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ISOTHIAZOLE CHEMISTRY—X

ACYLATION, ALKYLATION AND TAUTOMERISM IN 3-HYDROXYISOTHIAZOLE

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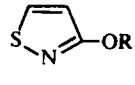
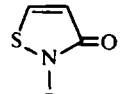
Abstract— 3-Hydroxyisothiazole exists as the lactim in nonpolar solvents, the lactam form predominating in aqueous solution. Acylation, although extremely rapid in nonpolar solvents, depends on the relative rates of reaction of the two tautomers rather than on their relative proportions. The size of the acyl group, and the steric requirements of the catalyst, are shown to be the critical factors in determining the site of acylation. Alkylation of 3-hydroxyisothiazole leads to mixtures of products, the 3-alkoxyisothiazoles predominating. No migration of the alkyl group is observed.

INTRODUCTION

IN connection with our interest in the reactivity of the S—N bond in 3-isothiazolones,[1,2] a requirement for various N-substituted derivatives (II) led us to examine acylation[3] and alkylation of the potentially tautomeric 3-hydroxyisothiazole (I ⇌ II, R = H). The first 3-hydroxyisothiazole to be synthesized was the 5-phenyl derivative,[4] which was assigned the lactim structure on the grounds that its UV spectrum resembled that of 3-methoxy-5-phenylisothiazole; the corresponding N-methylated derivative was not available at that time to complete the comparison.



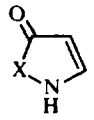
I



II

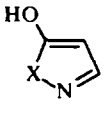
Few topics have produced more conflicting claims and counter-claims than that of lactim-lactam tautomerism in compounds containing the structural feature —Ẍ—C=O, both cyclic and acyclic. Katritzky and Lagowski[5] have collated and discussed the evidence for a large number of heterocyclics in recent articles. In the adjacent-atom 5-ring heterocycles the isoxazol-5-ones[6] and the 1-substituted pyrazolin-5-ones[7a] have been examined in some detail. The position can be broadly summarized as predominance of the form IIIc in nonpolar media, with variable contributions from IIIa and (to a lesser extent) IIIb in solvents of higher polarity. The position of equilibrium is also influenced by substituents, however, and it is clear that generalizations should be avoided. The 3-oxygenated derivatives, on the other hand, have been shown to exist as the 3-hydroxyisoxazoles[8] and 3-hydroxypyrazoles[7b] IVb in nonpolar media, with contributions from the lactam forms IVa increasing in polar solvents.

Early workers in the tautomerism field sought to establish the equilibrium position by "freezing" the system with a rapid reaction, followed by product analysis. The requirements for validity of this approach were in general not recognised, i.e. (1) that the rate of reaction of both tautomers be greater than the rate of their interconversion, and (2) that there should be no rapid interconversion of products.

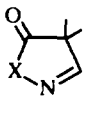


IIIa

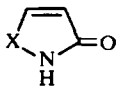
(X = O or NR)



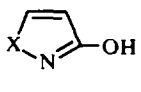
IIIb



IIIc



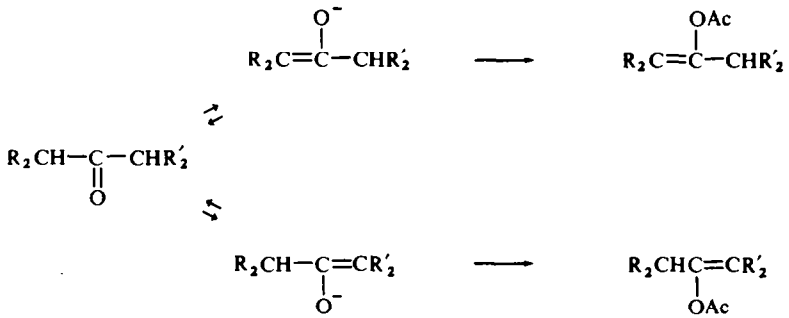
IVa



IVb

A case in which both criteria appear to be met is the determination of enolate ratios* in unsymmetrical ketones by quenching with excess acetic anhydride.[9]

Acylation of 3-hydroxyisothiazole with $Et_3N/RCOCl$ in benzene gave every indication of being an extremely rapid reaction, even at 4°, and should therefore be a reliable estimate of the lactam-lactim ratio. Although we have found[3] a relatively slow acyl migration in the products, the rate was insufficient to materially effect the results of even a leisurely analysis of the acylation products.



