Synthetic Applications of N–N Linked Heterocycles. Part 12.[1] The Preparation of 4-Alkylthio- and 4-Arylthio-pyridines by Regiospecific Attack of Thioalkoxide Ions on *N*-(4-Oxopyridin-1-yl)pyridinium Salts[2]

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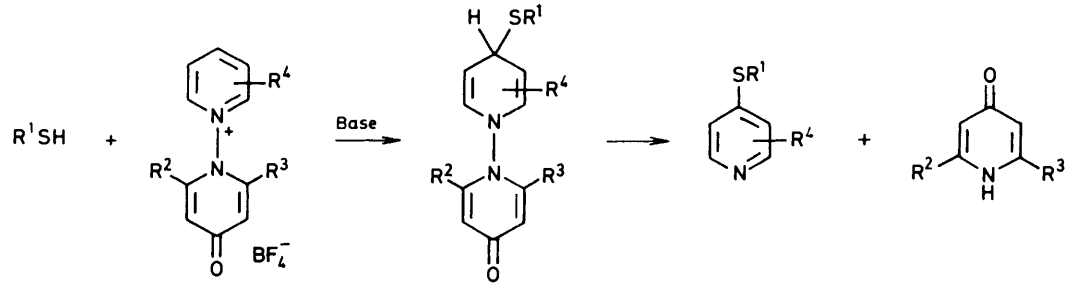
Thiolate ions add regiospecifically to *N*-(4-oxopyridin-1-yl)pyridinium salts (2)—(7) to give in good to excellent yields only the 1,4-dihydropyridine adducts (8)—(13), regardless of whether or not the pyridone moiety carries substituents for sterically shielding the 2- and 6-positions of the pyridinium ring. The addition is believed to be thermodynamically controlled. Decomposition of the dihydro-adducts under free-radical conditions, or by pyrolysis, gives good yields of pyridin-4-yl thioethers (14) and (16) though the reaction failed with the 2-methyl adducts (9). An improved synthesis of 6-methyl-4-oxopyran-2-carboxylic acid is also described.

In a recent paper[2] we gave a preliminary account of the synthesis of five classes of 4-substituted pyridines, including the thioethers (14) *via* regiospecific attack of nucleophiles on the *N*-(2,6-dimethyl-4-oxopyridin-1-yl)-pyridinium salt (2). The methyl groups on the pyridone moiety direct the nucleophile to the 4-position of the pyridinium ring by sterically shielding the 2- and 6-positions. The resulting 1,4-dihydro-intermediates [*e.g.* (8)] may then be fragmented to give 4-substituted pyridines and the pyridone (17).



	R²	R³	R⁴		R²	R³	R⁴		R⁴		R²	R³
(1)	(2)	Me	Me	H	(8)	Me	Me	H	(14)	H	(17)	Me	Me
	(3)	Me	Me	2-Me	(9)	Me	Me	2-Me	(15)	2-Me	(18)	H	H
	(4)	Me	Me	3-Me	(10)	Me	Me	3-Me	(16)	3-Me	(19)	Me	H
	(5)	H	H	H	(11)	H	H	H			(20)	Ph	H
	(6)	H	Me	H	(12)	H	Me	H					
	(7)	H	Ph	H	(13)	H	Ph	H					

We report now in full (*a*) the synthesis by this method of the pyridin-4-yl thioethers (14) and (16), (*b*) a comparison between different methods for decomposing the dihydro-intermediates (8)—(10), and (*c*) the effect of varying the pyridone substituents R^2 and R^3 on the course of the reaction.

Most syntheses of pyridin-4-yl thioethers have been from pyridines already bearing a 4-substituent. In one group of methods, a 4-thiopyridone (or its anion) has been reacted with an active halide[3] or conjugated ester or nitrile.[4] In a second group of methods a 4-halogeno-,[5] 4-phenoxy-,[6] or 4-pyridinio-pyridine[7] has been treated with a thiol (or its anion). Although attack of thiolate anions on *N*-alkoxy-pyridinium salts lacking a 4-substituent does give a small amount of the pyridin-4-yl thioether, it is in admixture with larger amounts of the 3-isomer, and substantial quantities of product resulting from attack of the nucleophile on the alkoxy-group.[8] The presence of ring methyl groups in the *N*-alkoxy-pyridinium salts leads to more complex mixtures.[9] Treatment of pyridine *N*-oxides with thiols in the presence of acyl or sulphonyl halides, or acyl anhydrides gave mixtures of pyridin-2-yl and pyridin-3-yl thioethers,[8b,10] but, with one exception, none of the 4-isomer was detected.

