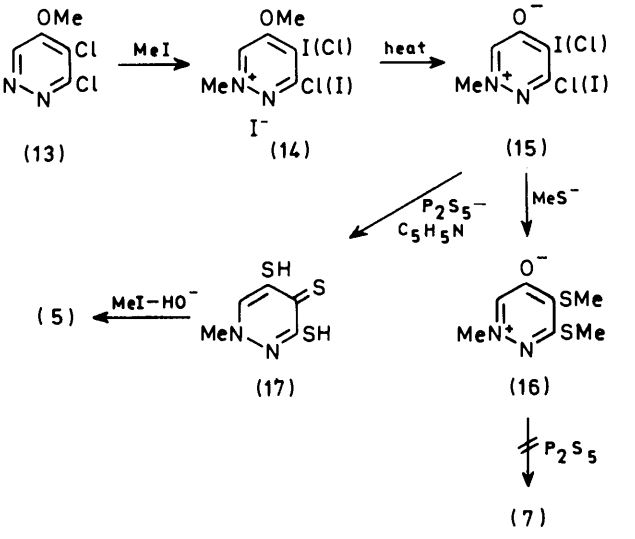
We prepared 3,4,5-trimercaptopyridazine from 3,4,5-trichloropyridazine [5] and phosphorus pentasulphide in pyridine; it was separated from an insoluble product formed simultaneously and then purified by recrystallisation from ethanol. The pure 3,4,5-trimercaptopyridazine was methylated with methyl iodide in alkali to give a high yield of 3,4,5-trismethylthiopyridazine. The insoluble product under similar conditions gave a bismethylthio-compound which has been tentatively assigned the dithiinodipyridazine structure (2), since its m.p. differed from that of another possible product, [1,4]dithiino[2,3-*d*:5,6-*d'*]dipyridazin-1,6(2*H*,7*H*)dione, reported by Castle *et al.*[4]

Schemes 1—4 illustrate the synthesis of some fixed tautomers of 3,4,5-trimercapto- and -trihydroxy-pyridazine, showing relevant intermediates and by-products.



SCHEME 2

Methylation of compound (10) occurred at sulphur as shown by the ^{1}H n.m.r. spectrum; and the methylation of 3,4,5-trismethylthiopyridazine took place at N-1



SCHEME 3

probably because the reactivity of N-2 is lowered by the $-I$ effect of the adjacent methylthio-substituent.[6] The structure of the product shown as (5) is consistent with

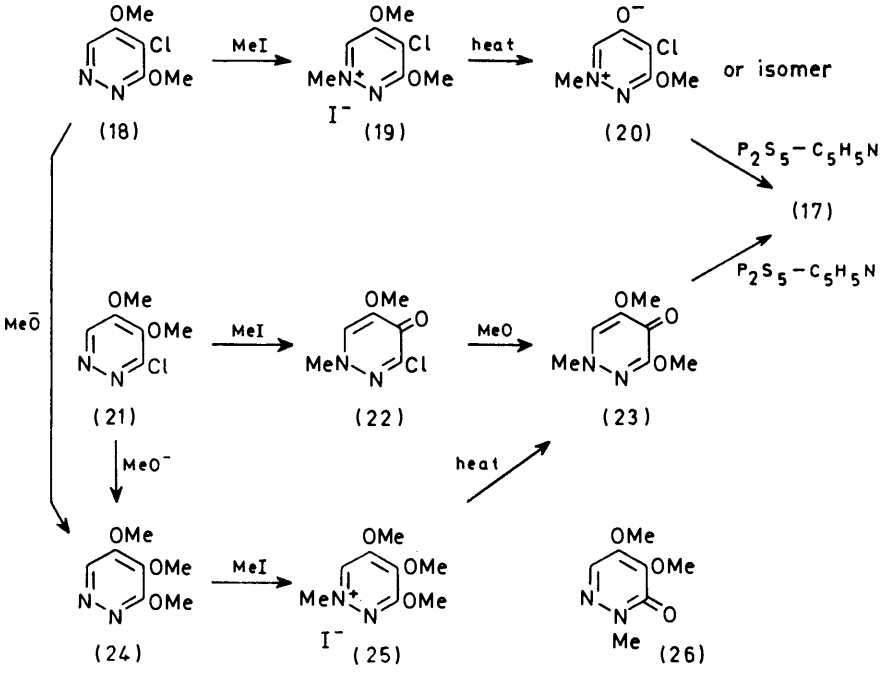
[1] Part 2, G. B. Barlin, *J.C.S. Perkin II*, 1974, 1199.
[2] R. N. Castle and K. Kaji, *Tetrahedron Letters*, 1962, 393.
[3] R. N. Castle, K. Kaji, G. A. Gerhardt, W. D. Guither, C. Weber, M. P. Malm, R. R. Shoup, and W. D. Rhoads, *J. Heterocyclic Chem.*, 1966, **3**, 79.
[4] R. N. Castle, K. Kaji, and D. Wise, *J. Heterocyclic Chem.*, 1966, **3**, 541.
[5] R. H. Mizzoni and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1954, **76**, 2201.
[6] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 1959, 3789.

its ^1H n.m.r. spectrum, but isomeric zwitterions, *e.g.* (7), cannot be completely excluded. We were unable to convert compound (16) with phosphorus pentasulphide in various solvents into the sulphur analogue (7).