Rapid analysis of the acylation products from 3-hydroxyisothiazole indicated a high proportion of O-acylation, but there was evidence for the operation of steric factors, and it seemed desirable to probe more deeply into the reaction mechanism.

Lactam-Lactim tautomerism in 3-hydroxyisothiazole

A range of 3-alkoxyisothiazoles and N-alkyl-3-isothiazolones was available from alkylation studies (*vide infra*), and the UV spectra of these two classes of compound differed substantially. The way was thus open to approximate estimation of K_T =

* This particular information was of considerable interest to us in connection with the selectivity of carbanion attack on the S—N bond in N-alkyl-3-isothiazolones.

[lactim]/[lactam] by the routine method.† In cyclohexane the spectra of I (R = Et) and 3-hydroxyisothiazole were essentially the same, and differed substantially from that of II (R = Et) (Fig 1a). There is little doubt that in this type of solvent the potentially tautomeric system is entirely in the lactim form; similar results were obtained in ether solution. In ethanol 3-hydroxyisothiazole showed a shoulder at 275 nm, characteristic of the N-alkyl-3-isothiazolones, and this became more pronounced as the solvent composition was changed to pure water. The extremes are presented in Fig 1b and 1c, and values for K_T are given for intermediate compositions.

It should be stressed that these findings apply only to the parent 3-hydroxyisothiazole itself, although we have also made a limited examination of the 5-methyl derivative with essentially similar conclusions (Figs 1d, e). Comparison of Figs 1a–e shows that the absorption maxima for the fixed N-alkyl derivatives undergo a hypsochromic shift with increasing polarity of the solvent. This is consistent with stabilization of a dipolar form in the ground state by solvation, and thus with the observed tendency of the lactam form to predominate in aqueous solution.

Essentially similar conclusions can be reached from consideration of PMR data. The fixed alkyl derivatives represent the only available models for chemical shifts and coupling constants in the lactam and lactim forms, and it is assumed that these models are valid. In Table 1 are listed the chemical shifts and coupling constants for

TABLE 1

Compound	$CDCl_3$			DMSO			CH_3OH		
	H_4	H_5	J_{45}	H_4	H_5	J_{45}	H_4	H_5	J_{45}
I R = Me	3·31	1·53	4·6	3·25	1·12	4·7	3·38	1·32	4·6
II R = Me	3·73	1·95	6·1	3·81	1·55	6·3	3·76	1·55	6·2
I/II R = H	3·32	1·54	4·6	3·41	1·22	5·1	3·47	1·37	5·0
K_T	40	40	—	2·5	3·3	3·0	3·2	3·6	3·0
		Large			2·9			3·3	

a number of solvents. Calculation of K_T from the data for methanol solution shows fair agreement with the value obtained from UV data, although no particular attempt was made to obtain accurate chemical shifts at infinite dilution. The sharpness of the peaks obtained confirms that the rate of lactam-lactim interconversion is rapid. As to whether it might be rapid enough on the NMR time scale to materially affect the product yields in a reaction as rapid as acylation was a point of some interest.

Acylation of 3-hydroxyisothiazole

Acylation of I (R = H) has been shown earlier[3] to result largely in electrophilic attack at oxygen, with relatively little N-acyl-3-isothiazolone formed. The small contribution from attack at nitrogen became negligible as the size of the acyl group

* Similar acyl migrations have been reported by Curtin[10] and by Taylor[11] in the acylation of 2-pyridone, and coincide with our own observations in this system.

† 3-Hydroxyisothiazole is weakly acid (pKa ~ 7), but almost nonbasic (pKa = −0·33). In order to supress ionisation, measurements in aqueous media were carried out at pH 4.