RESULTS AND DISCUSSION

Preparation of 1,4-*Dihydro-intermediates* (8)—(10).—The addition of 2 mol of a thiol (1) in the equivalent amount of 2M aqueous sodium hydroxide to 1 mol of a 4-oxopyridinyl-pyridinium salt (2)—(4) in water at 25 °C (Method A), gave on subsequent cooling a precipitate of the corresponding 1,4-dihydro-intermediate (8)—(10). However, these dihydro-intermediates could be prepared

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in generally higher yields in acetonitrile using sodium ethoxide as the base (Method B), when only a slight excess of the thiol (1) was required. It is probable that the stronger base in conjunction with the enhanced pK_a of thiols * in non-aqueous media,[11] shifts the equilibrium for formation of the 1,4-dihydro-intermediate to the hydrolysed. Unlike analogous dihydro-intermediates isolated in earlier parts of this work,[12] compounds (8) were generally sufficiently stable to be purified and characterised by microanalysis,‡ though with one exception (10k) those derived from salts (3) and (4) were too unstable. Most contained various amounts of water

TABLE 1

Preparative details and yields for dihydro-intermediates (8)—(13) and for pyridin-4-yl thioethers (14)—(16)

R¹	R²	R³	R⁴	Intermediate	Method of preparation [a]	Temp. (°C)	Yield (%)	Product	Conditions [b]	Time/h	Yield (%)
Et	Me	Me	H	(8a)	A	25	45	(14a)	C	19	60
				(8a)	B	25	74				
Bu^n	Me	Me	H	(8b)	A	25	58	(14b)	C	14	91
				(8b)	B	25	76				
Cyclohexyl	Me	Me	H	(8c)	A	25	70	(14c)	C	14	83
				(8c)	B	25	85	(14c)	D	14	88
$PhCH_2$	Me	Me	H	(8d)	A	25	89	(14d)	C	14	90
				(8d)	B	25	80	(14d)	E	14	78
								(14d)	D	14	89
								(14d)	G	1	26
$MeOCOCH_2$	Me	Me	H	(8e)	A	0	53	(14e)	D	15	99
				(8e)	B	25	77	(14e)	C	7	88
$EtOCOCH_2$	Me	Me	H	(8f)	A	0	64	(14f)	C	7	92
				(8f)	B	25	75	(14f)	E	3.5	54
								(14f)	F	3.5	36
								(14f)	G	1	18
$MeOCO(CH_2)_2$	Me	Me	H	(8g)	A	10	76	(14g)	D	13	96
				(8g)	B	25	87				
Furfuryl	Me	Me	H	(8h)	A	25	68	(14h)	C	14	80
				(8h)	B	25	62				
Ph	Me	Me	H	(8i)	A	25	75	(14i)	C	14	80
				(8i)	B	25	89	(14i)	E	14	88
4-MeC_6H_4	Me	Me	H	(8j)	A	0	70	(14j)	C	14	92
				(8j)	B	25	71	(14j)	E	4	89
								(14j)	G	1	67
4-ClC_6H_4	Me	Me	H	(8k)	A	25	83	(14k)	C	14	84
				(8k)	B	25	75	(14k)	G	1	83
								(14k)	D	14	96
2-$NH_2C_6H_4$	Me	Me	H	(8l)	A	25	66	*c*			
				(8l)	B	0	88				
4-Br,3-MeC_6H_3	Me	Me	H	(8m)	A	25	72	(14m)	E	18	87
				(8m)	B	0	72				
N-Me-Imidazol-2-yl	Me	Me	H	(8n)	A	25	0	*c*			
				(8n)	B	25	82				
4-ClC_6H_4	Me	Me	2-Me	(9k)	B	25	59	*d*			
Et	Me	Me	3-Me	(10a)	B	25	49	(16a)	C	16	86
4-ClC_6H_4	Me	Me	3-Me	(10k)	B	25	62	(16k)	C	16	83
Et	H	H	H	(11a)	B	25	74	(14a)	C	16	10
$PhCH_2$	H	H	H	(11d)	B	25	19	(14d)	C	16	24
4-ClC_6H_4	H	H	H	(11k)	B	25	76	(14k)	C	16	30
Et	Me	H	H	(12a)	B	25	27	(14a)	C	16	48
$PhCH_2$	Me	H	H	(12d)	A	25	61 [e]	(14d)	G	1	22
4-ClC_6H_4	Me	H	H	(12k)	B	25	34	(14k)	C	16	66
$PhCH_2$	Ph	H	H	(13d)	A	25	76	*f*			
4-MeC_6H_4	Ph	H	H	(13j)	A	25	51	*f*			