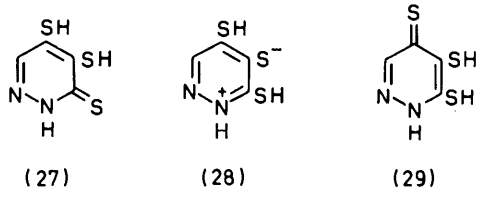
An attempted preparation of 3,4,5-trihydroxypyridazine by hydrolysis of 3,4,5-trichloropyridazine was unsuccessful. Oxidation of 3,4,5-trismethylthiopyridazine with aqueous potassium permanganate or peracetic acid afforded no 3,4,5-trismethylsulphonylpyridazine but a bismethylsulphonylmethylthiopyridazine and 3,5-bismethylsulphonylpyridazin-4-one, respectively. No product was isolated from hydrolysis of the latter with sodium hydroxide; but with sodium methoxide in methanol at 66 °C and 150 °C it gave the mono- and di-methoxypyridazin-4-ones, respectively. Itai and Kamiya [7] did not obtain 3,4,5-trimethoxypyridazine (24) by heating 4-chloro-3,5-dimethoxy- (18) or 3-chloro-4,5-dimethoxy-pyridazine (21) with sodium methoxide at 130 °C, most of the starting material being recovered. Contrary to these observations, we found that 3,4,5-trimethoxypyridazine could be prepared from 3,4,5-trichloropyridazine or 3-chloro-4,5-dimethoxypyridazine with an excess of sodium methoxide at room temperature, or from 4-chloro-3,5-dimethoxypyridazine with sodium methoxide at 100 °C. Also 3,4,5-trichloropyridazine with an excess of sodium methoxide at 100 °C gave 3,5-dimethoxypyridazin-4-one as the major product with some 3,4,5-trimethoxypyridazine, but none of the chlorodimethoxypyridazines.

4,5-Dimethoxy-2-methylpyridazin-3-one (26) (prepared from 4,5-dichloro-2-methylpyridazin-3-one with methanolic sodium methoxide at reflux) and 4-chloro-5-methoxy-2-methylpyridazin-3-one [8] could not be quaternised with methyl iodide under a variety of conditions.

Ionization Constants and Spectra.—A comparison of the basic ionization constants (involving proton addition) of 3,4,5-trimercaptopyridazine (pK_a 0.20) with those of the available methyl derivatives (Table) revealed a close similarity of the parent to the *N*(2)-monomethyl derivative (0.51) but a considerable difference from the *N*(1)-monomethyl isomer (2.30), and also from 3,4,5-trismethylthiopyridazine (2.07). Of the three possible N(2)H tautomeric forms (27)—(29), structure (27) for the predominant form of 3,4,5-trimercaptopyridazine was excluded because of the lack of similarity of the basic pK_a value of the non-tautomeric 4,5-bismethylthio-2-methylpyridazine-3-thione (−1.77). Unfortunately compounds of fixed structures (28) and (29) were not available for study, but previous research [9] suggests that the thione structure (29), because of the extra stabilisation in the thione form, is the more likely of



SCHEME 4



[7] T. Itai and S. Kamiya, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1059.

[8] Badische Anilin- and Soda-Fabrik, A.-G. (F. Reicheneder, K. Dury, A. Fischer, and H. Stummeyer), B.P. 917,849 (*Chem. Abs.*, 1963, **59**, 1663b).

[9] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.

these two possibilities for the neutral species of 3,4,5-trimercaptopyridazine.

We could not determine any of the acidic pK_a values for 3,4,5-trimercaptopyridazine because of overlapping.

The u.v. spectra confirmed the conclusions based on ionization constants. The u.v. spectra of the neutral species and monocation of 3,4,5-trimercaptopyridazine were closely similar to those of the neutral species and monocation of its *N*(2)-monomethyl derivative, respectively, but significantly different from those of the *N*(1)-monomethyl derivative and of 2-methyl-4,5-bismethylthiopyridazine-3-thione.

Amongst the monocation spectra, that from 3,4,5-trismethylthiopyridazine was similar to the spectrum of its *N*(1)-methiodide and generally similar to that of the monocation of 3,5-bismethylthio-1-methylpyridazine-4-thione.

groups occurred in the range δ 2.56—3.1 and those due to *N*-methyl groups at δ 4.60 and 4.77. The signal due to the aromatic 6-proton in compound (4) appeared relatively downfield at δ 10.1 owing to deshielding by the adjacent quaternary *N*-methyl group [*cf.* δ 9.15 for the *N*(2)-methiodide].

EXPERIMENTAL

All compounds were examined for impurities by t.l.c., and were recrystallised to constant m.p. M.p.s were taken for samples in Pyrex capillaries. Solids for analysis were dried at 100 °C or *ca.* 30 °C below the m.p. and 20 mmHg. Analyses were performed by the Australian National University Analytical Services Unit.

U.v. spectra were recorded with a Unicam SP 800 spectrophotometer and $\lambda_{max.}$ and ε values were checked with an Optica CF 4 manual instrument (Mr. D. T. Light);

