Polyhalogeno-aromatic Compounds. Part XXXIII.[1] Structures of Polyhalogenopyridine-2(and 4)-thiols, Polyhalogenopyridin-2(and 4)-ols, and their *N*- and *S*(or *O*)-Methyl Derivatives

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Comparative u.v. studies of tetrachloropyridine-2-thiol and its *N*- and *S*-methyl derivatives in methanol show that the thiol exists predominantly as the thiol tautomer, while tetrachloropyridin-2-ol and 3,5-dichloro-2,4-difluoropyridin-6-ol exist predominantly in the enol form in methanol. U.v. data are given also for a number of polyhalogeno-pyridin-4-thiols and -pyridin-4-ols and their *S*- or *O*-methyl derivatives. Chemical shift values for the methyl protons in *N*- and *S*(or *O*)-methyl derivatives of polyhalogeno-pyridinethiols or -pyridinols allow them to be distinguished. Mass spectroscopic data are reported.

It is well known that pyridines containing a 2- or 4-hydroxy-[2] or mercapto-group exist usually as pyridinones or pyridinethiones, respectively.[2] Substitution in pyridin-2(or 4)-one by increasing numbers of chlorine [3-7] or fluorine [8,9] atoms, particularly in the α- and γ-positions, results in a significant displacement of the tautomeric equilibrium towards the enol tautomer. Methylation of tetrachloropyridine-2-thiol (4a),[1] tetrachloropyridine-4-thiol (1a),[10] or 3,5-dichloro-2,6-difluoropyridine-4-thiol (2a) [11] with dimethyl sulphate yields only the corresponding *S*-methyl derivatives (9), (5), and (6), respectively. The structures of these compounds followed from the n.m.r. spectra (see below) of the crude products, which showed only one proton signal, and from oxidation to the corresponding sulphoxide or sulphone. Recently, the *N*-methyl isomer (12) of tetrachloro-2-methylthiopyridine (9) was prepared from pentachloro-*N*-methylpyridinium fluorosulphonate and aqueous sodium hydrogen sulphide.[12] This prompted us to study the structure of tetrachloropyridine-2-thiol (4a) by a comparison of its u.v. spectrum † with those of its *S*- (9) † and *N*-methyl derivative (12).†, ‡ The results (Table 1) suggest that compound (4a) exists in methanol predominantly in the thiol form. The u.v. spectrum of tetrachloropyridine-4-thiol (1a) † shows a close similarity with that of its *S*-methyl derivative (5) † and it is probable that this compound also exists predominantly in the thiol form in methanol and in the solid state although, in the absence of its *N*-methyl

Table 1

U.v. data for polyhalogeno-pyridine-2(and 4)-thiols and -pyridin-2(and 4)-ols and their *N*- and *S*(or *O*)-methyl derivatives

Compound	$\lambda_{max.}$ MeOH/nm			
(4a)	210sh	221	259	306
(9)	213sh	223	269	320
(12)		223	236sh	310
(1a)	231	257	306	
(5)	213	236	302	
(2a)	214	248	298	
(6)	218	235sh	289	
(4b)	213	301		
(10)	217	300		
(13)	223	336		
		338 *	350sh †	
(11b)		223	277	
(11a)	209sh	226	276	
(14)	212	232	309	
(1b)		220	241 sh	285
(7)		222	236 sh	285
(15)		232	238 sh	282
(2b)		218	257	
(8)		220	269	

* log ε 7·41. † Recorded in ethanol (from ref. 13).

‡ U.v. spectra marked with a dagger (†) are available in Supplementary Publication No. SUP 21124 (9 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

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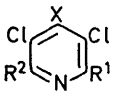
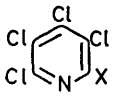
[12] E. Ager and H. Suschitzky, *J.C.S. Perkin I*, 1973, 2839; *J. Fluorine Chem.*, 1973–74, **3**, 230.