[a] Method A, NaOH–H_2O; Method B, NaOEt–EtOH–MeCN. [b] Method C, reflux in CCl_4 with initiator; Method D, reflux in CCl_4–CH_2Cl_2 (75 : 25) with initiator; Method E, reflux in CCl_4–MeOH (75 : 25), no initiator; Method F, reflux in CCl_4 without initiator; Method G, vacuum sublimation, 120 °C at 0.1 mmHg. [c] Only black tars isolated under all conditions attempted. [d] Decomposition of intermediate (9k) gave only complex mixtures. [e] Two rotational isomers, ratio 56 : 44 (see Figure). [f] The decomposition of intermediates (13) was not investigated.

right.† This would explain the successful formation of the intermediate (8n) from 1-methylimidazole-2-thione in acetonitrile, while the reaction failed in water, in which this anion would presumably be extensively (broad signal in ^1H n.m.r. spectra near δ 2.4) which could not be removed without decomposing the intermediate. Yields of intermediates prepared by the two methods are given in Table 1, and physical and analytical data in Table 2.

Fragmentation of Dihydro-intermediates into Pyridin-4-yl Thioethers (14) and (16) (*Tables* 1 *and* 3).—Initially,

* Thiol pK_a values show a linear correlation with carbon basicities, measured as thermodynamic affinities for 1,3,5-trinitrobenzene (M. R. Crampton, *J. Chem. Soc. B*, 1971, 2112).

† Zoltewicz and co-workers have demonstrated the reversibility of the addition of thiolate anions to pyridinium salts in liquid ammonia (J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.*, 1976, **41**, 1308).

‡ A stable 1,4-dihydro-intermediate was isolated by Okamoto and co-workers [13] from the addition of methanethiolate anion to 1-(*N*-methylacetamido)pyridinium iodide.

considerable difficulty was experienced in fragmenting the dihydro-intermediates into the desired products. Although the decomposition of intermediates from the addition of cyanide ion appeared to be catalysed by borate and the intermediate (8j) gave *p*-tolyl triphenylmethyl thioether (21).

Vacuum sublimation of the intermediates was more successful, the desired product condensing in good yields

TABLE 2

Physical and analytical data for dihydro-intermediates (8), (10k), and (12k)

Compound	R^1	R^2	R^3	R^4	M.p. (°C) [a]	Crystal form	$M^{+\cdot}$	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(8a)	Et	Me	Me	H	102—103	plates	262	60.4	7.1	10.3	$C_{14}H_{18}N_2OS\cdot H_2O$	60.0	7.2	10.0
(8b)	Bu^n	Me	Me	H	98—99	plates	290	62.2	7.8	8.9	$C_{16}H_{22}N_2OS\cdot H_2O$	62.3	7.8	9.1
(8c)	Cyclohexyl	Me	Me	H	117—118	prisms	316	64.4	7.7	8.3	$C_{18}H_{24}N_2OS\cdot H_2O$	64.6	7.8	8.4
(8d)	$PhCH_2$	Me	Me	H	116—117	prisms	324	66.9	6.1	8.3	$C_{19}H_{20}N_2OS\cdot H_2O$	66.7	6.4	8.2
(8e)	$MeOCOCH_2$	Me	Me	H	110	plates	306	56.9	6.1	8.9	$C_{15}H_{18}N_2O_3S\cdot \frac{1}{2}H_2O$	57.1	6.1	8.9
(8f)	$EtOCOCH_2$	Me	Me	H	101—102	plates	320	58.2	6.2	8.4	$C_{16}H_{20}N_2O_3S\cdot \frac{1}{2}H_2O$	58.3	6.4	8.5
(8g)	$MeOCO(CH_2)_2$	Me	Me	H	70—71	plates	320	57.7	6.3	8.4	$C_{16}H_{20}N_2O_3S\cdot \frac{3}{4}H_2O$	57.8	6.5	8.4
(8h)	Furfuryl	Me	Me	H	113—114	plates	314	62.2	6.0	8.7	$C_{17}H_{18}N_2O_2S\cdot H_2O$	62.2	6.0	8.5
(8i)	Ph	Me	Me	H	107—108	plates	310	65.2	6.2	8.4	$C_{18}H_{18}N_2OS\cdot \frac{2}{3}H_2O$	65.2	6.2	8.5
(8j)	$4\text{-}MeC_6H_4$	Me	Me	H	118—119	prisms	324	66.1	6.2	8.2	$C_{19}H_{20}N_2OS\cdot \frac{2}{3}H_2O$	66.1	6.5	8.1
(8k)	$4\text{-}ClC_6H_4$	Me	Me	H	115	prisms	344—346	60.3	5.0	7.9	$C_{18}H_{17}ClN_2OS\cdot \frac{2}{3}H_2O$	60.6	5.2	7.8
(8l)	$2\text{-}NH_2C_6H_4$	Me	Me	H	115—116	prisms	325	[b]						
(8m)	$4\text{-}Br,3\text{-}MeC_6H_3$	Me	Me	H	99—100	prisms	402—404	55.5	5.1	6.7	$C_{19}H_{19}BrN_2OS\cdot \frac{1}{2}H_2O$	55.3	4.9	6.8
(10k)	$4\text{-}ClC_6H_4$	Me	Me	3-Me	103—104	prisms	358—360	63.8	5.3	7.8	$C_{19}H_{19}ClN_2OS$	63.6	5.3	7.8
(12k)	$4\text{-}ClC_6H_4$	Me	H	H	53.5—54.5	prisms	330—332	[b]						