pK_a Values and spectra

Pyridazine	Ionization (water; 20 °C) Charged species [a]	pK_a	Spread (±)	Conc. (M)	Analyt. [b] λ/nm	Spectroscopy in water [c] λ_{max}/nm	log ε	pH [d]
3,4,5-$(SH)_3$ [e]	0					*254*, 269, 291, 376	*4.09*, 4.10, 4.05, 3.96	5.0
	+	0.20	0.04	0.000 09	376	227, 243, 258, 283, *305*, 364	4.04, 4.09, 4.03, 4.10, *3.70*, 3.75	−1.90
2-Me-3(5)-(:S)-4,5(3,4)-$(SH)_2$	0					221, 253, 269, 290, 370	4.04, 4.12, 4.14, 4.14, 4.07	7.0
	+	0.51	0.02	0.000 015	395	230, 244, 260, 282, 352	4.06, 4.135, 4.08, 4.15, 3.75	−1.60
	−	9.23	0.03	0.000 015	400	246, 288, 344, 400	4.12, 4.31, 3.695, 4.05	12.0
1-Me-4-(:S)-3,5-$(SH)_2$	0					258, 304, 390	4.29, 4.44, 3.67	5.0
	+	2.30	0.07	0.000 05	304	226, 276, 378	4.17, 3.94, 4.01	0.0
2-Me-3-(:S)-4,5-$(SMe)_2$	0					*263*, 291, 364	*3.81*, 4.37, 3.57	7.0
	+	−1.77	0.06	0.000 5	340	251, 271, 337	3.92, 4.015, 3.97	−4.1
1-Me-4-(:S)-3,5-$(SMe)_2$	0					246, 284, 327, 383	4.03, 4.01, 3.28, 4.01	7.0
	+	−1.97	0.09	0.000 01	395	251, 283, 359	4.06, 4.27, 3.62	−4.1
3,4,5-$(SMe)_3$	0					*222*, 262, *300*	*3.60*, 4.27, *3.72*	7.0
	+	2.07	0.05	0.000 3	350	(209), *258*, 280, 344	(3.96), *3.97*, 4.23, 3.81	0.0
4-SMe-3,5-$(SO_2Me)_2$	0					*225*, *260*, 318, *356*	*3.74*, *3.22*, 3.075, *2.91*	7.0
	+	0.0	0.06	0.000 025	300	251, *258*, 293 [g]		
3,4,5-$(SMe)_3$-1-MeI [f]	+					209, 285, 353	3.98, 4.28, 3.55	7.0
3,4,5-$(SMe)_3$-2-MeI [f]	+					237, 293, 341	3.63, 3.93, 4.01	7.0

[a] 0, neutral species; +, cation; −, anion. [b] Analytical wavelength for spectroscopic determinations 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) have been assigned. [e] The acidic pK_a could not be determined because of overlapping pK_a values. [f] For the determination of the spectra the reference cell was compensated with potassium iodide. [g] Instability of the cation did not permit the determination of log ε values.

The ^1H n.m.r. spectra * afforded a clear distinction between *N*- and *S*-methyl groups in the methyl derivatives of 3,4,5-trimercaptopyridazine, and also the sites of nuclear quaternisation. Low-field signals assignable to *N*-methyl groups appeared in the range δ 3.7—4.5, and those due to *S*-methyl groups in the range δ 2.2—2.7. In the oxygen analogues it was not possible to make a clear distinction between the signals from *N*- and *O*-methyl groups.

In the spectra of 3,4,5-trismethylthiopyridazinium methiodides (4) and (12) the signals due to *S*-methyl

* Available in Supplementary Publications No. SUP 22007 (3 pp.). For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

† See Supplementary Publication.

i.r. spectra † were measured with a Unicam SP 1000 instrument. ^1H N.m.r. spectra † were recorded at 60 MHz and 35° with a Varian T-60A spectrometer with tetramethylsilane as internal standard. Mass spectra † were measured with an A.E.I. MS9 instrument (Dr. J. K. MacLeod). Ionization constants were determined spectroscopically.[10]

3,4,5-*Trimercaptopyridazine* (1).—A mixture of 3,4,5-trichloropyridazine [11] (4.6 g), phosphorus pentasulphide (22.2 g), and dry pyridine (300 ml) was refluxed for 1.5 h. The excess of pyridine was removed under reduced pressure, water was added, and the mixture was warmed on a steam-

[10] A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971, 2nd edn.

[11] T. Kuraishi, *Chem. and Pharm. Bull.* (*Japan*), 1956, **4**, 497.

bath for 2 h to decompose the excess of phosphorus pentasulphide. After cooling, a dark brown solid (0.63 g) was filtered off. The filtrate was adjusted to pH 1 with concentrated hydrochloric acid and the orange-red solid (3.37 g) collected, dried, and recrystallised from ethanol to give 3,4,5-trimercaptopyridazine, m.p. >360° (lit.,[2,3] >400°) (Found: C, 27.2; H, 2.5; N, 15.9; S, 54.4. Calc. for $C_4H_4N_2S_3$: C, 27.25; H, 2.3; N, 15.9; S, 54.6%).

The dark brown solid (0.63 g) was soluble in N-sodium hydroxide and was reprecipitated with 2N-hydrochloric acid at pH 1. It had m.p. >360° but could not be purified by recrystallisation as it was highly insoluble. This product (0.63 g) was dissolved in N-sodium hydroxide (25 ml) and shaken with methyl iodide (1.0 ml) for 30 min. The precipitate (0.42 g) was collected, dried, and recrystallised from pyridine to give dull white crystals of a *bismethylthiodithiinodipyridazine* [probably (2)], m.p. 309—311° (decomp.) (Found: C, 38.5; H, 2.4; N, 17.7; S, 41.3. $C_{10}H_8N_4S_4$ requires C, 38.4; H, 2.6; N, 17.9; S, 41.0%).

The proportion of dithiinodipyridazine increased as the ratio of phosphorus pentasulphide in the thiation was decreased.

3,4,5-*Trismethylthiopyridazine* (3).—A solution of 3,4,5-trimercaptopyridazine (1.28 g) in N-sodium hydroxide (20 ml) was shaken vigorously with methyl iodide (1.0 ml) for 0.5 h, then extracted with chloroform. The extract was dried (Na_2SO_4), the solvent distilled off, and the product (1.3 g) recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give 3,4,5-*trismethylthiopyridazine* as light yellow crystals, m.p. 105—106° (Found: C, 38.2; H, 4.7; N, 13.0; S, 44.2. $C_7H_{10}N_2S_3$ requires C, 38.5; H, 4.7; N, 12.8; S, 44.1%).