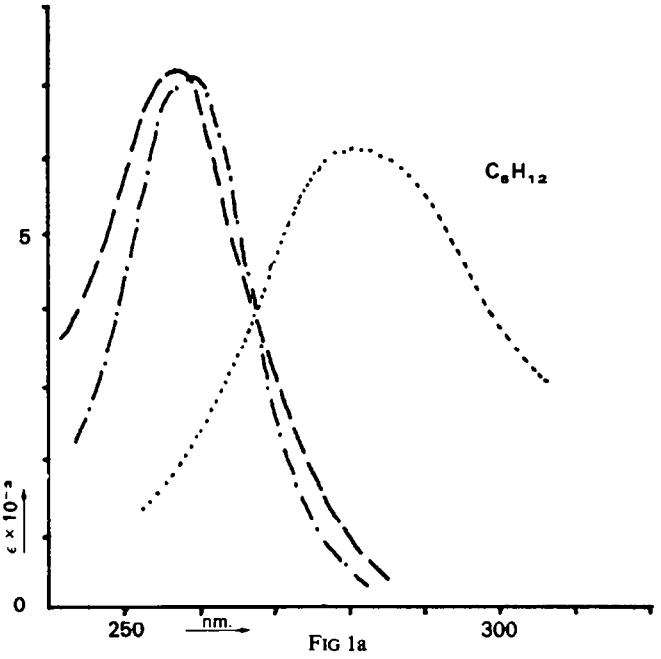

C_6H_{12}
5
0
$\epsilon \times 10^{-3}$
250
nm.
300

FIG 1a

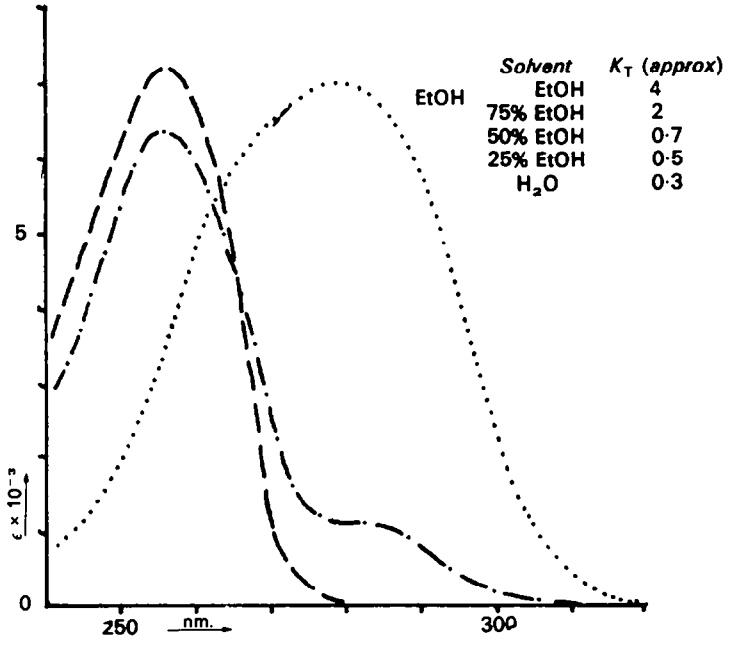

EtOH
Solvent
K_T (approx)
EtOH 4
75% EtOH 2
50% EtOH 0·7
25% EtOH 0·5
H_2O 0·3
5
0
$\epsilon \times 10^{-3}$
250
nm.
300

