Radical–Nucleophilic Substitution ($S_{RN}1$) Reactions. Part 2.[1] Preparation and Reactions of α-Nitrosulphides

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A range of α-nitrosulphides [$Me_2C(SR)NO_2$, with R = 2-pyridyl, pyrimidin-2-yl, 1,3-benzothiazol-2-yl, 1-methylimidazol-2-yl, and 4,5-dihydro-1,3-thiazol-2-yl] have been prepared by oxidative addition of thiolate anion to the anion of 2-nitropropane, S_N2 attack of the anion of 2-nitropropane on symmetrical disulphides, and $S_{RN}1$ reaction of 2-substituted-2-nitropropanes with thiolate anions. The α-nitrosulphides undergo $S_{RN}1$ substitution with the anion of 2-nitropropane, and $S_{RN}1$ substitution or redox reactions with thiolate anions. The electron spin resonance (e.s.r.) spectrum of the radical-anion of 1-methyl-1-nitroethyl pyrimidin-2-yl sulphide has been observed.

Thiolate anions have been shown to react with various aliphatic α-substituted nitro compounds [1-3] to yield α-nitrosulphides by substitution of the α-substituent (X) or disulphides by oxidative dimerisation [equations (1) and (2)].

$$R^1{}_2C(X)NO_2 + R^2S^- \longrightarrow R^1{}_2C(SR^2)NO_2 + X^- \quad (1)$$

$$R^1{}_2C(X)NO_2 + 2R^2S^- \longrightarrow R^1{}_2CNO_2{}^- + R^2SSR^2 + X^- \quad (2)$$

The substitution reaction is favoured by thiolates derived from relatively acidic thiols [1,2] and proceeds by a radical radical-anion chain ($S_{RN}1$)[4,5] mechanism (Scheme 1a). On the other hand the redox reaction is favoured by thiolates derived from relatively less acidic thiols and proceeds by an ionic abstraction [X-philic[6] or $S_N2(X)$] mechanism [1] (Scheme 2a). A possible alternative redox mechanism proceeding by single-electron transfer (S.E.T.) has been suggested [2c] (Scheme 2b).

The competition between the two routes of reaction is influenced by two factors, namely the nucleophilicity of the thiolate and the nature of the α-substituent (X). The more nucleophilic the thiolate and the easier the abstraction of the α-substituent (*e.g.* I > SCN > Br > Cl > NO_2) the more disulphide formation is favoured, and *vice-versa* for the formation of the α-nitrosulphide.

2-Azido-2-nitropropane [7] and 2-cyano-2-nitropropane [5b] react with *p*-chlorophenylthiolate and phenylthiolate respectively, by an analogous $S_{RN}1$ mechanism with substitution of nitrite instead of the α-substituent (X) (Scheme 1b).

Our initial investigations [1,2a] indicated that certain α-nitrosulphides were particularly susceptible to reaction with strongly nucleophilic thiolates to yield disulphides, a factor which is of medicinal importance. Most α-substituted nitro compounds exhibit good antimicrobial activity.[8] This activity has been shown [9] to be due to the ability of these compounds to oxidise protein thiolates to the corresponding disulphides, thus killing the micro-organisms by denaturing essential proteins in the cell.

The antimicrobial activity [8] of 2-substituted-2-nitropropanes also correlates well with the ease of abstraction of the α-substituent by thiolates and the rate at which they undergo $S_{RN}1$ reactions (I > Br > Cl > NO_2). Our earlier work [1,2] had shown, as expected, that the rate of both $S_{RN}1$ and redox reactions increased markedly with increasing electron-withdrawing power of substituents on the aryl portion of aryl 1-methyl-1-nitroethyl sulphides (*e.g.* *p*-NO_2 > *o*-NO_2 > *p*-Cl). We therefore sought to prepare and study a range of new α-nitrosulphides which would have similar or improved reactivity in $S_{RN}1$ and redox reactions and thus possibly exhibit high antimicrobial activity.

α-Nitrosulphides derived from acidic thiols with α-heteroatoms appeared to offer an interesting, and potentially reactive, group of compounds. This paper details the synthesis and novel radical-anion reactions of a range of new hetero α-nitrosulphides

(a) and (b) $Me_2C(X)NO_2 + RS^- \overset{\text{S.E.T.}}{\rightleftharpoons} [Me_2C(X)NO_2]^{\cdot-} + RS^{\cdot}$ (Initiation)

(a) X = I, Br, Cl, NO_2, SCN

$$[Me_2C(X)NO_2]^{\cdot-} \rightleftharpoons Me_2\dot{C}NO_2 + X^-$$
$$Me_2\dot{C}NO_2 + RS^- \rightleftharpoons [Me_2C(SR)NO_2]^{\cdot-}$$
$$[Me_2C(SR)NO_2]^{\cdot-} + Me_2C(X)NO_2 \rightleftharpoons Me_2C(SR)NO_2 + [Me_2C(X)NO_2]^{\cdot-}$$

} (Propagation)

(b) X = CN, N_3

$$[Me_2C(X)NO_2]^{\cdot-} \rightleftharpoons Me_2\dot{C}X + NO_2^-$$
$$Me_2\dot{C}X + RS^- \rightleftharpoons [Me_2C(SR)X]^{\cdot-}$$
$$[Me_2C(SR)X]^{\cdot-} + Me_2C(X)NO_2 \overset{\text{S.E.T.}}{\rightleftharpoons} Me_2C(SR)X + [Me_2C(X)NO_2]^{\cdot-}$$

} (Propagation)

Scheme 1.

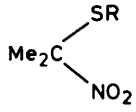
(a) $Me_2C(X)NO_2 + RS^- \longrightarrow Me_2CNO_2{}^- + RSX$ (S_N2 on X)

(b) $Me_2C(X)NO_2 + RS^- \overset{\text{S.E.T.}}{\rightleftharpoons} [Me_2C(X)\dot{N}O_2{}^-RS^{\cdot}]_{\text{solvent cage}} \longrightarrow Me_2CNO_2{}^- + RSX$

(a) and (b) $RS^- + RSX \longrightarrow RSSR + X^-$ (S_N2 on S)

Scheme 2.

(**1a**—**f**). Compounds (**1a**) and (**1c**) show excellent antifungal activity but only moderate antibacterial activity. The other compounds (**1d**, **e**, and **f**) show moderate activity against both fungi and bacteria. A study of their mode of action is underway and the results so far indicate the same mode of action as the 2-halogeno-2-nitropropanes. Full details of the antimicrobial activity of these compounds will be published in the near future.



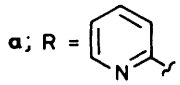
(**1**)

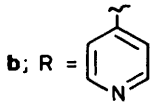
RSSR

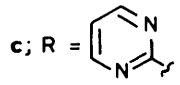
(**2**)

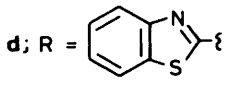
RS^-

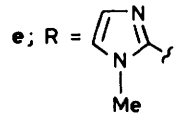
(**3**)

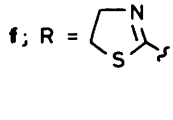


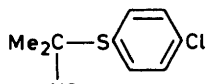












(**4**)

Results and Discussion

Preparation of α-Nitrosulphides.—(a) *Oxidative addition of thiolates to the anion of 2-nitropropane.* A number of α-substituted nitro compounds have been prepared by oxidative addition of the respective anion to the anions of aliphatic nitro compounds using potassium ferricyanide [$K_3Fe(CN)_6$] [2b,10] as the oxidant. We have also reported [2a] that *p*-chlorophenyl 1-methyl-1-nitroethyl sulphide (**4**) can be synthesised in high yield (72%) by this method. Further application of the procedure gave good yields (40—70%) of the target compounds (**1a**—**f**). The mechanism of oxidative addition is shown in Scheme 3.

$$Me_2CNO_2^- + Fe^{III} \longrightarrow Me_2\dot{C}NO_2 + Fe^{II}$$
$$Me_2\dot{C}NO_2 + RS^- \longrightarrow [Me_2C(SR)NO_2]^{-\cdot}$$
$$[Me_2C(SR)NO_2]^{-\cdot} + Fe^{III} \longrightarrow Me_2C(SR)NO_2 + Fe^{II}$$
$$\text{Summary: } Me_2CNO_2^- + RS^- \longrightarrow Me_2C(SR)NO_2 + 2e^-$$

Scheme 3.