1-*Methyl*-3,4,5-*trismethylthiopyridazinium Iodide* (4).—A mixture of 3,4,5-trismethylthiopyridazine (0.215 g), benzene (15 ml), and methyl iodide (0.8 ml) was kept at room temperature overnight. The orange red 1-*methyl*-3,4,5-*trismethylthiopyridazinium iodide* (0.30 g) was collected and washed with benzene. It coalesces at *ca.* 148—149 °C and decomposes at 312—313 °C (Found: C, 26.8; H, 3.7; N, 7.4; S, 26.65. $C_8H_{13}IN_2S_3$ requires C, 26.7; H, 3.6; N, 7.8; S, 26.7%).

1-*Methyl*-3,5-*bismethylthiopyridazine*-4-*thione* (5).—(*a*) A mixture of 1-methyl-3,4,5-trismethylthiopyridazinium iodide (0.26 g) and chloroform–benzene (2 : 1; 20 ml) was heated under reflux for *ca.* 2 h. After cooling the yellow solid (0.21 g) was collected and recrystallised from dimethylformamide–ethanol to give yellow needles of 1-*methyl*-3,5-*bismethylthiopyridazine*-4-*thione*, m.p. 317—318° (Found: C, 38.4; H, 4.85; N, 12.7; S, 44.3. $C_7H_{10}N_2S_3$ requires C, 38.35; H, 4.7; N, 12.8; S, 44.1%).

(*b*) A mixture of 3,4,5-trimercaptopyridazine (0.88 g), methyl iodide (2.0 ml), and anhydrous dimethylformamide (30 ml) was refluxed for 2 h. The solvent was removed under reduced pressure, and the product washed with chloroform, collected, and recrystallised from dimethylformamide to give yellow needles (0.38 g), m.p. and mixed m.p. 317—318°.

(*c*) 3,5-Dimercapto-1-methylpyridazine-4-thione (0.1 g; see below) in N-sodium hydroxide (8.0 ml) was shaken with methyl iodide (0.8 ml) for 30 min. The yellow solid (0.12 g) was collected, washed with water, dried, and recrystallised from dimethylformamide to give 1-methyl-3,5-bismethylthiopyridazine-4-thione, m.p. and mixed m.p. 316—318°.

1-*Methyl*-3,5-*bismethylthiopyridazin*-4-*one* (6).—1-Methyl-3,4,5-trismethylthiopyridazinium iodide (0.55 g) was shaken with N-sodium hydroxide (20 ml) for 15 min. The white precipitate was extracted into chloroform and the extract washed with water, dried (Na_2SO_4), and evaporated. The product (0.3 g) crystallised from benzene–light petroleum (b.p. 60—80 °C) to give white crystals of 1-*methyl*-3,5-*bismethylthiopyridazin*-4-*one*, m.p. 150—152° (Found: C, 41.3; H, 4.8; N, 13.6; S, 31.4. $C_7H_{10}N_2OS_2$ requires C, 41.55; H, 5.0; N, 13.85; S, 31.7%).

4,5-*Dichloro*-2-*methylpyridazin*-3-*one* (8).—Prepared by methylation of 4,5-dichloropyridazin-3-one with methyl iodide in the presence of sodium carbonate in dimethylformamide,[12] and also by methylation with dimethyl sulphate in aqueous sodium hydroxide, this compound had m.p. 91—92° [from light petroleum (b.p. 60—80 °C)] (lit.,[12] 91°).

4,5-*Dimercapto*-2-*methylpyridazine*-3-*thione* (9).—A mixture of 4,5-dichloro-2-methylpyridazin-3-one (1.2 g), phosphorus pentasulphide (12 g), and dry pyridine (20 ml) was heated under reflux for 12 h. The solvent was removed under reduced pressure, water added, and the mixture warmed on a steam-bath for 2 h to decompose the excess of phosphorus pentasulphide, and filtered. The filtrate was acidified with hydrochloric acid to pH 1, and the yellow solid (0.89 g) was collected and recrystallised from light petroleum (b.p. 60—80 °C) to give 4,5-*dimercapto*-2-*methylpyridazine*-3-*thione*, m.p. 118—119° (Found: C, 31.9; H, 3.2; N, 14.6; S, 50.2. $C_5H_6N_2S_3$ requires C, 31.55; H, 3.2; N, 14.7; S, 50.5%).

2-*Methyl*-4,5-*bismethylthiopyridazine*-3-*thione* (10).—(*a*) A solution of 4,5-dimercapto-2-methylpyridazine-3-thione (0.4 g) in N-sodium hydroxide (10 ml) was shaken with methyl iodide (0.5 ml) for 30 min and the yellow solid was extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated and the residue (0.46 g) recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give light yellow crystals of 2-*methyl*-4,5-*bismethylthiopyridazine*-3-*thione*, m.p. 139—140° (Found: C, 38.5; H, 4.8; N, 12.7; S, 44.2. $C_7H_{10}N_2S_3$ requires C, 38.5; H, 4.7; N, 12.8; S, 44.1%).

(*b*) A mixture of 2-methyl-4,5-bismethylthiopyridazin-3-one (0.5 g; see below), phosphorus pentasulphide (2 g), and dry pyridine (30 ml) was heated under reflux for 70 h. The solvent was removed under reduced pressure, water was added, and the mixture was warmed on a steam-bath for 2 h to decompose the excess of phosphorus pentasulphide. This mixture was extracted with chloroform; the extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (0.38 g) was subjected to t.l.c. (silica; benzene–chloroform, 1 : 1) and the 2-methyl-4,5-bismethylthiopyridazine-3-thione was obtained as yellow needles (0.12 g), m.p. and mixed m.p. 138—140° [from benzene–light petroleum (b.p. 60—80 °C)]. Starting material (0.14 g) was recovered from the t.l.c. plate.