FIG 1b

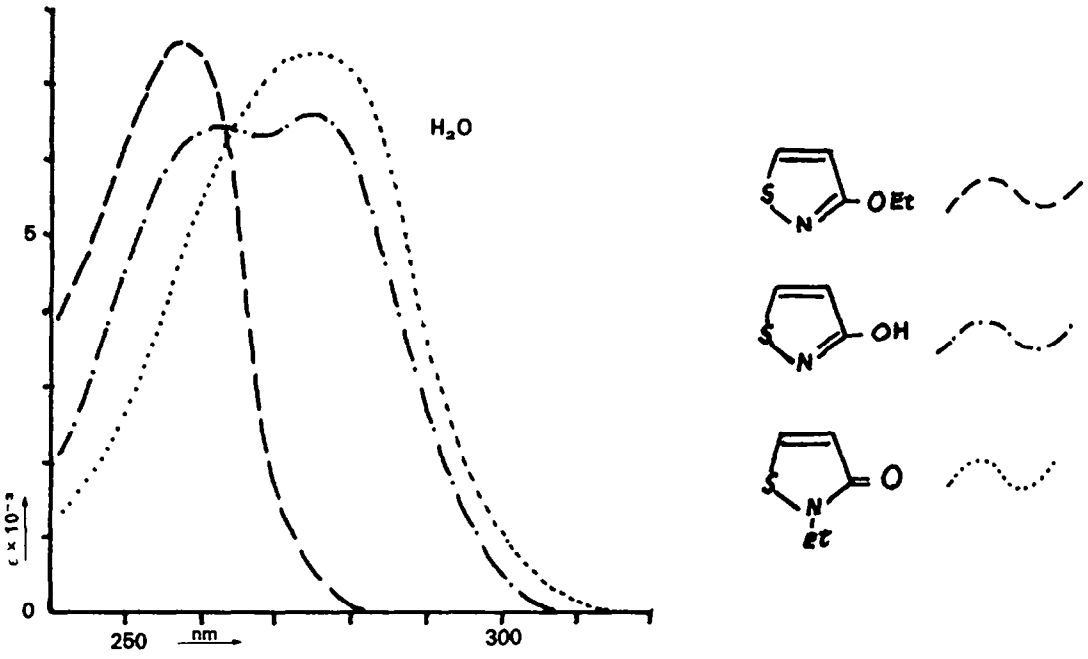


FIG 1c

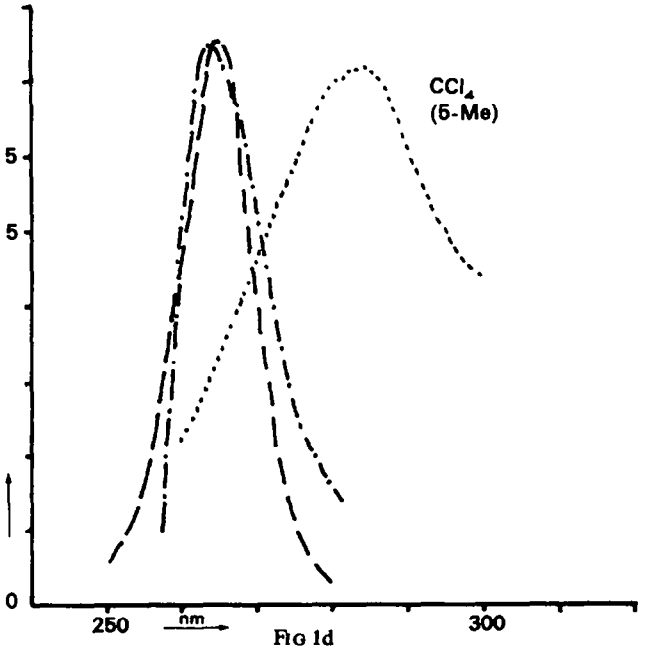


FIG 1d

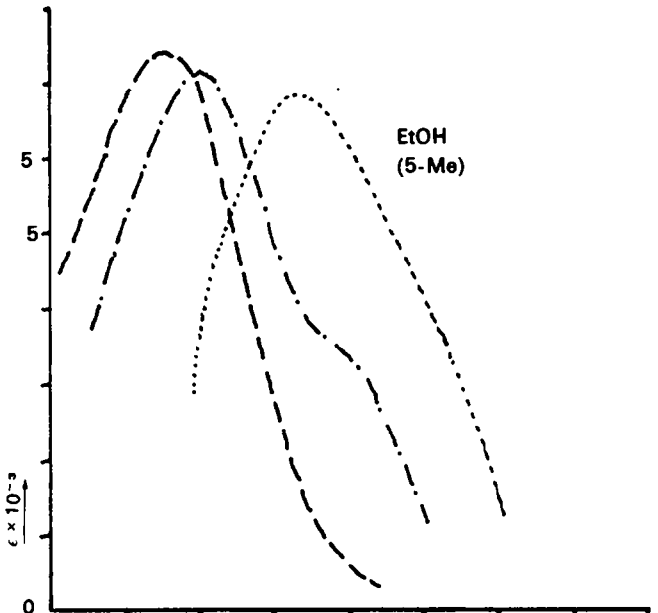
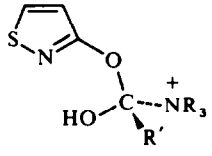


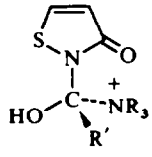
FIG 1e

was increased. Subsequent acyl migration O ⇌ N could be readily induced by nucleophiles, and established that the initial results were not due to product stability control of acylation, although the same steric factors were seen to be operative in the equilibration process.