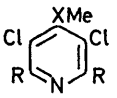
derivative, this evidence cannot be regarded as conclusive.[2] The similarity between the u.v. spectra of 3,5-dichloro-2,6-difluoropyridine-4-thiol (2a) † and its *S*-methyl derivative (6) † is not as close. However, the



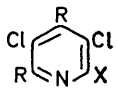
(1a) $R^1 = R^2 = Cl$, X = SH
(1b) $R^1 = R^2 = Cl$, X = OH
(2a) $R^1 = R^2 = F$, X = SH
(2b) $R^1 = R^2 = F$, X = OH
(3) $R^1 = Cl$, $R^2 = F$, X = SH



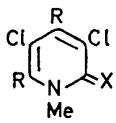
(4)
a ; X = SH
b ; X = OH



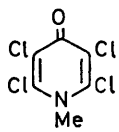
(5) X = S, R = Cl
(6) X = S, R = F
(7) X = O, R = Cl
(8) X = O, R = F



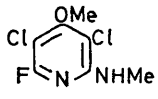
(9) X = SMe, R = Cl
(10) X = OMe, R = Cl
(11a) X = OMe, R = F
(11b) X = OH, R = F



(12) X = S, R = Cl
(13) X = O, R = Cl
(14) X = O, R = F



(15)



(16)

u.v. spectra of polyhalogenopyridinethiols are more difficult to record than those of the corresponding pyridinols because the former compounds are susceptible to oxidation to disulphides. Oxidation is particularly rapid in the case of tetrachloropyridine-2-thiol (4a). Hence, the spectra of the thiols measured may be distorted by the presence of small amounts of the disulphides. For this reason we did not carry out quantitative work.

For comparison purposes, the u.v. spectra of tetrachloropyridin-2-ol (4b) † and its *N*- (13) † and *O*-methyl derivative (10) † were recorded, also in methanol. In agreement with previous work [5] the data suggest that this pyridinol exists predominantly in its enol form. We prepared a mixture of tetrachloro-2-methoxypyridine (10) and tetrachloro-*N*-methylpyridin-2(1*H*)-one (13) from the pyridinol with dimethyl sulphate. Similar treatment of 3,5-dichloro-2,4-difluoropyridin-6-ol (11b) gave a separable mixture of its *N*- (14) and *O*-methyl derivative (11a). A comparison of the u.v. spectra of these compounds † shows that this pyridinol also exists predominantly as an enol in methanol.

In our hands, alkylation of tetrachloro- (1b) and 3,5-dichloro-2,6-difluoro-pyridin-4-ol (2b) with dimethyl sulphate at ambient temperature gave only the corresponding *O*-methyl derivatives, (7) and (8), respectively. Tomlin [13] has shown, however, that a mixture of the *O*- (7) and *N*-methyl derivative (15), of tetrachloropyridin-4-ol is obtained by alkylation with dimethyl sulphate at 90°. The spectra of tetrachloropyridin-4-ol † and its *O*-methyl derivative (7) † are similar and quite different from that of the *N*-methyl derivative (Table 1). Likewise, the spectra of 3,5-dichloro-2,6-difluoropyridin-4-ol † and its *O*-methyl derivative (8) † are similar.

Alkylation of 3,5-dichloro-2,6-difluoropyridin-4-ol with dimethyl sulphate, which involved addition of ammonium hydroxide to destroy the excess of the reagent, gave 3,5-dichloro-2-fluoro-4-methoxy-6-methylaminopyridine (16), identical with a sample prepared from 3,5-dichloro-2,6-difluoro-4-methoxypyridine and methylamine.

An attempt to prepare tetrachloro-*N*-methylpyridin-2(1*H*)-thione (12) from the corresponding oxygen compound (13) and phosphorus pentasulphide failed.