2-*Methyl*-3,4,5-*trismethylthiopyridazinium Iodide* (12).—A solution of 2-methyl-4,5-bismethylthiopyridazine-3-thione (0.3 g) in benzene (10 ml) with methyl iodide (0.4 ml) was kept overnight at room temperature. A yellow crystalline solid (0.165 g) separated, and was collected, washed with benzene, and dried. The 2-*methyl*-3,4,5-*trismethylthiopyridazinium iodide* decomposed in the range 115—138° (Found: C, 26.9; H, 4.0; N, 7.6. $C_8H_{13}IN_2S_3$ requires C, 26.7; H, 3.6; N, 7.8%). When heated in benzene the product reverted to starting material.

[12] K. Kaji, M. Kuzuya, and R. N. Castle, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 147.

2-*Methyl*-4,5-*bismethylthiopyridazin*-3-*one* (11).—(*a*) 2-Methyl-3,4,5-trismethylthiopyridazinium iodide (0.09 g) was shaken with N-sodium hydroxide (10 ml) at room temperature for 15 min. The resulting white solid was extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The residue (0.055 g) was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give 2-methyl-4,5-bismethylthiopyridazin-3-one, m.p. 99—100° (lit.,[13] 100—100.5°) (Found: C, 41.75; H, 5.3; N, 14.0; S, 31.5. Calc. for $C_7H_{10}N_2OS_2$: C, 41.6; H, 5.0; N, 13.8; S, 31.7%).

(*b*) A mixture of 4,5-dichloro-2-methylpyridazin-3-one (0.5 g) and sodium methanethiolate solution [prepared by saturating a solution of sodium hydroxide (0.5 g) in water (5.0 ml) and ethanol (10 ml) with methanethiol] was heated in a sealed tube at 120 °C for 4 h. The contents were then adjusted to pH 1, warmed to expel methanethiol, adjusted to pH 7, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated and the white solid (0.38 g) was recrystallised from light petroleum (b.p. 60—80 °C) to give 2-methyl-4,5-bismethylthiopyridazin-3-one, m.p. and mixed m.p. 99—100°.

4-*Chloro*-3,5-*dimethoxy*-1-*methylpyridazinium Iodide* (19).—A solution of 4-chloro-3,5-dimethoxypyridazine [8] (0.5 g) in benzene (50 ml) with methyl iodide (2.5 ml) was kept overnight at room temperature. The yellow needles of 4-*chloro*-3,5-*dimethoxy*-1-*methylpyridazinium iodide* (0.65 g) were collected, washed well with benzene, and dried. The product changes colour and shrinks at 145—150 °C, and melts at 203—205 °C (Found: C, 26.35; H, 3.0; Cl, 10.6; I, 40.8; N, 8.9. $C_7H_7ClIN_2O$ requires C, 26.5; H, 3.2; Cl, 11.1; I, 40.1; N, 8.8%).

5-*Chloro*-6-*methoxy*-2-*methylpyridazinium*-4-*olate* (20).—4-Chloro-3,5-dimethoxy-1-methylpyridazinium iodide (0.28 g) and freshly prepared silver chloride (1.7 g) were shaken in aqueous ethanol for 30 min. The solid was filtered off and washed with hot water and ethanol and the combined filtrates were evaporated to dryness under reduced pressure. The residue was recrystallised from benzene–methanol to give a pale cream *compound* (0.107 g), m.p. 206—207° (decomp.) (Found, for sample dried at 100 °C for 8 h: C, 41.0; H, 4.2; N, 15.6. $C_6H_7ClN_2O_2$ requires C, 41.3; H, 4.0; N, 16.0%). The same product was obtained when 4-chloro-3,5-dimethoxy-1-methylpyridazinium iodide was refluxed in dioxan.

3-*Chloro*-5-*methoxy*-1-*methylpyridazin*-4-*one* (22).—Methyl iodide (1 ml) was added to a solution of 3-chloro-4,5-dimethoxypyridazine [8] (0.3 g) in benzene and the mixture was set aside overnight at room temperature. The crystalline solid (0.21 g) was collected and dried but attempts to characterise the methiodide were unsuccessful. The product was recrystallised from chloroform and gave 3-*chloro*-5-*methoxy*-1-*methylpyridazin*-4-*one*, m.p. 235—237° (Found: C, 41.3; H, 4.2; Cl, 20.9; N, 15.95. $C_6H_7ClN_2O_2$ requires: C, 41.3; H, 4.0; Cl, 21.3; N, 16.0%).

3,4,5-*Trimethoxy*-1-*methylpyridazinium Iodide* (25).—Methyl iodide (0.9 ml) was added to a solution of 3,4,5-trimethoxypyridazine (0.35 g; see below) in benzene (30 ml) and the mixture was kept at room temperature overnight. The greenish yellow needles of 3,4,5-*trimethoxy*-1-*methylpyridazinium iodide* (0.45 g) were collected, washed with benzene, and dried. The product shrinks at 98—100 °C and melts at 148—150 °C (Found: N, 9.1. $C_{10}H_{13}IN_2O_3$ requires N, 8.9%).

3,5-*Dimethoxy*-1-*methylpyridazin*-4-*one* (23).—(*a*) 3,4,5-Trimethoxy-1-methylpyridazinium iodide (0.35 g) was refluxed in benzene for 1 h. The solution was then filtered with charcoal, and evaporated, and the residue (0.23 g) was crystallised from benzene to give 3,5-*dimethoxy*-1-*methylpyridazin*-4-*one*, m.p. 153—154° (Found: C, 49.8; H, 6.2; N, 16.5. $C_7H_{10}N_2O$ requires C, 49.4; H, 5.9; N, 16.45%).