The transition site for base-catalyzed acylation[12] is generally accepted to involve attack in the acylammonium cation,[13] as shown in V and VI for the substrates I and II (R = H). Examination of Dreiding models showed that, even when R′ is small (Me) there is more steric crowding in VI, i.e. N-acylation would be discriminated against on a kinetic basis. Such discrimination should be aggravated by any increase in



V



VI

the size of the alkyl group R′ or the base catalyst R_3N, and both effects may be observed. Table 2 shows the product ratios measured immediately after acylation, using triethylamine as the base catalyst. Although there is a systematic increase in O-acylation with the size of R′, it is small compared to the corresponding effect in the equilibrium ratio. The acylation results are obviously due to kinetic control, and the ratio of O:N acylation happens to coincide with the observed lactim/lactam ratio. A study of the effect of base size on the ratio, however, serves to dispel any notion

that the technique could be used to establish the lactim/lactam ratio in I. Acetylation using trimethylamine, and pyridine as the base catalysts gives O:N ratios of 4 and 0·8 respectively. It is evident that the rates of acylation are not sufficiently greater than the rate of tautomerization, and that therefore the O:N acylation ratio is not controlled by the lactim/lactam ratio, but by the relative rates of reaction of these two species.

TABLE 2

Acylating agent	% O-Acyl	% N-Acyl	Ratio O:N	Equilibrium Ratio
$CH_3COCl/Et_3N/C_6H_6$	92	8	11·5	0·33
$CH_3CH_2COCl/Et_3N/C_6H_6$	95	5	19	0·5
$CH_3CH_2CH_2COCl/C_6H_6$	95	5	19	0·62
$(CH_3)_3COCl/Et_3N/C_6H_6$	100	0	∝	∝
CH_2CO^*/CCl_4	0	100	0·0	0·33
$CH_3COCl/pyr./C_6H_6$	45	55	0·8	0·33
$CH_3COCl/Me_3N/C_6H_6$	80	20	4	0·33

* It has been claimed that acetylation with CH_3COCl/base systems occurs *via* ketene production.[14] Reaction with ketene gas is slow, due to the impossibility of adding a mole equivalent of ketene all at once, thus some acyl migration could be expected (due to unacylated I). The results in Table 3 differ from both the acetyl chloride and equilibrium results, indicating that ketene is not the reactive intermediate in this case, at least.

When acylation was carried out with acid anhydrides in the absence of a tertiary base catalyst[3] (i.e. R_3N^+ in V and VI is replaced by —O—CO—R′) the lower steric requirement resulted in substantially increased N-acylation, although the steric effect of R′ was still apparent.

Alkylation of 3-hydroxyisothiazole

The action of diazomethane in ether on I (R = H) gave approximately equal proportions of N- and O-alkylation products (55:45). Both products were inert to the action of either methyl iodide or 3-hydroxyisothiazole, i.e. N ⇌ O migration did not occur. In this solvent system K_T is large, so it is apparent that the product ratio must again be controlled by faster reaction at N, and rapid tautomerization of the substrate.* The use of triethyloxonium fluoborate, a much bulkier reagent, resulted in 70% O-alkylation, a not unexpected result in the light of the preceding acylation studies.

Alkylation of ambident anions has recently been investigated by Tieckelmann and coworkers,[15] who suggest that the problem of O *vs* N alkylation might be less complex than has been indicated. Similar alkylation of metal salts of 3-hydroxyisothiazole gave the results in Table 4. Although the results are incomplete, there is sufficient data to indicate a fairly complex interplay between solvent, metal counterion, and

* The necessity for tautomerization is more apparent than real. In fact there is no compelling reason to believe that 3-hydroxyisothiazole does not coordinate with the electrophile through the tertiary nitrogen, followed by proton loss from oxygen. i.e. the "tautomerization" occurs simultaneously with electrophilic attack.