α-Nitrosulphides (**1c**—**f**) were obtained in high purity after work-up, but in the reactions with 2- and 4-pyridylthiolates large amounts of the corresponding disulphides and traces of 2,3-dimethyl-2,3-dinitrobutane (**5**) were also obtained.

Several aspects of the mechanism need to be considered. First it is possible that the ferricyanide initially oxidises the thiolate anion instead of the nitro-anion, and that the resulting thiyl radical adds to the anion of 2-nitropropane to yield the intermediate α-nitrothioether radical-anion, $[Me_2C(SR)NO_2]^{-\cdot}$. The addition of thiyl radicals to nitronate anions to form radical-anions has been reported and observed by e.s.r. spectroscopy.[11] The formation of disulphide in the preparations of (**1a**) and (**1b**) could therefore arise from dimerisation of thiyl radicals. The absence of disulphide in the other reactions suggests that the disulphide observed in the two reactions is formed by another route, *i.e.* the subsequent reaction of thiolate with the α-nitrosulphide product (see later section).

Secondly, the intermediate 2-nitropropyl radical ($Me_2\dot{C}NO_2$) can react by several possible routes. One possible route, dimerisation, has not been observed.[2,5] The addition of anions to the 2-nitropropyl radical ($Me_2\dot{C}NO_2$) to form radical-anions is well known.[5b] The 2-nitropropyl radical can be attacked by either thiolate or nitronate anions [equations (3) and (4)] in these reactions.

$$Me_2\dot{C}NO_2 + RS^- \longrightarrow [Me_2C(SR)NO_2]^{-\cdot} \quad (3)$$

$$Me_2\dot{C}NO_2 + Me_2CNO_2^- \longrightarrow [Me_2C(NO_2)C(NO_2)Me_2]^{-\cdot} \quad (4)$$

The nitronate anion is strongly solvated on the oxygen atoms by water, which drastically lowers the nucleophilicity of the nitronate anion.[12] The thiolate anion, however, is only weakly solvated and is known to be a very strong nucleophile, even in protic solvents.[13] Several authors have observed that competitive attack between different nucleophiles on free radicals proceeds by kinetic control.[14] Attack by the strongly nucleophilic thiolate would therefore be strongly favoured over that by the weakly nucleophilic nitronate anion.

$$RSSR + Me_2CNO_2^- \rightleftharpoons Me_2C(SR)NO_2 + RS^- \quad (5)$$

$$Me_2C(SR)NO_2 + Me_2CNO_2^- \longrightarrow Me_2C(NO_2)C(NO_2)Me_2 + RS^- \quad (6)$$

(b) *Reaction of the sodium salt of 2-nitropropane with symmetrical disulphides.* α-Nitrosulphides were prepared in good yield by a procedure adapted from the previously published [1,15] method [equation (5)]. A ten-fold molar excess of the nitronate anion proved successful in pushing the equilibrium [as shown in equation (5)] almost completely over to α-nitrosulphide. As noted before,[1,15] the reaction proceeds in good yield if the disulphide has strongly electron-withdrawing R-groups [disulphides (**1a**—**d**)] to increase the rate of the S_N2 substitution. No product was observed, even after long reaction times, for the reaction with 2,2′-bis(4,5-dihydro-1,3-thiazol-2-yl) disulphide (**2f**). The use of an atmosphere of oxygen did not completely inhibit the formation of the dinitrobutane (**5**) impurity which is formed by an $S_{RN}1$ mechanism [equation (6); see also later section].

The S_N2 mechanism and the equilibrium are fully discussed in the literature.[12,15]

(c) *Radical-nucleophilic substitution* ($S_{RN}1$). The results of $S_{RN}1$ reactions between thiolates (**3a**—**f**) and 2-bromo-2-nitropropane, 2-chloro-2-nitropropane, and 2,2-dinitropropane are presented in Table 1. Reactions in *N*,*N*-dimethylformamide

Table 1. Reaction between thiolates and 2-substituted-2-nitropropanes $RS^- + Me_2C(X)NO_2$

R	X	Conditions[a]	% Yield[b] $Me_2C(SR)NO_2$	RSSR	$Me_2C(NO_2)$-$C(NO_2)Me_2$	$Me_2C(X)NO_2$
2-Pyridyl	NO_2	2 h	32	32	Trace	0
		2 h, O_2	13	10	0	30
		2 h, dark	7	4	0	52
		2 h, *p*-dinitrobenzene (10 mol. %)[c]	25	7	3	3
		2 h, O_2, dark	10	5	0	47
	Cl	2 h	16	25	0	17
	Br	1 h	12	28	21	0
		DMF, 2 h	10	5	10	25
		DMF, 3 h	5	29	7	7
		MeOH, 21 h	0	66	32	0
Pyrimidin-2-yl	NO_2	23 h	15	15	11	0
	Br	18 h	13	10	13	28
4-Pyridyl	NO_2	20 h	3	4	Trace	11
	Cl	6 h	7	7	0	30
4,5-Dihydro-1,3-thiazol-2-yl	NO_2	2 h	20	10	10	0
1-Methylimidazol-2-yl	NO_2	22 h	12	0	Trace	7
	Cl	6.5 h	13	3	Trace	25
1,3-Benzothiazol-2-yl[d]	Br	DMF, 1 h	89	0	0	0

[a] HMPA was used as the solvent with light catalysis under nitrogen unless otherwise stated. [b] The % yield based on $Me_2C(X)NO_2$. [c] *p*-Dinitrobenzene [10 mol. % of $Me_2C(X)NO_2$]. [d] Ref. 2.

(DMF) and dimethyl sulphoxide (DMSO) proceeded slowly with considerable decomposition of starting material (2-substituted-2-nitropropanes). The use of hexamethylphosphoramide (HMPA) as solvent gave better results but yields were still poor. The thiolates show a reluctance to participate in $S_{RN}1$ substitution. The use of 2,2-dinitropropane gave less decomposition but the reaction was slower than that with 2-bromo-2-nitropropane.

We studied the reaction of 2,2-dinitropropane with 2-pyridylthiolate (**3a**), in detail, to ascertain the mechanism. The formation of the corresponding α-nitrosulphide (**1a**) and disulphide (**2a**) was clearly catalysed by light, as well as inhibited by strong electron-acceptors (oxygen and *p*-dinitrobenzene) and radical scavengers (oxygen). These criteria are well established methods [5] for determining the $S_{RN}1$ mechanism. These experiments, along with the fact that the α-nitrosulphide is formed by nucleophilic substitution at a tertiary carbon centre, provide good evidence that the α-nitrosulphide is formed by the $S_{RN}1$ mechanism as shown in Scheme 1a.