(*b*) A solution of 3-chloro-5-methoxy-1-methylpyridazin-4-one and methanolic sodium methoxide [from sodium (0.15 g) and dry methanol (20 ml)] was refluxed for 3 h. The solvent was removed, the residue extracted with chloroform, and the product (0.17 g) recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give 3,5-dimethoxy-1-methylpyridazin-4-one, m.p. and mixed m.p. 153—154°.

(*c*) 3,5-Dimethoxypyridazin-4-one (0.25 g; see below) was dissolved in N-sodium hydroxide (30 ml) and shaken with methyl iodide (0.8 ml) for 2.5 h. The mixture was extracted with chloroform, the extract dried (Na_2SO_4), the solvent removed, and the product recrystallised from benzene to give 3,5-dimethoxy-1-methylpyridazin-4-one (0.19 g), m.p. 153—154°.

(*d*) A mixture of 4-chloro-3,5-dimethoxy-1-methylpyridazinium iodide (0.105 g) and sodium methoxide [from sodium (0.015 g) and methanol (20 ml)] was stirred at room temperature for 0.5 h, then heated on a steam-bath for 20 min. The solvent was removed and the residue dissolved in water, adjusted to pH 7, and extracted with chloroform. Distillation left a solid (0.03 g) which was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give 3,5-dimethoxy-1-methylpyridazin-4-one, m.p. 153—155°.

Conversion of 3,4-*Dichloro*-5-*methoxypyridazine into* 3,4,5-*Trimercaptopyridazine*.—A mixture of 3,4-dichloro-5-methoxypyridazine [7] (0.4 g) and phosphorus pentasulphide (2.5 g) in dry pyridine (25 ml) was heated under reflux for 4 h. The solvent was removed under reduced pressure and the excess of phosphorus pentasulphide decomposed by addition of water and heating on a steam-bath for 2 h. The aqueous solution was cooled, filtered, and acidified to pH 1 to give 3,4,5-trimercaptopyridazine (0.28 g), m.p. >360°. This was methylated with methyl iodide as described above to give 3,4,5-trismethylthiopyridazine (0.2 g), m.p. and mixed m.p. 105—106°.

3(4)-*Chloro*-4(3)-*iodo*-5-*methoxy*-1-*methylpyridazinium Iodide*.—A mixture of 3,4-dichloro-5-methoxypyridazine [7] (0.4 g) and methyl iodide (10 ml) was refluxed on a steam-bath for 4 h. After cooling, benzene was added, and the crystalline yellow solid (0.55 g) was collected, and recrystallised from water to give 3(4)-*chloro*-4(3)-*iodo*-5-*methoxy*-1-*methylpyridazinium iodide*, which shrinks at 150—155 °C and melts at 228—230 °C (Found: C, 17.7; H, 2.5; Cl, 8.5; I, 61.6; N, 6.5. $C_6H_7ClI_2N_2O$ requires C, 17.45; H, 1.7; Cl, 8.6; I, 61.6; N, 6.8%).

5(6)-*Chloro*-6(5)-*iodo*-2-*methylpyridazinium*-4-*olate* (15).—3(4)-Chloro-4(3)-iodo-5-methoxy-1-methylpyridazinium iodide (1.1 g) in dioxan (15 ml) was refluxed for 3 h until the colour had changed from dark brown to light yellow. The solvent was removed under reduced pressure and the white crystalline solid (0.65 g) was recrystallised from ethanol to give the *anhydro-base*, m.p. 230—231° (Found: C, 22.7; H, 1.45; Cl, 13.4; I, 45.9; N, 9.9. $C_5H_4ClIN_2O$ requires C, 22.2; H, 1.4; Cl, 13.1; I, 46.0; N, 10.35%).

[13] Badische Anilin- and Soda-Fabrik, A.-G., Neth. Appl. 6,516,856 (*Chem. Abs.*, 1966, **65**, 18599e).

3,5-*Dimercapto*-1-*methylpyridazine*-4-*thione* (17).—(*a*) A mixture of the foregoing anhydro-base (0.3 g), phosphorus pentasulphide (1.5 g), and pyridine (20 ml) was refluxed for 3 h, then evaporated under reduced pressure. Water was added and the product was warmed on a steam-bath for 2 h to decompose the excess of reagent. After cooling, the solution was filtered and acidified and the yellow precipitate extracted into chloroform. The extract was dried (Na_2SO_4) and evaporated to give a yellow crystalline solid (0.15 g), which was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to afford 3,5-*dimercapto*-1-*methylpyridazine*-4-*thione*, m.p. 151—152° (Found: C, 31.6; H, 3.3; N, 14.7; S, 50.5. $C_5H_6N_2S_3$ requires C, 31.55; H, 3.2; N, 14.7; S, 50.5%).

(*b*) A mixture of the anhydro-base (20) (0.2 g), phosphorus pentasulphide (4.0 g), and dry pyridine (10 ml) was refluxed for 3 h. The solvent was removed under reduced pressure, water was added, and the mixture was warmed on a steam-bath. After cooling, the mixture was filtered and adjusted to pH 1, and the yellow precipitate was extracted into chloroform. The product (0.16 g) was recrystallised from benzene–chloroform to give 3,5-dimercapto-1-methylpyridazine-4-thione, m.p. and mixed m.p. 148—150°.