TABLE 3

		Solvent							
		DMSO		DMF		MeCN		DME	
R-X	M^+	O	N	O	N	O	N	O	N
MeI	K^+	46	54	41	59	40	60	20	80
	Ag^+	68	32	—	—	—	—	—	—
	Li^+	34	66	17	83	—	—	—	—
EtI	K^+	25	25	77	23	70	30	50	50
	Li^+	—	—	55	45	—	—	—	—
Pr Br	K^+	78	22	80	20	80	20	—	—
iPr Br	K^+	88	12	—	—	86	14	—	—
Ba Br	K^+	80	20	81	19	80	20	78	22
$\emptyset CH_2Cl$	K^+	68	32	59	41	45	55	34	66
Me $O_2C(CH_2)_3Br$	K^+	77	23	—	—	78	22	—	—
EtCHBrCOOMe	K^+	87	13	—	—	84	16	—	—

TABLE 4. PMR DATA (τ C/S) OF 3-ALKYLOXYISOTHIAZOLES[a] AND N-ALKYL-3-ISOTHIAZOLONES[b]

R	H_4	H_5	Other Signals	B.P. 0°/mm
		O-Alkylation		
n-Pr	3·48	1·64	5·67 (T, 2H), 7·86–8·45 (M, 2H), 8·95 (T, 3H)	58/2
i-Pr	3·51	1·64	4·51–5·12 (M, 1H), 8·66 (D. 6H)	53/1
n-Bu	3·49	1·68	5·66 (T, 2H), 7·97–9·2 (M, 7H)	60/2
$COOMe(CH_2)_3$	3·50	1·61	5·61 (T, 2H), 6·37 (S, 3H), 7·38–8·18 (M, 4H)	92–94/0·3
$COOEtCHCH_2CH_3$	3·40	1·64	4·92 (T, 1H), 5·87 (Q, 2H), 7·81–8·32 (M, 2H), 8·6–9·14 (2T, 6H)	91–93/0·6
		N-Alkylation		
n-Pr	3·75	1·81	6·22 (T, 2H), 7·9–8·6 (M. 2H), 9·04 (T, 3H)	[c]
i-Pr	3·75	1·83	4·85–5·5 (M, 1H), 8·59 (D, 6H)	[c]
n-Bu	3·77	1·84	6·21 (T, 2H), 7·96–9·2 (M, 7H)	[c]
$COOMe(CH_2)_3$	3·74	1·82	6·13 (T, 2H), 6·30 (3H, S), 7·35–8·2 (M, 4H)	[c]
$COOEtCHCH_2CH_3$	3·75	1·82	5·52–5·95 (1Q & 1T, 3H) 7·8–8·3 (M, 2H) 8·55–9·2 (2H, 6H)	[c]

[a] in CCl_4 ($J_{4,5}$ = 3·6 c/s)
[b] in $CDCl_3$ ($J_{4,5}$ = 6·4 c/s)
[c] B.P. above 130°/0·1 mm; decomposed above this temperature.
D = Doublet; M = Multiplet; Q = Quartet; S = Singlet; T = Triplet.

size of the reagent.* The significant point which emerges is the preference for O-alkylation, enhanced by increase in the size of the alkylating reagent. Once again, it is clear that K_T plays little or no part in the O:N alkylation ratio.

CONCLUSIONS

3-Hydroxyisothiazole exists as such in nonpolar solutions, with increasing contributions from the 3-isothiazolone tautomer as the dielectric constant of the solvent is increased. Even in nonpolar solvents, however, acylation and alkylation reactions are controlled by the relative rates of attack by the two nucleophilic centres in the molecule, not by the lactam/lactim ratio. This probably means that the two forms interchange more rapidly than they react with the electrophiles, but it is not mandatory that this should be the case. It will be seen for example that the alkylation ratios with diazomethane and triethyloxonium fluoborate (in which 3-hydroxyisothiazole is the substrate) do not materially differ from those with methyl and ethyl iodides respectively (in which the 3-oxyisothiazole anion is the substrate and no prototropic shift is required.)

EXPERIMENTAL

All m.ps and b.ps are uncorrected. UV and IR spectra were measured on Beckmann DK-2A and Unicam SP200G instruments; the latter were as Nujol mulls unless otherwise stated. PMR spectra were recorded in deuterochloroform on a 60 Mhz Perkin Elmer R.10 spectrometer unless otherwise stated, and results are quoted in units.