All the thiolates used in these experiments are ambident anions and could therefore react either *via* the sulphur atom or *via* the nitrogen atom [equations (7) and (8)]. All the products result from attack by the corresponding *S*-centred anion on the intermediate 2-nitropropyl radical (see Schemes 1 and 3). $S_{RN}1$ substitutions involving ambident anions [2b,5,10] appear to yield only one product. Kornblum [16] suggests that the product is obtained by thermodynamic control, *i.e.* an equilibrium [as shown in equations (7) and (8)] occurs with the ambident

$$Me_2\dot{C}NO_2 + R^1\text{–}\overset{S}{\overset{\|}{C}}\text{–}\overset{-}{N}\text{–}R^2 \rightleftharpoons [Me_2C(NO_2)\text{–}S\text{–}C(R^1){=}NR^2]^{-\bullet} \xrightarrow{-e^-} Me_2C(NO_2)\text{–}S\text{–}C(R^1){=}NR^2 \quad (7)$$

$$\rightleftharpoons [Me_2C(NO_2)\text{–}N(R^2)\text{–}CSR^1]^{-\bullet} \xrightarrow{-e^-} Me_2C(NO_2)\text{–}N(R^2)\text{–}CSR^1 \quad (8)$$

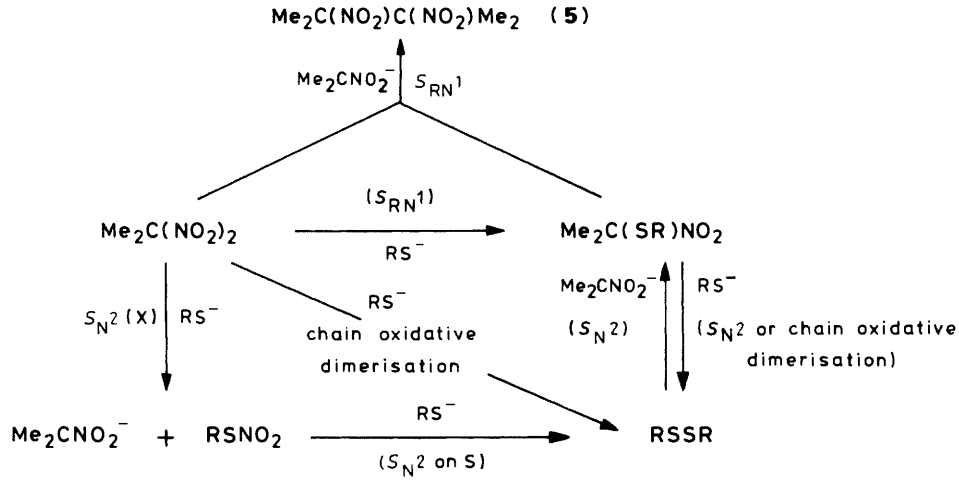
anion leaving from, and adding to, the 2-nitropropyl radical, and the most stable radical-anion losing an electron to complete the chain reaction to yield the product.

Tolbert [14a] and Russell,[14b] however, suggest that the addition of the ambident anion is kinetically controlled and that the stability of the radical-anion intermediate is a function of the π* orbital in the nitro group, a stability which is not achieved until well past the transition state. The unpaired electron in the radical-anion initially resides in the σ* orbital of the C–S or C–N bond. It is therefore this radical-anion which determines the transition state. The σ* radical-anion undergoes reorganisation of molecular orbitals [17] to yield the nitro π* radical-anion. During this reorganisation of molecular orbitals the planar nitro group undergoes relaxation to yield a radical-anion [17] which has the unpaired electron residing on a pyramidal nitro-group. [The structure of the radical-anion of (**1c**) is discussed later.] If the reaction is kinetically controlled the product derived from the most basic/nucleophilic anion should result.

N- and *S*-Alkylated 2-thiopyridines have similar stabilities [18] which leads to the conclusion that the reactions with 2-pyridylthiolate are not thermodynamically controlled because only *S*-alkylation is observed and both products would be expected.

Tolbert [14a] suggests that the relative basicity of the two centres in the ambident anion is the determining factor in the kinetic control, and that the differences between basicity and nucleophilicity may be indistinguishable because there is no polarisation of charge in the transition state for the reaction of an anion with a radical. His comments are, however, confined to two carbon-centres in the ambident anion and he suggests that if heteroatoms are involved the conclusions may be different. In the 2-pyridylthiolate anion the *N*-anion is *ca.* 10^4 times more basic than the *S*-anion [18] but the *S*-anion is more nucleophilic towards carbon than is the *N*-anion,[18] which suggests that nucleophilicity and not basicity is the dominating factor in the kinetic control.

A similar argument can be applied to the $S_{RN}1$ reactions of 2-substituted-2-nitropropanes with arylthiolate anions [1] which



Scheme 4. R = 2-pyridyl

$$Me_2C(X)NO_2 + RS^- \overset{S.E.T.}{\rightleftharpoons} [Me_2C(X)\dot{N}O_2^- \; RS\cdot]_{solv.} \xrightarrow{diffusion} Me_2C(X)\dot{N}O_2^- + RS\cdot$$

$$Me_2C(X)\dot{N}O_2^- + RS^- \overset{S.E.T.}{\rightleftharpoons} [Me_2CNO_2^- \; X^- \; RS\cdot] \xrightarrow{diffusion} Me_2CNO_2^- + X^- + RS\cdot$$

$$RS\cdot + RS^- \rightleftharpoons [RSSR]^{-\cdot}$$

$$[RSSR]^{-\cdot} + Me_2C(X)NO_2 \overset{S.E.T.}{\rightleftharpoons} RSSR + Me_2C(X)\dot{N}O_2$$

Scheme 5.

proceed exclusively *via* *S*-alkylation rather than *C*-alkylation. Other ambident anions which have been observed to react *via* selective alkylation are enolates [14b] (*C*-alkylation), phosphites and thiophosphites [19] (*P*-alkylation), nitronates [5] (*C*-alkylation), and thiocyanates [2b] and sulphinates [5] (*S*-alkylation). We therefore suggest that the addition of ambident anions to alkyl nitro-radicals ($R_2\dot{C}NO_2$) is under kinetic control *via* the more nucleophilic centre.

The corresponding disulphides and 2,3-dimethyl-2,3-dinitrobutane (**5**) are also formed in the reaction of thiolates with 2-substituted-2-nitropropanes (Table 1). The possible mechanisms for reaction of 2-pyridylthiolate with 2,2-dinitropropane are shown in Scheme 4. The formation of all three products was inhibited by oxygen and *p*-dinitrobenzene, and was catalysed by light. We suggest that the dinitrobutane (**5**) is formed by the $S_{RN}1$ reaction of the anion of 2-nitropropane (formed during the reaction) with the α-nitrosulphide (**1a**) or with 2,2-dinitropropane. The former reaction is discussed later and the latter has been reported.[5]

The strong inhibition of disulphide formation largely rules out disulphide formation by S_N2 reactions (Scheme 2a with X = NO_2). We therefore suggest that the disulphide is formed by nucleophilic attack by the thiolate (**3a**) on the α-nitrosulphide product (**1a**). As the formation of α-nitrosulphide is inhibited, the formation of disulphide would therefore also be inhibited. This nucleophilic attack could proceed either by an S_N2 mechanism or by a radical radical-anion chain oxidative dimerisation mechanism [19] (see Scheme 5). In the next section we show that this reaction is in fact inhibited, which suggests that the chain mechanism is operative. The higher inhibition of disulphide than that of α-nitrosulphide supports the idea of disulphide formation by two successive chain reactions or by chain oxidative dimerisation directly from reaction between the thiolate (**3a**) and 2,2-dinitropropane.