(*c*) A mixture of 3,5-dimethoxy-1-methylpyridazin-4-one (0.2 g), phosphorus pentasulphide (1.5 g), and pyridine (20 ml) was heated under reflux for 2 h. The solvent was removed under reduced pressure, water was added, and the mixture was warmed on a steam-bath for 2 h to decompose the excess of phosphorus pentasulphide. The aqueous solution was adjusted to pH 1 and the yellow precipitate extracted into chloroform. The product was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give 3,5-dimercapto-1-methylpyridazine-4-thione (0.11 g), m.p. 150—151°.

5,6-*Bismethylthio*-2-*methylpyridazinium*-4-*olate* (16).—The anhydro-base (15) (0.5 g) and sodium methanethiolate solution [from sodium hydroxide (0.5 g) in aqueous ethanol (10 ml; 1 : 1) saturated with methanethiol] were heated in a sealed tube at 100 °C for 5 h. After cooling, the mixture was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4), and evaporated. The light yellow residue (0.25 g) was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give yellow needles of the *anhydro-base* (16), m.p. 153—155° (Found: C, 41.8; H, 5.0; N, 13.7; S, 31.7. $C_7H_{10}N_2OS_2$ requires C, 41.6; H, 4.9; N, 13.8; S, 31.7%).

4-*Chloro*-5-*methoxypyridazin*-3-*one*.— 4,5-Dichloropyridazin-3-one (0.85 g) was added to a solution of sodium methoxide [from sodium (0.5 g) and methanol (40 ml)] and the mixture heated in a sealed tube at 100 °C for 6 h. The solvent was evaporated off, and the residue diluted with water and acidified to pH 1. The crystalline solid (0.39 g) was collected and recrystallised from ethanol to give 4-*chloro*-5-*methoxypyridazin*-3-*one*, m.p. 245—246° (Found: C, 37.3; H, 3.4; N, 17.4. $C_5H_5ClN_2O_2$ requires C, 37.4; H, 3.1; N, 17.4%); M^+ 160/162.

4-*Chloro*-5-*methoxy*-2-*methylpyridazin*-3-*one*.—(*a*) 4,5-Dichloro-2-methylpyridazin-3-one (0.2 g) and a solution of sodium hydroxide (0.15 g) in anhydrous methanol (20 ml) were stirred at room temperature for 3 h. The mixture was then concentrated under reduced pressure, water was added, and the product was extracted with chloroform. The extract was dried (Na_2SO_4), the solvent distilled off, and the residue (0.18 g) crystallised from benzene–light petroleum (b.p. 60—80 °C) to give 4-chloro-5-methoxy-2-methylpyridazin-3-one, m.p. 153—155° (lit.,[8] 155—156°).

(*b*) 4,5-Dichloro-2-methylpyridazin-3-one (0.75 g) and sodium methoxide [from sodium (0.2 g) and dry methanol (20 ml)] at reflux for 2 h gave a white solid (0.56 g) which after repeated recrystallisation from benzene–light petroleum (b.p. 60—80 °C) had m.p. and mixed m.p. 154—155°.

(*c*) 4-Chloro-5-methoxypyridazin-3-one (0.13 g) dissolved in N-sodium hydroxide (15 ml) was shaken with methyl iodide (0.5 ml) for 1 h. The mixture was extracted with chloroform, the extract dried (Na_2SO_4) and evaporated and the product recrystallised from benzene to give 4-chloro-5-methoxy-2-methylpyridazin-3-one (0.065 g), m.p. and mixed m.p. 151—152°.

4,5-*Dimethoxy*-2-*methylpyridazin*-3-*one* (26).—A mixture of 4,5-dichloro-2-methylpyridazin-3-one (1.6 g) and sodium methoxide solution [from sodium (1.2 g) and dry methanol (40 ml)] was heated under reflux for 8 h. After cooling, the sodium chloride was filtered off, the filtrate evaporated *in vacuo*, and the residue extracted with benzene. The extract was passed through a short column of alumina and gave a viscous liquid which solidified on cooling. It was recrystallised from light petroleum (b.p. 60—80 °C) to give 4,5-*dimethoxy*-2-*methylpyridazin*-3-*one* (0.4 g), m.p. 70—71° (Found: C, 49.2; H, 6.1; N, 16.7. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.45%).

Reaction of 3,4,5-*Trichloropyridazine with Sodium Methoxide*.—(a) *With one equivalent of sodium methoxide*. 3,4,5-Trichloropyridazine with 1 equiv. of sodium methoxide at reflux according to literature procedures[7] gave 3,4-dichloro-5-methoxypyridazine, m.p. 100—102° [from benzene–light petroleum (b.p. 60—80 °C)] (lit.,[7] 101—102°).

(b) *With two equivalents of sodium methoxide*. The reaction of 3,4,5-trichloropyridazine (5.22 g) with 2 equiv. of sodium methoxide was carried out by stirring at room temperature and then refluxing for 1.5 h according to literature procedures,[7] and gave 4-chloro-3,5-dimethoxypyridazine (1.27 g), m.p. 163—164° (lit.,[7] 161—162°) and 3-chloro-4,5-dimethoxypyridazine (2.2 g), m.p. 91—92° (lit.,[7] 89—90°). These products were isolated by crystallisation first from methanol, and then (the product in the filtrate) from benzene–light petroleum (b.p. 60—80 °C). The residue in the benzene–light petroleum (b.p. 60—80 °C) filtrate was repeatedly recrystallised from light petroleum (b.p. 60—80 °C) to give 3,4,5-*trimethoxypyridazine* (0.060 g), m.p. 79—80° (Found: C, 49.4; H, 5.6; N, 16.9. $C_7H_{10}N_2O_3$ requires C, 49.4; H, 5.9; N, 16.5%).