[a] From CH_2Cl_2 and light petroleum (b.p. 60—80 °C), see text. [b] Too unstable for satisfactory microanalysis.

base,[14] neither aqueous sodium hydroxide, nor sodium ethoxide in ethanol converted compounds (8) into the thioethers (14). Both Brønsted (ethanolic HCl), and Lewis acids (PhCOCl; BF_3 in methanol; $Ph_3C^+ BF_4^-$) caused a reversal of the addition reaction to the parent pyridinium salt (2) and the thiol (or its derivative). Thus the reaction between triphenylmethyl tetrafluoro-

in the cases of aryl thioethers [*e.g.* from compounds (8j) and (8k), Table 1], but in low yield in other cases [*e.g.* from compounds (8d) and (8f)].

The observation that dihydro-intermediates from the addition of enolate anions to the pyridinium salts (2)—(4) were readily fragmented under free-radical conditions, [12b] suggested a similar approach here. Prolonged periods

TABLE 3

Physical and analytical data for pyridin-4-yl thioethers (14) and (16)

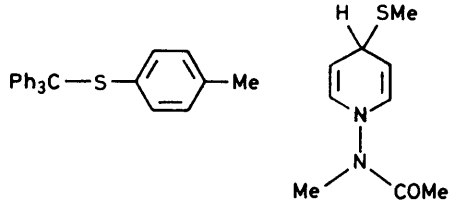
Compound	R^1	R^4	Picrate derivative [a] M.p. (°C)	Crystal form	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(14a)	Et	H	144—145 [b]	needles	42.4	3.5	15.2	$C_{13}H_{12}N_4O_7S$	42.4	3.3	15.2
(14b)	Bu^n	H	112—113 [c]	needles	45.3	4.4	13.9	$C_{15}H_{16}N_4O_7S$	45.5	4.1	14.1
(14c)	Cyclohexyl	H	173—174	plates	48.5	4.3	13.3	$C_{17}H_{18}N_4O_7S$	48.3	4.3	13.3
(14d)	$PhCH_2$	H	67—68 [d,e]	prisms	71.5	5.5	6.8	$C_{12}H_{11}NS$ [d]	71.6	5.5	7.0
(14e)	$MeOCOCH_2$ [f]	H	139—140	needles	41.0	3.2	13.3	$C_{14}H_{12}N_4O_9S$	40.8	2.9	13.6
(14f)	$EtOCOCH_2$ [g]	H	104—105	needles	42.5	3.5	13.3	$C_{15}H_{14}N_4O_9S$	42.3	3.3	13.1
(14g)	$MeOCO(CH_2)_2$	H	155—156 [h]	plates				$C_{15}H_{14}N_4O_9S$	42.3	3.3	13.1
(14h)	Furfuryl	H	120—121	prisms	45.5	3.0	13.4	$C_{16}H_{12}N_4O_8S$	45.7	2.9	13.3
(14i)	Ph	H	165.5—166.5 [i]	needles	49.2	3.1	13.2	$C_{17}H_{12}N_4O_7S$	49.0	2.9	13.4
(14j)	$4\text{-}MeC_6H_4$	H	50—51 [d]	prisms	71.7	5.4	7.1	$C_{12}H_{11}NS$ [d]	71.6	5.5	7.0
(14k)	$4\text{-}ClC_6H_4$	H	53—54 [d,j]	prisms	59.6	3.7	6.4	$C_{11}H_8ClNS$ [d]	59.6	3.6	6.3
(14m)	$3\text{-}Br,4\text{-}MeC_6H_4$	H	193—194	needles	42.6	2.7	10.7	$C_{18}H_{13}BrN_4O_7S$	42.4	2.6	11.0
(16a)	Et	3-Me	150—151	plates	44.3	4.0	14.8	$C_{14}H_{14}N_4O_7S$	44.0	3.7	14.7
(16k)	$4\text{-}ClC_6H_4$	3-Me	50—51 [d]	prisms	61.4	4.4	6.0	$C_{12}H_{10}ClNS$ [d]	61.1	4.3	5.9