The disulphide products in the other reactions can be explained in the same way although, as shown in Table 2, the reaction of thiolates with their corresponding α-nitrosulphides in DMF (as opposed to HMPA) was slower than in the 2-pyridyl series. Pyrimidin-2-ylthiolate and 4,5-dihydro-1,3-thiazol-2-ylthiolate, however, did not react in DMF with the corresponding α-nitrosulphides (**1c** and **f**) to yield disulphide (**2c** or **d**). This difference in reactivity is possibly due to the solvent.

Reaction between α-Nitrosulphides (**1a**, **c**—**f**) *and the Corresponding Thiolates* (**3a**, **c**—**f**). The results of these reactions are shown in Table 2. The reactions were slow, except for the reaction of 2-pyridylthiolate with the corresponding α-nitrosulphide (**1a**). This latter reaction was significantly inhibited by oxygen, *p*-dinitrobenzene, and the absence of light, suggesting a chain reaction proceeding by intermediate radicals and radical-anions.

Most of the previously reported reactions between thiolates and 2-substituted-2-nitropropanes [1,2a,2b] proceed rapidly without inhibition. The slow reaction between *p*-chlorophenylthiolate and 2-chloro-2-nitropropane in MeOH [2c] is, however, significantly inhibited. In order to explain the effect of solvent on the fast reactions of thiolates with α-substituted nitroalkanes we suggested in our last communication [2c] that the nucleophilic abstraction of the α-substituent by thiolate may possibly proceed by a single-electron transfer (S.E.T.) mechanism (Scheme 2b) rather than by an X-philic [6] S_N2 reaction.

We suggest that a feasible explanation for the lack of inhibition in fast reactions is as shown in Scheme 2b,[2c] *i.e.* the radical-anion [$Me_2C(X)\dot{N}O_2^-$] and thiyl (RS·) radical are sufficiently reactive to react faster than they diffuse apart, while on the other hand the inhibition observed in slower reactions is explained by Scheme 5, *i.e.* the radical-anion and thiyl radical are less reactive and diffuse apart faster than they react, and the free thiyl radical then enters a chain reaction to yield disulphide.

Table 2. Reactions between α-nitrosulphides (**1a**, **c**—**f**) and the corresponding thiolates (**3a**, **c**—**f**)

R	Conditions[a]	% Yield[b] RSSR	$Me_2C(NO_2)$-$C(NO_2)Me_2$	$Me_2(SR)NO_2$
2-Pyridyl	5 h	49	8	6
	5 h, O_2	15	0	38
	5 h, dark	18	0	60
	5 h, *p*-dinitrobenzene (10 mol. %)[c]	18	16	25
Pyrimidin-2-yl	5 h and 23 h[d]	0	0	100
1,3-Benzothiazol-2-yl	5 h	10	6	50
1-Methylimidazol-2-yl	5 h	11	10	42
4,5-Dihydro-1,3-thiazol-2-yl	5 h	0	0	100

[a] The molar ratio RS^- : $Me_2C(SR)NO_2$ was 2:1. DMF was used as the solvent with light catalysis under nitrogen, unless otherwise stated. [b] The % yield is based on $Me_2C(SR)NO_2$. [c] 10 mol. % of $Me_2C(SR)NO_2$. [d] The molar ratio RS^- : $Me_2C(SR)NO_2$ was 10:1.

Table 3. Reaction between α-nitrosulphides (**1a**, **c**—**f**) and *p*-chlorophenylthiolate, benzylthiolate, and cysteine

R^1 in $Me_2C(SR^1)NO_2$	R^2 in R^2S^-	Conditions[a]	% Yield[b] R^2SSR^2	$Me_2C(SR^2)$-NO_2	$Me_2C(SR^1)$-NO_2
1-Methylimidazol-2-yl	*p*-Chlorophenyl	MeOH–H_2O (85:15)	55	0	0
		DMF	23	46	0
		DMF, O_2	8	0	48
		DMF, dark[c]	0	76	7
		DMF, *m*-DNB[d]	14	35	0
		DMF, *p*-DNB[d]	31	0	42
	Benzyl	DMF	0	0	85
Pyrimidin-2-yl	*p*-Chlorophenyl	MeOH–H_2O (85:15)	47	0	
		DMF	32	20	0
		DMF, dark	0	36	6
		DMF, O_2	0	0	62
		DMF, O_2, dark	0	0	100
	Benzyl	DMF[e]	29	0	41
	L-Cysteine	MeOH–H_2O (50:50); 5 h, 18 h	15, 44	0, 0	48, 40
2-Pyridyl	*p*-Chlorophenyl	DMF	17	20	8
	L-Cysteine	MeOH–H_2O (50:50), 12 h	38	0	18
1,3-Benzothiazol-2-yl	*p*-Chlorophenyl	DMF	17	35	0
	Benzyl	DMF[e]	11	0	48
4,5-Dihydro-1,3-thiazol-2-yl	*p*-Chlorophenyl	MeOH–H_2O (85:15)	46	0	0

[a] The reactions were carried out for 5 h under nitrogen and light catalysis with a molar ratio $Me_2C(SR^1)NO_2$: R^2S^- of 1:2, unless otherwise stated. [b] The yields are based on $Me_2C(SR^1)NO_2$. [c] Average of three closely agreeing runs. [d] DNB = dinitrobenzene; 10 mol. % of $Me_2C(SR^1)NO_2$. [e] The reaction mixture contained a large amount of polymeric material.

This latter mechanism has been fully described by Russell and co-workers[20] for the oxidative dimerisation of enolate anions by 2-substituted-2-nitropropanes. The equilibrium (step 3 in Scheme 5) between thiyl radical and thiolate anion, and the corresponding disulphide radical-anion, has been suggested in a related chain reaction.[21] This equilibrium has also been observed by e.s.r. spectroscopy.[22] The unpaired electron in the disulphide radical-anion $[(RSSR)^{-\bullet}]$ lies in the relatively low-energy LUMO σ* molecular orbital of the S–S bond.[22] The addition of thiolate anion to thiyl radical to form a disulphide radical-anion is therefore possible, giving support for the proposed chain-reaction mechanism. Electron transfer from the disulphide radical-anion $[(RSSR)^{-\bullet}]$ to the 2-substituted-2-nitropropane to yield disulphide and the radical-anion $[Me_2C(X)\dot{N}O_2^-]$ completes the chain reaction.

An alternative explanation is that the fast reactions proceed by an X-philic S_N2 mechanism and that the slow reactions proceed by the oxidative dimerisation mechanism (Scheme 5). Strongly nucleophilic thiolates and less electronegative α-substituents will favour both the X-philic S_N2 and the non-chain S.E.T. (Scheme 2b) mechanisms. Both mechanisms will not be inhibited and both have a reactive sulphenyl (RSX) intermediate. Weakly nucleophilic thiolates and/or more electronegative α-substituents will favour a slower reaction and the chain oxidative dimerisation. 2-Pyridylthiolate is a relatively weak thiolate nucleophile and therefore the reaction with the α-nitrosulphide (**1a**) proceeds by the chain mechanism as shown in Scheme 5. The reaction between *p*-chlorophenylthiolate and 2-chloro-2-nitropropane proceeds similarly and the chlorine α-substituent is not easily abstracted, again favouring the chain oxidation.