(c) *With an excess of sodium methoxide at* 20 °C. To a solution of sodium methoxide [from sodium (2.5 g) and dry methanol (50 ml)] 3,4,5-trichloropyridazine (2.76 g) was added, and the mixture was stirred at room temperature for 2 h, and then set aside overnight. The colourless needles of the product and sodium chloride were filtered off, washed with water, and recrystallised from aqueous methanol to give 4-chloro-3,5-dimethoxypyridazine (0.65 g), m.p. 163—164°. The methanolic filtrate was evaporated and the residue crystallised from benzene–light petroleum (b.p. 60—80 °C) to give 3,4,5-trimethoxypyridazine (0.95 g), m.p. 78—79°.

(d) *With an excess of sodium methoxide at* 100 °C. 3,4,5-Trichloropyridazine (2.76 g) and a solution of sodium methoxide [from sodium (2.5 g) and methanol (50 ml)] were heated in a sealed tube at 100 °C for 5 h. The sodium chloride was filtered off and the filtrate evaporated, diluted

with water, and extracted with chloroform to give 3,4,5-trimethoxypyridazine (0.46 g), m.p. 76—77° [from light petroleum (b.p. 60—80 °C)]. The aqueous solution was acidified to pH 2 and concentrated to 5 ml to give a white solid (1.2 g). This was recrystallised from ethanol to give *4-hydroxy-3,5-dimethoxypyridazine*, m.p. 240—241° (Found: C, 46.3; H, 5.1; N, 17.6. $C_6H_8N_2O_3$ requires C, 46.15; H, 5.2; N, 18.0%); M^+ 156.

Conversion of 3-Chloro-4,5-dimethoxypyridazine into 3,4,5-Trimethoxypyridazine (24). 3-Chloro-4,5-dimethoxypyridazine (0.34 g) was added to a solution of sodium methoxide [from sodium (0.2 g) in methanol (30 ml)] at room temperature. The mixture was stirred for 1 h, then set aside overnight. The solvent was removed under reduced pressure and the residue extracted with benzene; the product (0.26 g) crystallised from light petroleum (b.p. 60—80 °C) to give 3,4,5-trimethoxypyridazine, m.p. 76—77°.

Conversion of 4-Chloro-3,5-dimethoxypyridazine into 3,4,5-Trimethoxypyridazine (24).—A mixture of 4-chloro-3,5-dimethoxypyridazine (0.35 g) and sodium methoxide solution [from sodium (0.2 g) and methanol (20 ml)] was heated in a sealed tube at 100 °C for 6 h. The solvent was distilled off, the residue extracted with benzene, and the product (0.25 g) recrystallised from light petroleum (b.p. 60—80 °C) to give 3,4,5-trimethoxypyridazine, m.p. 76—77°.

Oxidation of 3,4,5-Trismethylthiopyridazine with Aqueous Potassium Permanganate.—To a solution of 3,4,5-trismethylthiopyridazine (0.218 g) in glacial acetic acid (8 ml), potassium permanganate (0.7 g) in water (5 ml) was added dropwise with stirring at 25 °C, and stirring was continued for 0.5 h. The mixture was cooled and decolourised by passing in sulphur dioxide, adjusted to pH 7 with ammonia, and extracted with chloroform. The extract was dried and evaporated, and the residue (0.19 g) recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give a bismethylsulphonylmethylthiopyridazine, m.p. 173—175° (Found: C, 29.1; H, 3.6; N, 9.8; S, 33.8. Calc. for $C_7H_{10}N_2O_4S_3$: C, 29.1; H, 3.6; N, 9.9; S, 34.1%).

Oxidation of 3,4,5-Trismethylthiopyridazine with Peracetic Acid.—Acetic anhydride (10 ml) was stirred and cooled to <5 °C and hydrogen peroxide (2.5 ml; 30%) was added. To this cooled solution, 3,4,5-trismethylthiopyridazine (0.436 g) was added and stirring was continued for 10 min until the exothermic reaction was complete. The mixture was then heated on a steam-bath for 10 min, cooled, and diluted with water, and the white solid (0.175 g) was collected. It was recrystallised from dimethylformamide–ethanol to give *3,5-bismethylsulphonylpyridazin-4-one*, m.p. 312—314° (Found: C, 28.7; H, 3.6; N, 10.8. $C_6H_8N_2O_5S_2$ requires C, 28.5; H, 3.2; N, 11.1%).

Reaction of 3,5-Bismethylsulphonylpyridazin-4-one with Methanolic Sodium Methoxide.—(*a*) A mixture of sodium methoxide [from sodium (0.15 g) and methanol (15 ml)] and 3,5-bismethylsulphonylpyridazin-4-one (0.15 g) was heated in a sealed tube at 150—155 °C for 3 h. The solvent was removed and the residue dissolved in water (2 ml), acidified with hydrochloric acid to pH 1, and set aside overnight. The precipitate (0.032 g) was collected and recrystallised from aqueous ethanol to give 3,5-dimethoxypyridazin-4-one, m.p. and mixed m.p. 238—240°.

(*b*) A mixture of sodium methoxide [from sodium (0.11 g) and methanol (15 ml)] and 3,5-bismethylsulphonylpyridazin-4-one (0.2 g) was heated under reflux for 4 h, then concentrated under reduced pressure. The residue was dissolved in water (2 ml), acidified with hydrochloric acid to pH 1, and set aside. The white solid (0.090 g) was collected and recrystallised from ethanol to give *3(5)-methoxy-5(3)-methylsulphonylpyridazin-4-one*, m.p. 268—270° (Found: C, 35.1; H, 4.2; N, 13.2; S, 15.9. $C_6H_7N_2O_4S$ requires C, 35.3; H, 3.9; N, 13.0; S, 15.7%).

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