[a] Recrystallised from 95% EtOH. [b] Lit., 146 °C (A. M. Comrie, *J. Chem. Soc.*, 1963, 688). [c] Lit.,[6] 106—108 °C. [d] Physical and analytical data refer to the pyridin-4-yl thioether, and not to the picrate derivative. [e] Lit., 69—71 °C. Only N analysis reported previously (J. E. Cranham, W. A. W. Cummings, A. M. Johnston, and H. A. Stevenson, *J. Sci. Food Agric.*, 1958, **9**, 143). [f] Reported previously [3a] in crude form only. [g] Reported [7] b.p. 128—129 °C at 1 mmHg. [h] Lit.,[4] 152—154 °C (decomp.). [i] Lit.,[5a] 166.5 °C. [j] Lit., 54—56° [N. V. Philips' Gloeilampenfabrieken, Belg. P. 618,679/1962 (*Chem. Abstr.*, 1963, **59**, 9999*b*)].

of reflux proved to be successful in three different solvent systems, namely in CCl_4 with an initiator (Method C); in CCl_4–CH_2Cl_2 with an initiator (Method D); and CCl_4–MeOH without an initiator (Method E). Results shown in Table 1 indicate that Methods C and D were the most generally effective; while Method E was equally successful with intermediates from arene thiols, yields were substantially lower in other cases. One reaction carried out in CCl_4 alone (Method F) [see (14f), Table 1] showed the importance of the initiator. All methods, however, failed to fragment intermediates (8l) and (8n) successfully, only black tars being isolated. Also, attempts to prepare the 2-methyl derivative (15k) from the intermediate (9k) gave only complex mixtures.

Thus, preparation of dihydro-intermediates by Method B, and their subsequent decomposition by Methods C or D makes pyridin-4-yl thioethers, uncontaminated by other isomers, available in 54—90% overall yields from pyridinium salts (2)—(4).

Effect of Varying the Pyridone Substituents R^2 *and* R^3.—1,4-Dihydropyridines are thermodynamically more stable than the 1,2-isomers,[15] though the latter are generally formed from pyridinium salts under conditions of kinetic control. In view of the indications that addition of thiolate anions to the pyridinium salts (2)—(4) was reversible, it seemed possible that 1,4-dihydro-intermediates might be formed from the pyridinium salts, even when groups R_2 and R_3 were too small to sterically shield the pyridinium 2- and 6-positions. Any 1,2-dihydro-intermediate formed might rearrange subsequently to the 1,4-isomer. A similar effect had been observed [14] with cyanide as the nucleophile,* and Okamoto and his co-workers found only the 1,4-dihydro-intermediate (22) from the addition of methanethiolate anion to 1-(*N*-



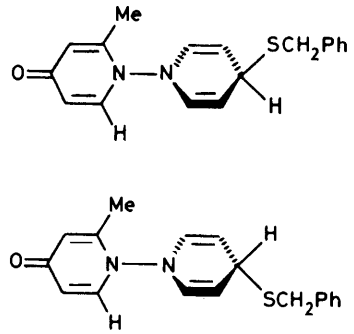
(21) (22)

methylacetamido)pyridinium iodide.[13] Therefore pyridinium salts (5), (6), and (7), having R^2 = H, and R^3 = H, Me, and Ph, respectively, were treated with thiolate ions, and as can be seen from Table 1, intermediates (11)—(13) were isolated, some in very good yield [*e.g.* (11a), (11k), and (13d)].† This result appears to substantiate the reversibility of thiolate addition under the conditions described here.

Where fragmentations of intermediates (11) and (12) to thioethers (14) were attempted, yields were always smaller than those from intermediates (8), showing that the salts (5)—(7) are less useful than the 2,6-dimethyl analogue (2) in the preparation of pyridin-4-yl thioethers.

Spectroscopic Data.—*1,4-Dihydro-intermediates* (8)—(13). As observed with analogous compounds,[14] u.v. spectra were dominated by absorption due to the pyridone chromophore ($\lambda_{max.}$ near 262 nm; log ε 4.25—4.40). The i.r. spectra showed the expected pyridone absorptions ($\nu_{max.}$ 1 650—1 630, 1 560—1 535 cm^{-1}) and a band assigned to ν(C=C) for the dihydropyridine ring near 1 680 cm^{-1}.[12b]