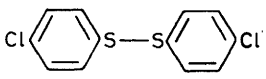
Reactions of the α-Nitrosulphides (**1a**, **c**—**f**) *with* p-*Chlorophenylthiolate, Benzylthiolate, and* L-*Cysteine.*—α-Nitrosulphides (**1a**, **c**—**f**) were treated with various thiolates as an *in vitro* guide to their biological activity (the results are shown Table 3). *p*-Chlorophenylthiolate was initially chosen because of its similar pK_a value to that of cysteine. To our surprise the reaction between α-nitrosulphides (**1a**, **c**, and **e**) and *p*-chlorophenylthiolate in DMF yielded large amounts of

Table 4. Reaction between α-nitrosulphides (**1b**, **d**, **e**, and **f**) and the anion of 2-nitropropane

R	Conditions[a]	% Yield of $Me_2C(NO_2)C(NO_2)Me_2$[b]	% Recovery of starting material
1-Methylimidazol-2-yl	DMF, 5 h	39	22
	DMSO, 6 h	53	0
	DMSO, 6 h, O_2	5	21
	DMSO, 6 h, dark	7	56
	DMSO, 6 h, 10 mol. % of di-t-butyl nitroxide[c]	22	37
	DMSO, 6 h, 10 mol. % of *p*-dinitrobenzene[c]	5	22
Pyrimidin-2-yl	DMF, 5 h	7	55
	DMF, 5 h, O_2	6	70
	DMF, 5 h, dark	0	100
	DMF, 5 h, 10 mol. % of *p*-dinitrobenzene[c]	4	96
1,3-Benzothiazol-2-yl	DMF, 4 h	25	Not measured
4,5-Dihydro-1,3-thiazol-2-yl	DMF, 5 h	16	Not measured

[a] The reactions were carried out under nitrogen with light catalysis with the ratio $Me_2CNO_2^-$: α-nitrosulphide = 3:2, unless otherwise stated. [b] The % yield is based on α-nitrosulphide. [c] Mol. % of $Me_2C(SR)NO_2$.

p-chlorophenyl 1-methyl-1-nitroethyl sulphide (**4**) as well as the expected bis(*p*-chlorophenyl) disulphide (**6**). Inhibition studies (see Table 3) for the reaction of α-nitrosulphides (**1b** and **e**) clearly indicate an $S_{RN}1$ mechanism for the formation of the α-nitrosulphide product (**4**). This is the first reported $S_{RN}1$ substitution of one thiolate by another. This reaction is theoretically reversible and the direction depends on the relative nucleofugicity of the thiolates involved. The reaction between 1-methylimidazol-2-ylthiolate (**3e**) and the α-nitrosulphide (**6**) yielded only unchanged starting materials. $S_{RN}1$ Reactions with a nucleophile and nucleofuge of the same functional group have been reported for arenesulphinates.[3a]



(**6**)

The inhibition studies contain some odd results, especially the complete inhibition of disulphide (**6**) formation and the increased yields of α-nitrosulphide (**4**) [46—76% and 20—36%, respectively, for the reactions of (**1e**) and (**1c**)] in the absence of light. If disulphide was formed by the reaction between *p*-chlorophenylthiolate and the α-nitrosulphide product (**4**), which has been shown to proceed in high yield by a non-chain mechanism [1] (Scheme 2a or b, with X = RS = *p*-chlorophenylthiolate), exactly the opposite results for light catalysis would be expected. We therefore propose (i) that the disulphide (**6**) is formed directly from the reaction between *p*-chlorophenylthiolate and the α-nitrosulphide starting material (**1c** or **e**) by a chain mechanism (Scheme 5), in which the S.E.T. step between the radical-anion of (**1c**) or (**1e**) and thiolate is strongly light catalysed, and (ii) that the α-nitrosulphide (**6**) is formed by a weakly light catalysed $S_{RN}1$ reaction. S.E.T. between α-nitrosulphide (**1c** or **e**) and thiolate (a step present in both mechanisms) will almost certainly require much less light energy than the highly energetic S.E.T. between the thiolate and the radical-anions of (**1c**) or (**1e**) in the chain redox mechanism. Oxygen strongly inhibits both disulphide (**6**) and α-nitrosulphide (**4**) formation but *p*-dinitrobenzene only inhibits the $S_{RN}1$ reaction. *m*-Dinitrobenzene is known [5] to be a poorer electron-acceptor than *p*-dinitrobenzene which is reflected by the poorer inhibition result for the reaction of α-nitrosulphide (**1e**).

The reaction between benzylthiolate and α-nitrosulphides (**1c**, **d**, and **e**) gave disappointing yields, which was surprising because of the strong nucleophilicity of the thiolate. The first two reactions yielded large amounts of a polymeric material which showed no benzyl ($-CH_2-$) resonance when studied by n.m.r. spectroscopy. The polymer possibly arises from thiobenzaldehyde formed as shown in equations (9) and (10).

$$Me_2C(SR)NO_2 + PhCH_2S^- \longrightarrow Me_2CNO_2^- + PhCH_2S\text{–}SR \quad (9)$$

$$B: + PhCH_2S\text{–}SR \longrightarrow PhCHS + BH^+ + RS^- \quad (10)$$

Thiobenzaldehyde has been reported [23] to be very unstable and to polymerise rapidly.

The reaction of α-nitrosulphides (**1a** and **c**) with cysteine was slow which gives a good *in vitro* indication as to why these compounds show only moderate antibacterial activity. The reactions of α-nitrosulphides (**1b**, **e**, and **f**) with *p*-chlorophenylthiolate in MeOH–water solution, however, give reasonable yields of the expected bis(*p*-chlorophenyl) disulphide only.

The contrast in product composition between reactions in protic solvents and in dipolar aprotic solvents is significant. These latter three reactions, as well as the reaction between 2-pyridylthiolate and 2-bromo-2-nitropropane (see Table 1), yield only the disulphide in protic solvents. We have proposed in an earlier communication [2c] that this remarkable difference in reactivity between protic and dipolar aprotic solvents for the reactions between 2-substituted-2-nitropropanes and thiolates is due to two factors. First, strong protic solvation of the nitro-oxygens in the intermediate radical-anion $[Me_2C(X)\dot{N}O_2^-]$ decreases the rate of dissociation to the 2-nitropropyl radical ($Me_2\dot{C}NO_2$) and X^-, required for the $S_{RN}1$ mechanism. Secondly, the rate of disulphide formation is faster [2c] in protic solvent than in dipolar aprotic solvent which was explained by strong protic solvation of the nitro-oxygens in either $Me_2C(X)NO_2$, thereby increasing the rate of the $S_N2(X)$ reaction (Scheme 2a), or in the intermediate radical-anion $[Me_2C(X)\dot{N}O_2^-]$, thereby increasing the rate of the non-chain radical-anion redox reaction (Scheme 2b). A combination of these two factors therefore provides an explanation for the selective disulphide formation (*i.e.* by decreasing the rate of $S_{RN}1$ reaction and increasing the rate of the redox reaction) in the four reactions in protic solvent reported in Tables 1 and 3.

Reaction between α-Nitrosulphides (**1b**, **d**—**f**) *and the Anion of 2-Nitropropane.*—The results of the reaction between α-nitro-

sulphides (**1b**, **d**—**f**) and the anion of 2-nitropropane are shown in Table 4. The reaction proceeds slowly to yield 2,3-dimethyl-2,3-dinitropropane (**5**). The inhibition studies for α-nitrosulphides (**1c** and **e**) clearly show increased recovery of unchanged starting material (α-nitrosulphide) and decreased yield of the dinitrobutane (**5**). In the former reaction the decrease in yield of the dinitrobutane (**5**) is not particularly significant due to the low yield in the control reaction but the increase in recovery of starting material is. These results clearly suggest that the reaction proceeds by an $S_{RN}1$ mechanism (Scheme 1a, with X = SR, and $RS^- = Me_2CNO_2^-$).