Acylation of 3-hydroxyisothiazole

3-Hydroxyisothiazole (1·01 g, 0·01 mole) in benzene (50 ml) was treated with the appropriate base (0·01 mole) and cooled to incipient crystallization of the solvent. An ice-cooled soln of the acid chloride (0·01 mole) in benzene (25 ml) was added all at once. The soln was shaken for a minute, the base hydrochloride (~98–100% yield) filtered off, and the solvent removed on a rotary film evaporator at 30–40°. The residual oil was immediately analysed by PMR. No change in composition was apparent when the measurements were repeated after some 30 min standing. The 3-acyloxyisothiazoles and N-acyl-3-isothiazoles have been reported in an earlier paper.[3]

Acetylation of 2-1(H)-pyridone

The reaction was carried out as described above, and resulted in 46% 2-acetoxypyridine and 54% N-acetyl-2-1(*H*)-pyridone (PMR analysis). Acetylation of the thallium salt at −40° is reported to give a 60:40 mixture of these compounds. In contrast to the previous work, only a slow N O migration was observed in d^6-DMSO, and after 24 hr a mixture containing 92% 2-acetoxypyridine was obtained. The rate of migration was accelerated (~10%) by addition of 2-1(*H*)-pyridone, suggesting that the heterogeneous nature of earlier experiments had resulted in incomplete reaction.

Alkylation of 3-hydroxyisothiazole

(1) *Diazomethane.* An ethereal soln of diazomethane (slight excess, freshly distilled) was added to 3-hydroxyisothiazole (3 g) in ether, cooled to 0°. N_2 was evolved immediately. The mixture was concentrated to 15 ml and chromatographed over alumina. Removal of ether from the eluates, and distillation of the residual oil gave 3-*methoxyisothiazole* (48%) as a colourless oil b.p. 142–144°. (Found: C, 41·7; H, 4·4; N, 12·4. C_4H_5NOS requires: C, 41·7; H, 4·4; N, 12·2%); UV (96% EtOH): λ_{max} 255 nm (7300); IR (Film): 3130, 3000, 2960, 1880, 1539, 1500, 1452, 1401, 1380, 1231, 1052, 1020, 921, 829, 811, 746, 664 cm^{-1}; PMR (CCl_4): 1·62–3·49 (*d*'s; H,H; J = 4·6, 6·00 (*s*, 3H). Further elution of the column with chloroform gave N-methyl-3-isothiazolone[1] (43%).

* It will be noted that the hardness of the leaving group in the alkylating reagent has not been investigated. Murphy and Buckley[15] have recently shown that this is also a factor which influences the rate of alkylation in ambident species.

(2) *Triethyloxonium fluoborate.* the reagent (0·035 mole) was prepared in CH_2Cl_2 as described by Pacquette,[17] and added gradually to a cold soln of 3-hydroxyisothiazole (3 g, 0·03 mole) in dry CH_2Cl_2 (60 ml). After stirring overnight the soln was treated with 5N K_2CO_3, filtered, and the aqueous layer extracted with ether. The combined organic solvents were evaporated, and the residue chromatographed over alumina as described above. 3-*Ethoxyisothiazole* (60%) distilled at 147–149°. (Found: C, 46·7; H, 5·4; N, 10·9. C_5H_7NOS requires: C, 46·5; H, 5·5; N, 10·9%); UV (96% EtOH): λ_{max} 255 nm (7350); IR (film): 3130, 3000, 2880, 1531, 1480, 1424, 1381, 1350, 1230, 1055, 1035, 980, 881, 840, 810, 744, 682, 664 cm^{-1}; PMR (CCl_4): 1·60–3·46 (*d*'s; H, H; J = 4·6), 5·58 (*q*, 2H), 8·61 (*t*, 3H). N-Ethyl-3-isothiazolone[1] was obtained in 30% yield.

(3) *Alkyl halide/metal salts.* 3-Hydroxyisothiazole (0·5 g, 0·005 mole) and anhyd K_2CO_3 (0·36 g, 0·0026 mole—finely ground) were placed in a dry 50 ml ampoule with the appropriate solvent (3 ml) and the alkyl halide (0·007 mole), sealed and heated in a constant temp (±2°) bath. Methylation and ethylation in DMSO or DMF was 100% in 24 hr at 35°, but other alkyl halides required longer (48–60 hr at 50°). The corresponding conditions for MeCN or DME were 48 hr at 40° to 65 hr at 65°. PMR Analysis was carried out immediately on opening the ampoule, and products were isolated as described above. The silver and lithium salt alkylations were performed in the same way. PMR data are summarized in Table 5

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