Integrals of ^1H n.m.r. spectra ($CDCl_3$) showed the compounds to be essentially pure. For the 1,4-dihydropyridine ring, the 2- and 6-protons gave a broadened doublet ($J_{2,3}$ 8 Hz) between δ 5.85—6.25, the 3- and 5-protons a double doublet ($J_{2,3}$ 8 Hz; $J_{3,4}$ 4 Hz) between 4.80—5.05, and the 4-proton as a multiplet between 4.55—4.68 for R^1 = aryl, and 4.22—4.44 in other cases. 2-Methyl and 3-methyl groups for compounds (9) and (10) appeared as broadened singlets between δ 1.45 and 1.90, respectively. For the pyridone ring in compounds (8)—(10), 3-H and 5-H gave a broadened singlet between δ 5.93—6.12, while the 2- and 6-methyl groups showed evidence of restricted rotation about the N–N bond. Thus, for intermediates having R^1 = aryl, a broad signal (close to coalescence) was observed centred between δ 1.5—1.9, while for other substituents, two separate signals, centred respectively near δ 2.2 and 2.3, were found. Further measurements by variable-temperature n.m.r. are planned. For intermediates (11), 2-H and 6-H in the pyridone ring gave a broadened doublet near δ 6.8, again indicative of restricted rotation, while the 2-methyl group in compound (12d) appeared as two singlets of unequal intensity (δ 2.2 and 2.15), corresponding to the two isomers arising from restricted rotation about the N–N bond (Figure).‡ The 2-phenyl derivatives (13) appeared to comprise single isomers, the steric bulk of the phenyl group probably increasing



Isomers of intermediate (12d) arising from restricted rotation about the N–N bond

substantially the energy difference between the two possible rotamers.

Mass spectra were dominated by fragmentations into the ions derived from products (14)—(16) and (17)—(20).

* For nucleophiles which add non-reversibly to give relatively stable dihydro-intermediates, we have found that regiospecific attack at the pyridinium 4-position occurs only when neither R^2 nor R^3 are hydrogen (unpublished results).

† Intermediates derived from salts (5), (6), and (7) all proved to be too unstable for microanalysis, but were identified from their i.r. and ^1H n.m.r. spectra.

‡ Doubling of other groups of lines in the spectrum of (12d) supported the presence of two isomers.

Pyridin-4-yl thioethers (14) *and* (16). Spectroscopic data were fully consistent with the proposed structures, and in the case of ^{1}H n.m.r. spectra, matched well with published data.[10a,16] Thus the pyridine ring protons in compounds (14) showed an AA'XX' system, the 2- and 6-protons being centred between δ 8.1—8.5, and the 3- and 5-protons between δ 6.5—7.2.

EXPERIMENTAL

U.v. spectra were recorded in absolute MeOH on a Beckman Acta CIII spectrophotometer; i.r. spectra as liquid films or in Nujol on a Perkin-Elmer 577 instrument; ^{1}H n.m.r. spectra on a Perkin-Elmer R-20 spectrometer as solutions in $CDCl_3$ with $SiMe_4$ as internal reference; and mass spectra on a Hitachi RMS-4 instrument.

Thiols (1) were used as supplied by manufacturers, and (4-oxopyridin-1-yl)pyridinium salts (2)—(5) prepared as described previously.[17] The preparation of salt (6) is described in full as it includes an improvement on Dorman's synthesis [18] of 6-methyl-4-oxopyran-2-carboxylic acid.

Preparation of N-(2-*Methyl*-4-*oxopyridin*-1-*yl*)*pyridinium Tetrafluoroborate* (6).—1-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*propan*-2-*one*. Pentane-2,4-dione (100 g, 1.0 mol), ethylene glycol (41.5 g, 0.67 mol), and toluene-*p*-sulphonic acid (3 g) were heated in dry THF (500 ml) under brisk reflux for 6 h, such that the condensed vapours passed through molecular sieves (3A; 150 g) in a Soxhlet apparatus before returning to the flask. The solution was cooled, stirred vigorously with anhydrous K_2CO_3 (15 g) for 10 min (essential), and filtered. Removal of the solvent at 80 °C *in vacuo* gave a light brown oil, which was combined with the product from an identical run and fractionated under reduced pressure using a 40-cm vacuum-jacketed Vigreux column. A forerun comprising mostly unreacted pentane-2,4-dione was collected between 60—137 °C at 155 mmHg. The main fraction (137—147 °C at 155 mmHg) comprised the desired monoacetal (92 g, 0.64 mol; 64% based on unrecovered pentane-2,4-dione); δ 3.98 (4 H, s,), 2.76 (2 H, s), 2.20 (3 H, s), and 1.39 (3 H, s); and the diacetal of pentane-2,4-dione (10 g, 0.05 mol; 7.5%); δ 3.94 (8 H, s), 2.00 (2, H s), and 1.39 (6 H, s). The residue (25 g) was mostly the diacetal.

This modification of Dorman's method [18] suppresses entirely the formation of 2-acetoxyethanol and gives a higher yield of the monoacetal, which can be used directly in the next step without separation from the diacetal.