No reaction was observed between α-nitrosulphides (**1a** and **e**) and sodium benzenesulphinate. Benzenesulphinate is almost certainly a better nucleofuge than 2-pyridylthiolate or 1-methylimidazol-2-ylthiolate, which would explain the lack of reaction. The first and second steps of the propagation of an $S_{RN}1$ reaction are in equilibrium [*i.e.*, in this case, dissociation of $Me_2C(SR)\dot{N}O_2^-$ to $Me_2\dot{C}NO_2$ and RS^-, and reaction of $Me_2\dot{C}NO_2$ and $PhSO_2^-$ to form $Me_2C(SO_2Ph)\dot{N}O_2^-$] and therefore if the second nucleophile ($PhSO_2^-$) is a better nucleofuge than the initial nucleofuge (RS^-) the $S_{RN}1$ reaction will not take place.

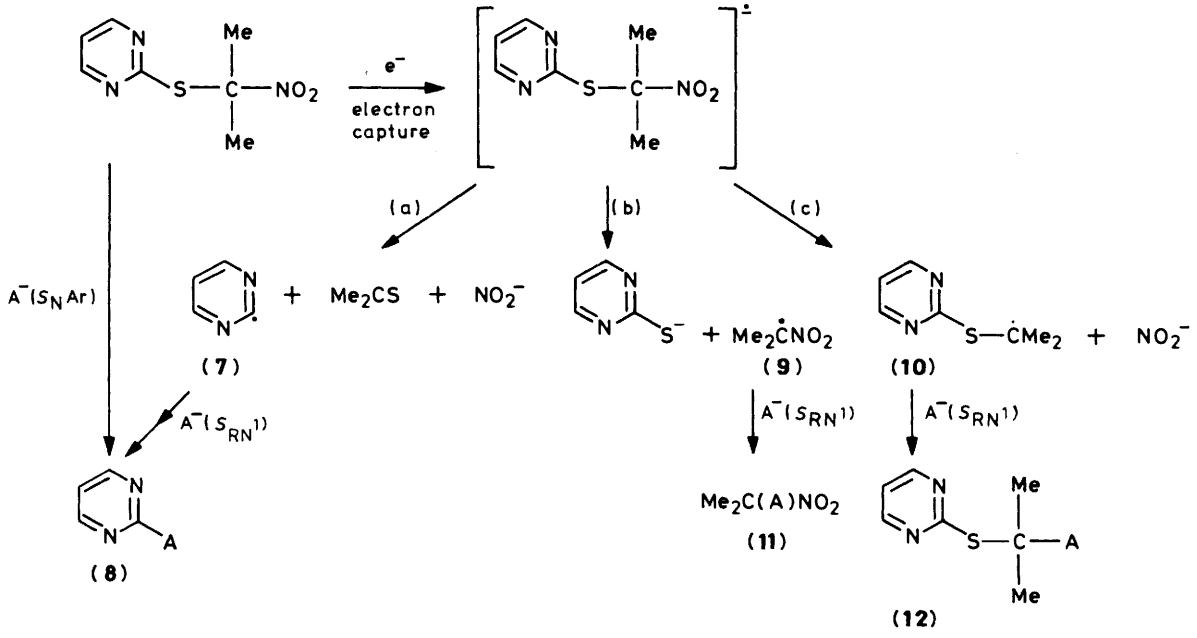
Reactivity of α-Nitrosulphides in Reactions Proceeding via Intermediate Radical-anions.—α-Nitrosulphides (**1a**—**e**) have the ability to react by a number of potential substitution mechanisms as illustrated for the pyrimidyl analogue (**1c**) in Scheme 6. 2-Substituted-pyridines and -pyrimidines are well known to undergo S_NAr substitution with nucleophiles to yield a substituted product [*i.e.* (**8**)]. 2-Substituted-pyridines and -pyrimidines have also been reported[24] to undergo $S_{RN}1$ substitution to yield the same products [*i.e.* (**8**)]. Substitution on the aromatic ring (Scheme 6, route a or S_NAr) was not observed in any of the reactions, indicating that dissociation of the intermediate radical-anion (Scheme 6) does not proceed to the intermediate free-radical (**7**) (route a).

The radical-anion intermediates can also dissociate with loss of thiolate to yield the 2-nitropropyl radical (**9**) or with loss of nitrite to yield isopropyl thioether radicals [*e.g.* (**10**)] and subsequently yield products (**11**) by route b or products such as (**12**) by route c. Breakdown by route b (loss of thiolate) would be kinetically favoured because thiolate is a better nucleofuge than nitrite, and route c would be thermodynamically favoured because radicals are more stabilised by thioether substituents than by nitro substituents [*i.e.* radical (**10**) is more stable than radical (**9**)]. Russell and co-workers report[25] that $Me_2\dot{C}SPh$ or $Me_2\dot{C}SMe$ are *ca.* 5—6 times more stable than $Me_2\dot{C}NO_2$.

The only products resulting from substitution are formed by an $S_{RN}1$ mechanism as shown in route b (Scheme 6). As the breakdown of the intermediate radical-anion is defined as the rate-determining step in the propagation steps of an $S_{RN}1$ mechanism,[5] the kinetically controlled dissociation would be expected.

E.S.R. Studies of 1-Methyl-1-nitroethyl Pyrimidin-2-yl Sulphide (**1c**).—The radical-anions of various 2-substituted-2-nitropropanes have been generated by γ-ray irradiation in solid matrices of methyltetrahydrofuran (MeTHF) and deuteriomethanol (CD_3OD) at low temperature (77 K), and observed by e.s.r. spectroscopy.[17] On annealing to *ca.* 140 K the dissociation of some of the radical-anions to free radicals ($Me_2\dot{C}NO_2$ by loss of X^- or $Me_2\dot{C}X$ by loss of NO_2^-) can also be observed by e.s.r. spectroscopy.[17]

One of the α-nitrosulphides, (**1c**), was studied by these techniques in order to gain corroborative evidence for the structure and behaviour of the intermediate radical-anions. α-Nitrosulphide (**1c**) undergoes electron-capture to yield the corresponding radical-anion on irradiation. In MeTHF at 77 K the radical-anion was observed by e.s.r. spectroscopy to be stable, and not to dissociate on annealing to *ca.* 140 K. The structure of the radical-anion has been assigned by comparison with previously assigned $Me_2C(X)\dot{N}O_2^-$ radical-anions. E.s.r. spectroscopy shows that the unpaired electron of the radical-anion is in the π* molecular orbital (MO) of a pyramidal nitro group as was observed[17] for all of the other radical-anions of 2-substituted-2-nitropropanes studied. A radical-anion with the unpaired electron in an aromatic π* orbital would be kinetically favoured because no deformation is required on electron-capture, but was not observed. The thermodynamic product (with the unpaired electron in the π* MO of a pyramidal nitro group) is formed by initial electron-capture to yield a 'hot' radical-anion (which has the odd



Scheme 6.

electron in the π^* MO of a planar nitro-group) which subsequently undergoes relaxation by bond-bending.[17]

Irradiation of the α-nitrosulphide (**1c**) in CD_3OD also yielded the corresponding radical-anion which was stable at 77 K. On annealing to *ca.* 140 K a small amount of dissociation took place to yield a radical species (minor compared with the radical-anion) which could not be definitely identified by e.s.r. spectroscopy. The e.s.r. spectrum shows a 6-H proton splitting of 21.6 G which is ill defined. The most likely free radical to fit these data is that arising by loss of nitrite from the radical-anion [*i.e.* (**10**) in Scheme 6]. The 2-nitropropyl radical ($Me_2\dot{C}NO_2$) can be clearly observed by e.s.r. spectroscopy and is definitely not present in observable concentrations, *i.e.* the breakdown observed in solid matrix at low temperature is different to that observed in the solution reactions.