Tetrachloro-*N*-methylpyridin-2(1*H*)-one (13), 3,5-dichloro-2,4-difluoro-*N*-methylpyridin-6(1*H*)-one (14), and tetrachloro-*N*-methylpyridin-4(1*H*)-one (15) are readily distinguishable from their *O*-methyl isomers (10), (11a), and (7) by strong i.r. carbonyl absorptions at 1650, 1680, and 1640 [13] cm^{-1}, respectively. A similar differentiation between tetrachloro-*N*-methylpyridine-2-(1*H*)-thione (12) and tetrachloro-2-methylthiopyridine (9) is not possible because the thiocarbonyl absorption cannot be assigned with certainty. However, as Table 2

TABLE 2

N.m.r. data for *N*- and *S*(or *O*)-methyl derivatives of polyhalogeno-pyridine-2(and 4)-thiols and -pyridin-2-(and 4)-ols

Compound	Solvent	Group	Chemical shift (τ)	Ref.
(12)	$CDCl_3$	NMe	5·63	12
C_6F_5OMe	Me_2CO	OMe	5·92	*a*
			5·88	*b*
(10)	$CDCl_3$	OMe	5·96	
(7)	$CDCl_3$	OMe	5·94	*c*
(11a)	CCl_4	OMe	5·97	
(8)	CCl_4	OMe	5·80	
(13)	$CDCl_3$	NMe	6·21	
Tetrabromo-*N*-methylpyridin-2(1*H*)-one	$CDCl_3$	NMe	6·08	12
(14)	CCl_4	NMe	6·40 (d)	
(9)	$CDCl_3$	SMe	7·43	1
(5)	$CDCl_3$	SMe	7·40	10
(6)	CCl_4	SMe	7·30	11
C_6F_5SMe	Me_2CO	SMe	7·54	*a*
$1,4\text{-}(MeS)_2C_6F_4$	$CDCl_3$	SMe	7·50	14
$1,4\text{-}(MeS)_2C_6Cl_4$	CCl_4	SMe	7·51	14

[a] J. Burdon, *Tetrahedron*, 1965, **21**, 1101. [b] A. G. Massey, E. W. Randall, and D. Shaw, *Chem. and Ind.*, 1963, 1244. [c] R. A. Fernandez, H. Heaney, J. M. Jablonski, K. G. Mason, and T. J. Ward, *J. Chem. Soc.* (*C*), 1969, 1908.

[13] C. D. S. Tomlin, personal communication.

shows, the chemical shift values for the methyl protons in the *N*- and *S*-(or *O*)-methyl derivatives (5)—(14) allow these compounds to be distinguished. Some values for typical fluorine compounds are given also for comparison purposes.

The *N*- and *O*-methyl derivatives of polyhalogenopyridinols (pyridones) are also readily distinguishable by mass spectrometry (Table 3). As expected, the

TABLE 3

Mass spectroscopic data for polyhalogeno-*N*-methylpyridones and -methoxypyridines

Compound	Peak intensities (% of base peak) [a]				
	M^+	M — CHO	M — HCHO	M — COMe	M — CO
(10)	100	100	70	38	
(11a)	100 [b]	100 [b]	50 [b]	47 [b]	
(7)	100			70	5
(8)	75 [b]	5	5	100 [b]	
(13)	100			10	60
(14)	100 [b]			58 [b]	100 [b]

[a] Peaks <5% intensity of base peak not included. [b] Peaks measured by high resolution spectrometry.

N-methyl compounds (13) and (14) (pyridones) fragment by loss of CO followed by Me. In contrast, the *O*-methyl isomers (10) and (11a) do not show a significant peak corresponding to (M — CO) but one corresponding to (M — COMe) is observed in each case. There are significant differences too between the fragmentation patterns of the 2- and 4-methoxy-compounds. While the former lose CHO, HCHO, and COMe (loss of CHO predominates) the latter appear to fragment mainly by loss of COMe.