Methyl 2,4-*dioxo*-6-(*ethylenedioxy*)*heptanoate*. A solution of sodium (17.6 g, 0.77 mol) in absolute MeOH (400 ml) was cooled to 5 °C, and with vigorous stirring the product from the previous step (102 g), and diethyl oxalate (109 g, 0.74 mol) in absolute MeOH was added during 30 min. The mixture was stirred at 0 °C (1 h), 25 °C (3 h), and left to stand overnight. The yellow suspension was cooled to 5 °C, and with stirring an ice-cold solution of H_2SO_4 (27.5 ml) in water (175 ml) added. The product was diluted with water (450 ml), extracted with $CHCl_3$ (4 × 300 ml), the $CHCl_3$ extracts washed with water (2 × 300 ml), dried ($MgSO_4$),* and the solvent removed (80 °C; *in vacuo*). The residual oil (166 g) contained the product (90% pure by ^{1}H n.m.r., essentially quantitative); δ 6.48 (1 H, s), 3.98 (4 H, s), 3.90 (3 H, s), 2.83 (2 H, s) ,and 1.43 (3 H, s); together with a small amount of diacetal from the previous step.

* The use of $MgSO_4$ in place of the recommended [18] K_2CO_3 gives a much cleaner product, and in higher yield.

† This is one-third of the quantity used by Dorman.[18]

6-*Methyl*-4-*oxopyran*-2-*carboxylic acid*. The product from the previous step was stirred with 0.5M HCl (1.4 l) † for 16 h at 25 °C, the resulting suspension being refluxed for 3 h. Cooling of the mixture to 25 °C, and then in ice for 3 h, gave the pyrone-carboxylic acid (66 g), a further quantity (13 g) being isolated on concentrating the filtrate to 400 ml and cooling again. Total yield 79 g (80% based on the monoacetal, 51% based on unrecovered pentane-2,4-dione); m.p. 256—257 °C (EtOH) [lit.,[18] 256—256.7 °C]; $\nu_{max.}$ 3 080, 2 420 (vbr), 1 900 (vbr), 1 752, 1 645, and 985 cm^{-1}; δ [$(CD_3)_2SO$] 9.1 (1 H, s, br), 6.82 (1 H, d, *J* 2.1 Hz), 6.35 (1 H, m), and 2.33 (3 H, d, *J* 0.9 Hz).

N-(2-*Methyl*-4-*oxopyridin*-1-*yl*)*pyridinium tetrafluoroborate* (6). 1-Aminopyridinium chloride (12 g, 0.092 mol), and 6-methyl-4-oxopyran-2-carboxylic acid (12.3 g, 0.083 mol) in concentrated HCl (80 ml) were refluxed together in a 500-ml flask (considerable foaming) for 72 h. The dark product was treated with charcoal (2 g), filtered hot, evaporated to dryness and the residue heated with aqueous HBF_4 (35%; 20 g, 0.08 mol) and absolute EtOH (25 ml). The solution was evaporated to dryness and the gummy product triturated with absolute EtOH (50 ml) to give the *pyridinium salt* (6), (17 g; 77%) as white prisms, m.p. 206—207 °C (95% EtOH) (Found: C, 48.1; H, 4.1; N, 10.1. $C_{11}H_{11}BF_4N_2O$ requires C, 48.2; H, 4.0; N, 10.2%); $\nu_{max.}$ 3 020, 1 630, 1 560, 1 480, and 1 060 cm^{-1}; δ (D_2O) 9.46 (2 H, d), 9.10 (1 H, t) ,8.52 (2 H, t), 8.20 (1 H, d), 6.60 (2 H, d), and 2.16 (3 H, s).

N-(2-*Phenyl*-4-*oxopyridin*-1-*yl*)*pyridinium Tetrafluoroborate* (7).—This was prepared from 1-aminopyridinium chloride and 2-phenyl-4-oxopyran, which in turn was synthesised by the following sequence of reactions. Methyl 2,4-dioxo-6-phenylhex-5-enoate, prepared [19] (50%) by the reaction between 1-phenylbut-1-en-3-one and diethyl oxalate in methanolic NaOMe, was treated with Br_2 in $CHCl_3$ at −1 to −2 °C to give methyl 5,6-dibromo-2,4-dioxo-6-phenylhexanoate (75%).[20] Reaction of this with anhydrous KOAc in absolute EtOH at 50 °C for 24 h gave [20] ethyl 6-phenyl-4-oxopyran-2-carboxylate (88%), which was hydrolysed [20] by refluxing in concentrated HCl (1 h) to give 6-phenyl-4-oxopyran-2-carboxylic acid (95%). Pyrolysis of the acid in the presence of Cu powder at 2 mmHg,[21] followed by sublimation of the product (110 °C, 0.05 mmHg) gave 2-phenyl-4-oxopyran (55%) as white needles, m.p. 104 °C (lit.,[21] 104 °C).