All the dissociations of radical-anions [$Me_2C(X)\dot{N}O_2^-$] observed so far by e.s.r. spectroscopy[17] in solid matrices proceed by the same route as in solution reactions. This exception [$(\mathbf{1c})^{-\bullet}$ to (**10**) instead of to (**9**)] can possibly be explained by strong solvation of the nitro group in the radical-anion by CD_3OD which assists dissociation by loss of nitrite (route c in Scheme 6).

Conclusions.—We have provided evidence to show that heterocyclic α-nitrosulphides undergo $S_{RN}1$ substitution with loss of the thiolate group. This substitution reaction is sluggish indicating that heterocyclic thiolates are not especially good nucleofuges for $S_{RN}1$ reactions. The slow rate of reaction can be explained by the stability of the intermediate radical-anions, as shown by e.s.r. spectroscopy for the 2-pyrimidyl analogue (**1c**). We have also obtained further evidence that some anions react with certain 2-substituted-2-nitropropanes by a chain oxidative dimerisation mechanism (Scheme 5) as suggested by Russell and co-workers.[20]

We have prepared a new range of α-nitrosulphides by three different synthetic methods and have shown that the reaction of these compounds with thiolates gives disulphide products in protic solvents, which is a useful *in vitro* indication of their antimicrobial activity.

Experimental

General.—DMF, DMSO, and HMPA were distilled at low pressure from calcium hydride and stored over molecular sieves. Methanol was dried using magnesium and iodine. M.p.s were determined on a Kofler block and are uncorrected. I.r. spectra were determined as Nujol mulls in the case of solids or thin films (liquids) on a Perkin-Elmer 177 spectrophotometer. N.m.r. spectra were determined at 90 MHz with a Perkin-Elmer R32 spectrometer or at 60 MHz on a Varian EM 360A instrument using $SiMe_4$ as internal standard. Analytical t.l.c. was carried out using Merck silica gel 60 PF_{254}. N.m.r. analyses of reaction mixtures were carried out using a known amount of an internal standard (*p*-dimethoxybenzene, *p*-dinitrobenzene, or phthalide).

2-Bromo-2-nitropropane,[26] 2-chloro-2-nitropropane,[26] 2,2-dinitropropane,[10] and the sodium salt[1] of 2-nitropropane were prepared by literature procedures.

Preparation of Thiolate Sodium Salts.—The various thiolate salts required were prepared from their corresponding thiols as previously described for sodium *p*-chlorophenylthiolate and 1,3-benzothiazol-2-ylthiolate.[1] All thiolate salts were thoroughly washed with dry diethyl ether to remove traces of disulphide or thiol impurities. The experimental data for the thiolates are: 2-pyridylthiolate, $\lambda_{max.}$(EtOH) 345 (ε 7 980) and 284 nm (16 790); δ(D_2O) 6.8—8.0 (m); 4-pyridylthiolate, $\lambda_{max.}$(EtOH) 340 nm; δ(D_2O) 7.6 (ABq); 1-methylimidazol-2-ylthiolate, $\lambda_{max.}$(EtOH) 242nm; δ(D_2O) 3.5 (3 H, s) and 6.8 (2 H, ABq); 4-5-dihydro-1,3-thiazol-2-ylthiolate, $\lambda_{max.}$(EtOH) 274 nm (ε 7 635); δ(D_2O) 3.4 (2 H, t) and 4.05 (2 H, t); 2-pyrimidylthiolate, $\lambda_{max.}$(EtOH) 283 nm; δ(D_2O) 6.85 (1 H, t) and 8.15 (2 H, d); benzylthiolate, δ(D_2O) 3.45 (2 H, s) and 7.15 (5 H, s). All the thiolates yielded the corresponding pure thiol on acidification with dil. hydrochloric acid.

Preparation of α-Nitrosulphides by Potassium Ferricyanide Oxidation of the Anion of 2-Nitropropane in the Presence of Thiolate.—(a) 1-*Methylimidazol-2-yl* 1-*methyl*-1-*nitroethyl sulphide* (**1e**) (*general procedure*). Freshly distilled 2-nitropropane (4.45 g, 50 mmol) was dissolved in a solution of sodium hydroxide (2.4 g, 60 mmol) in water (30 ml) under nitrogen. Freshly prepared sodium 1-methylimidazol-2-ylthiolate (5.05 g, 50 mmol) and diethyl ether (100 ml) were then added. A solution of potassium ferricyanide (32.9 g, 100 mmol, 2 equiv.) in water (40 ml) was added dropwise to the stirred, cooled solution, at a rate such that a temperature of 0—10 °C was maintained. When the addition was complete (*ca.* 1 h) the layers were separated and the aqueous layer was washed with diethyl ether (2 × 50 ml). The combined ethereal layers were washed with water (2 × 50 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield a crude powdery product which was recrystallised from chloroform to give needles of 1-*methylimidazol-2-yl* 1-*methyl*-1-*nitroethyl sulphide* (**1e**) (4.2 g, 42%), m.p. 79—81 °C (Found: C, 41.7; H, 5.7; N, 21.0; S, 16.0. $C_7H_{11}N_3O_2S$ requires C, 41.78; H, 5.51; N, 20.88; S, 15.93%); $\lambda_{max.}$(EtOH) 234 nm (ε 46 200); $\nu_{max.}$ 1 535, 1 348, and 960 cm^{-1}; δ($CDCl_3$) 1.9 (6 H, s), 3.6 (3 H, s), and 7.1 (2 H, dd).

(b) 1-*Methyl*-1-*nitroethylpyrimidin*-2-yl sulphide (**1c**). This was prepared as detailed as in the general procedure in 40—70% yield. Recrystallisation from acetone–water gave pure *yellow crystals* of (**1c**), m.p. 37—39 °C (Found: C, 42.5; H, 4.6; N, 21.1; S, 16.1. $C_7H_9N_3O_2S$ requires C, 42.2; H, 4.6; N, 21.1; S, 16.1%); $\lambda_{max.}$(EtOH) 239 nm (ε 26 820); $\nu_{max.}$ 1 545, 1 340, 1 192, 780, and 695 cm^{-1}; δ($CDCl_3$) 2.1 (6 H, s), 6.9 (1 H, t), and 8.4 (2 H, d).

(c) 4,5-*Dihydro*-1,3-*thiazol*-2-*yl* 1-*methyl*-1-*nitroethyl sulphide* (**1f**). This was prepared as detailed in the general procedure in 32% yield. Recrystallisation from light petroleum (b.p. 60—80 °C) gave *crystals* of (**1f**), m.p. 33—34 °C (Found: C, 34.9; H, 4.9; N, 13.5; S, 31.4. $C_6H_{10}N_2O_2S_2$ requires C, 34.9; H, 4.9; N, 13.6; S, 31.1%); $\lambda_{max.}$(EtOH) 275 nm (ε 10 050); $\nu_{max.}$ 1 565, 1 330, and 690 cm^{-1}; δ($CDCl_3$) 2.05 (6 H, s), 3.35 (2 H, t), and 4.20 (2 H, t).