The mass spectra of tetrachloro-2-methylthiopyridine (9) and tetrachloro-*N*-methylpyridine-2(1*H*)-thione (12) are similar. In the spectrum of the *S*-methyl compound (9) the molecular ion at *m/e* 261 is also the base peak. Peaks at *m/e* 226 (M — Cl, 83%) and 211 (M — CH_3Cl, 13) were prominent. The *N*-methyl compound (12) has its base peak at *m/e* 226 (M — Cl) and shows *m/e* 261 (M^+, 60%) and 211 (M — CH_3Cl, 15). Both compounds give fragments corresponding to loss of SMe. In the case of the *S*-methyl compound (9), however, the peak at *m/e* 214 (M — SMe) is significantly more intense (23%) than in the case of the *N*-methyl compound (12) (6%). Loss of CS does not appear to be important, although a low intensity peak (M — CS, 9%) is present in the spectrum of the pyridinethione (12). The fragmentation patterns of tetrachloro-4-methylthiopyridine (5) and 3,5-dichloro-2,6-difluoro-4-methylthiopyridine (6) are similar to that of compound (9).

It is noteworthy that compounds with the general formula C_6F_5SR give a base peak corresponding to $[C_6F_5S]^{+\cdot}$; polyfluorobenzenes containing two or more methylthio-groups fragment by successive loss of Me.[14,15]

Tetrachloropyridine-2-thiol (4a) (see Table 4) mainly loses Cl while the polyhalogenopyridine-4-thiols (1a), (2a), and (3) appear to fragment mainly by loss of HCl (and HF). Fragmentation by loss of sulphur as CS or CSH is significant only in the case of 3,5-dichloro-2,6-difluoropyridine-4-thiol (2a) (*cf.* ref. 14). By contrast, loss of

TABLE 4

Mass spectroscopic data for polyhalogenopyridinethiols

Compound	Peak intensities (% of base peak) [a]					
	M^+	M — Cl	M — HCl	M — CS	M — CSH	M — HF
(4a)	100 [b]	100 [b]	10	15	5	
(1a)	100	20	100			
(2a)	33	20	100		40	20
(3)	100	30	100		8	12

[a] Peaks <5% of base peak not included. [b] Peaks measured by high resolution spectrometry.

CS is important (78%) in pyridine-2-thione but less so in substituted pyridine-2-thiones.[16]

EXPERIMENTAL

Most of the instruments used are described in Part XXXII.[1] U.v. spectra were recorded in methanol with a Pye SP800 instrument.

Tetrachloropyridine-2-thiol,[1] tetrachloropyridine-4-thiol,[10] 3,5-dichloro-2,6-difluoropyridine-4-thiol,[11] 2,3,5-trichloro-6-fluoropyridine-4-thiol,[11] tetrachloro-2-methylthiopyridine,[1] tetrachloro-4-methylthiopyridine,[10] 3,5-dichloro-2,6-difluoro-4-methylthiopyridine,[11] tetrachloro-*N*-methylpyridine-2(1*H*)-thione,[12] tetrachloropyridin-2-ol,[1] tetrachloropyridin-4-ol,[17] and tetrachloro-4-methoxypyridine [17] were prepared as described previously. 3,5-Dichloro-2,6-difluoropyridin-4-ol was a gift from I.C.I. Ltd., Mond Division. The purity of all the *N*(and *O*)-methylated compounds used in the spectroscopic studies was confirmed by t.l.c. The thiols tail badly on chromatography.

Methylation of Tetrachloropyridin-2-ol with Dimethyl Sulphate.—Dimethyl Sulphate (2·52 g, 20·0 mmol) was added dropwise to a stirred mixture of the pyridinol (3·3 g, 14·2 mmol), anhydrous potassium carbonate (5·0 g), and anhydrous acetone (100 ml) at room temperature, and the resulting mixture was stirred at room temperature overnight, then filtered. Distillation of the solvent and the excess of reagent under reduced pressure gave a product (4·2 g) which was chromatographed on silica. Light petroleum (b.p. 60—80°) eluted tetrachloro-2-methoxypyridine (10) (2·6 g, 74%), m.p. 89—90° (from aqueous ethanol) (lit.,[18] 91°) and tetrachloro-*N*-methylpyridin-2(1*H*)-one (13) (0·7 g, 20%), m.p. 147—148° (from ethanol) (lit.,[19] 148·5—149·5°), $\nu_{max.}$ (Nujol) 1650 cm^{-1} (C:O), τ ($CDCl_3$) 6·21 (s, Me).