1-Aminopyridinium chloride (1.3 g, 0.01 mol) was refluxed in concentrated HCl, using an oil bath heated at 130 °C. 2-Phenyl-4-oxopyran (1.7 g, 0.01 mol) was added in seven equal portions over seven days, and refluxing continued for a second week.‡ The dark mixture was evaporated to dryness, and the residue triturated repeatedly with portions of absolute EtOH, the insoluble tar being rejected. The EtOH solution was stirred vigorously, and dry ether added dropwise to precipitate the product as the chloride.§ The hygroscopic product was separated and dissolved in water, the counter ion being changed to ClO_4^- on an ion-exchange column. Evaporation of the eluate and recrystallisation gave the *pyridinium perchlorate* (7) as white prisms (0.28 g, 8%), m.p. 216—219 °C (95% EtOH) (Found: C, 53.8; H, 3.8; N, 7.9. $C_{16}H_{13}ClN_2O_5 \cdot 0.5\ H_2O$ requires C, 53.7;

‡ Ten different solvent systems, and a variety of acidic and basic catalysts were tried at different temperatures. Only the conditions described here gave the desired product.

§ Addition of too much ether results in precipitation of unreacted 1-aminopyridinium chloride.

H, 3.9; N, 7.8%); $\nu_{max.}$ 3 030, 1 638, 1 583, and 1 088 cm^{-1}; δ [D_2O] 9.36 (2 H, d), 8.79 (1 H, t), 8.31 (2 H, t), 8.14 (1 H, d), 7.37 (5 H, m), and 6.74 (2 H, m).

Preparation of 1,4-*Dihydro-intermediates* (8)—(13).—*Method A.* To a solution of the appropriate thiol [(1); 0.002 mol] in 1M NaOH (2 ml), was added all at once, with vigorous stirring, a solution of the appropriate pyridinium salt (0.001 mol) in water (3 ml). The mixture was stirred in an ice-bath for 30 min, filtered, and the residue washed well with dry ether to remove excess of thiol. Products were recrystallised by dissolution in CH_2Cl_2, decolourisation with charcoal if necessary, and re-precipitation by slow addition of light petroleum (b.p. 60—80 °C) with stirring. Yields, and physical and analytical data, are given in Tables 1 and 2.

Method B. To a vigorously stirred suspension of the appropriate pyridinium salt (0.001 mol) in dry MeCN (8 ml), was added dropwise a solution of the appropriate thiol [(1); 0.0012 mol] in ethanolic NaOEt (1.2 ml; 1M). The clear red mixture was stirred for a further 15 min, evaporated to dryness *in vacuo* at 25 °C, and the residue purified as for Method A.

Fragmentation of Dihydro-intermediates to Pyridin-4-yl Thioethers (14)—(16).—*Method C.* The appropriate intermediate from the previous step was suspended in dry CCl_4 (30 ml), azoisobutyronitrile (AIBN) (0.01 g) added, and the mixture heated under reflux for 7—14 h (see Table 1). The cooled mixture was filtered, the filtrate extracted with 2M HCl (20 ml), and the acid layer basified to pH 8 with K_2CO_3. The thioether was extracted into CCl_4 (3 × 15 ml), the extracts dried ($MgSO_4$) and the solvent removed under reduced pressure. Products were recrystallised from light petroleum (b.p. 60—80 °C) if solids, or if oils, converted to picrates in the usual fashion. Physical and analytical data for thioethers are given in Table 3.

Method D. As for Method C, only a mixture of CCl_4 and CH_2Cl_2 (75 : 25) was used in place of pure CCl_4.

Method E. As for Method C, only a mixture of CCl_4 and MeOH (75 : 25) was used as solvent, and no AIBN was added.

Method F. As for Method C, only no AIBN added.

Method G. The dihydro-intermediate was sublimed at 120 °C and 0.1 mmHg, the thioether being collected on a cold finger, essentially pure. Further purification and characterisation was carried out as for Method C.

Attempted Decomposition Using Ph_3CBF_4.—The intermediate (8j) (0.34 g, 0.001 mol) in dry CH_2Cl_2 (5 ml) was treated with a solution of Ph_3CBF_4 (0.36 g, 0.0011 mol) also in dry CH_2Cl_2 (5 ml), and the precipitated salt (2) (0.23 g; 84%) filtered off. Evaporation of the filtrate, and separation of the yellow residue by t.l.c. on alumina using light petroleum (b.p. 60—80 °C) gave triphenylmethanol; the thioether (21) (187 mg; 51%), m.p. 145—146 °C (lit.,[22] 149 °C), δ [$CDCl_3$] 7.5—7.1 (15 H, m), 6.83 (4 H, s), and 2.20 (3 H, s); and also some di-*p*-tolyl disulphide.

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