Methylation of 3,5-Dichloro-2,4-difluoropyridin-6-ol with Dimethyl Sulphate.—The reaction was carried out as in the preceding experiment. The crude product was chromatographed on silica gel. Benzene eluted (i) a viscous oil, which n.m.r. [τ ($CDCl_3$) 5·97 (s, Me)] and mass spectroscopy (Found: M^+, 212·9562. Calc. for $C_6H_3Cl_2F_2NO$: M, 212·9559) showed to be 3,5-dichloro-2,4-difluoro-6-methoxypyridine (11a) (41%) and (ii) a solid, m.p. 81—82° (from ethanol), which i.r. [$\nu_{max.}$ (Nujol) 1680 cm^{-1}

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(C:O)], n.m.r. [τ (CCl_4) 6·40 (d, J 3·0 Hz), Me], and mass spectroscopy (Found: M^+, 212·9551. Calc. for $C_6H_3Cl_2F_2NO$: M, 212·9559) showed to be 3,5-dichloro-2,4-difluoro-*N*-methylpyridin-2(1*H*)-one (14) (15%).

3,5-Dichloro-2,6-difluoro-4-methoxypyridine (8) (52%), b.p. 38—42° at 0·7 mmHg (lit.,[20] 92—93° at 12·8 mmHg), τ (CCl_4) 5·80 (s, Me) (Found: M^+, 212·9560. Calc. for $C_6H_3Cl_2F_2NO$: M, 212·9559) was prepared similarly.

3,5-*Dichloro*-2-*fluoro*-4-*methoxy*-6-*methylaminopyridine* (16).—(*a*) Dimethyl sulphate (2·52 g, 20·0 mmol) was added dropwise to a stirred mixture of 3,5-dichloro-2,6-difluoropyridin-4-ol (2·0 g, 10·0 mmol), anhydrous potassium carbonate (2·0 g), and anhydrous acetone (100 ml) at room temperature, and the resulting mixture was stirred at room temperature overnight. 4N-Ammonium hydroxide (20 ml) was added and the mixture was stirred for a further 4 h. The mixture was then filtered, and extraction with chloroform followed by distillation of the solvent gave an oil (3·2 g) which was chromatographed on silica. Light petroleum (b.p. 60—80°) eluted the *methylaminopyridine* (16) (0·65 g, 29%), m.p. 76·5—77° (from methanol), τ ($CDCl_3$) 5·00br (1H, s, exchangeable, NH), 6·02 (3H, s, OMe), and 6·98 (3H, d, J 5·0 Hz, NMe), $\nu_{max.}$ (Nujol) 3460 cm^{-1} (NH) (Found: C, 37·9; H, 3·4; N, 12·8%; M^+, 223·9914. $C_7H_7Cl_2FN_2O$ requires C, 37·4; H, 3·1; N, 12·5%; M, 223·9919).

(*b*) A solution of methylamine (0·69 g, 22·0 mmol) in ethanol (20 ml) was added dropwise to a stirred solution of 3,5-dichloro-2,6-difluoro-4-methoxypyridine (2·14 g, 10 mmol) in ethanol (20 ml) at 0°, the mixture was stirred at room temperature for 30 min, then heated under reflux for 30 min. The mixture was cooled, concentrated to *ca.* 20 ml by distillation of the solvent under reduced pressure, and diluted with water (50 ml), to yield a precipitate of the *product* (2·0 g, 89%), m.p. 74—76°, identical (i.r. and n.m.r. spectra) with the sample prepared in (*a*).

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