(d) 1,3-*Benzothiazol*-2-*yl* 1-*methyl*-1-*nitroethyl sulphide* (**1d**). This was prepared as detailed in the general procedure in 60% yield. Recrystallisation from light petroleum ether (b.p. 60—80 °C) gave yellow crystals of (**1d**), m.p. 79—81 °C (lit.,[1] 80—81 °C). The i.r. and n.m.r. spectra, and t.l.c. properties, were identical with those of an authentic material.

(e) 1-*Methyl*-1-*nitroethyl* 2-*pyridyl sulphide* (**1d**). The general procedure yielded a mixture of products. N.m.r. analysis of the crude product showed the presence of (**1a**) (39%), 2,2′-dipyridyl disulphide (30%), and 2,3-dimethyl-2,3-dinitrobutane (3%). Separation by column chromatography (toluene; alumina) and recrystallisation from acetone–water yielded *yellow crystals* of (**1a**) (32%), m.p. 28—32 °C (Found: C, 48.1; H, 5.4; N, 14.2; S, 16.1. $C_8H_{10}N_2O_2S$ requires C, 48.5; H, 5.1; N, 14.1; S, 16.2%); $\lambda_{max.}$(EtOH) 279 nm (ε 9 770); $\nu_{max.}$ 1 545, 1 420, 1 340, and 1 125 cm^{-1}; δ($CDCl_3$) 1.95 (6 H, s), 7.30 (3 H, m), and 8.35 (1 H, dd). When the reaction was repeated with an eleven-fold excess of the sodium salt of 2-nitropropane over the thiolate, pure α-nitrosulphide (**1a**) was isolated (21% after recrystallisation).

(f) 1-*Methyl*-1-*nitroethyl* 4-*pyridyl sulphide* (**1b**). The general procedure yielded a mixture of products. N.m.r. analysis of the crude product showed the presence of (**1b**) (24%), 4,4′-dipyridyl disulphide (22%), and 2,3-dimethyl-2,3-dinitrobutane (2%).

Purification by preparative t.l.c. (chloroform; silica gel) gave compound (**1b**) as a light-yellow oil (14%) (Found: C, 48.9; H, 5.3, N, 14.3; S, 16.0. $C_8H_{10}N_2O_2S$ requires C, 48.5; H, 5.1; N, 14.1; S, 16.2%); $\nu_{max.}$ 1 550, 1 075, 808, and 700 cm^{-1}; $\delta(CDCl_3)$ 1.90 (6 H, s), 7.35 (2 H, dd), and 8.65 (2 H, dd).

Preparation of Disulphides.—Dipyrimidin-2-yl disulphide (**2c**), di-2-pyridyl disulphide (**2a**), di-4-pyridyl disulphide (**2b**), and di-1,3-benzothiazol-2-yl disulphide (**2d**) were prepared by oxidation of the corresponding thiolates with iodine.[27]

Bis(1-methylimidazol-2-yl) disulphide (**2e**) could not be prepared by this procedure. An intractable oil was obtained which decomposed when purification was attempted.

Bis(4,5-dihydro-1,3-thiazol-2-yl) disulphide (**2f**) was prepared by oxidation of the corresponding thiol with hydrogen peroxide.[28]

Preparation of α-Nitrosulphides by the Reaction of Disulphides with the Sodium Salt of 2-Nitropropane.—The preparation of 1-methyl-1-nitroethyl 2-pyridyl sulphide (**1a**) illustrates the procedure used. The sodium salt of 2-nitropropane (5.05 g, 45 mmol, 10 equiv.) was added to a solution of di-2-pyridyl disulphide (1.0 g, 4.5 mmol) in dry DMF (50 ml) under oxygen and the mixture was stirred for 8 h. The reaction mixture was then poured into ice–water (500 ml) and extracted with dichloromethane (3 × 50 ml), and the combined extracts were washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a yellow oil. N.m.r. analysis showed the oil to consist of compound (**1a**) (51%), 2,2′-dipyridyl disulphide (3%), and 2,3-dimethyl-2,3-dinitrobutane (4%). Pure sulphide (**1a**) was obtained in 25% yield after separation by preparative t.l.c. ($CHCl_3$; silica gel) and recrystallisation (acetone–water) which was identical with authentic material (m.p., i.r. and n.m.r. spectroscopy, and t.l.c.).

1-Methyl-1-nitroethyl 2-pyridyl sulphide (**1b**) was prepared by the same procedure from the corresponding disulphide. N.m.r. analysis of the crude mixture showed the presence of compound (**1b**) (24%) and 2,3-dimethyl-2,3-dinitrobutane (7%).

Similarly, 1,3-benzothiazol-2-yl 1-methyl-1-nitroethyl sulphide (**1d**) was prepared by the general procedure. N.m.r. analysis of the crude product showed the presence of compound (**1d**) (58%), unchanged disulphide (14%), and 2,3-dimethyl-2,3-dinitrobutane (11%).

1-Methyl-1-nitroethyl pyrimidin-2-yl sulphide (**1c**) was also prepared by the general procedure. N.m.r. analysis of the crude mixture showed the presence of compound (**1c**) (86%) and 2,3-dimethyl-2,3-dinitrobutane (7%). The sulphide (**1c**) was recrystallised directly from the crude mixture without the use of preparative t.l.c.

No 4,5-dihydro-1,3-thiazol-2-yl 1-methyl-1-nitroethyl sulphide (**1f**) was formed after 8 h in the reaction of the corresponding disulphide and the sodium salt of 2-nitropropane. The disulphide (**2e**) was recovered quantitatively.

Reactions between Thiolates and 2-Bromo-2-nitropropane, 2-Chloro-2-nitropropane, 2,2-Dinitropropane, or α-Nitrosulphides (**1a**, **c**—**f**) (*General Procedure for* $S_{RN}1$ *Reactions*).—The sodium salt of the thiolate (1 equiv., *ca.* 1 g) was added to the dry solvent (HMPA or DMF) (25 ml) under nitrogen and under anhydrous conditions. A further 30 min was allowed for complete de-oxygenation during which time the thiolate salt dissolved. A solution of the 2-substituted-2-nitropropane (1 equiv.) in a small volume of the solvent was then injected through a rubber septum into the reaction mixture, which was stirred either by a magnetic stirrer bar or an upward flow of nitrogen. The reaction mixture was then irradiated with two 150-W fluorescent discharge lamps [mercury blended tungsten universal mounted (MBTU) lamps emitting light maximally at 430 nm] from a distance of 10 cm.

The extent of reaction was monitored, when required, by removal of samples, work-up of the samples, and identification of the components by t.l.c. and n.m.r. spectroscopy. At the end of the determined time the reaction mixture was poured into ice–water (50 ml) and extracted with diethyl ether (4 × 50 ml). The combined extracts were washed with water (4 × 40 ml), dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was analysed by n.m.r. spectroscopy. When required, products were separated by preparative t.l.c. and characterised by t.l.c., n.m.r. and i.r. spectroscopy, and m.p. by comparison with authentic material. The results are tabulated in Tables 1 and 2.

General Procedure for Light Catalysis and Inhibition Studies on the Reactions between Anions (*Thiolates and the Anion of 2-Nitropropane*) *and 2-Substituted-2-nitropropanes.*—The general procedure was followed except as outlined in each method detailed below. (*a*) Inhibition studies with *p*-dinitrobenzene were carried out by adding the required amount of *p*-dinitrobenzene to the reaction mixture at the same time as the anion. (*b*) Inhibition studies with oxygen were carried out by replacing nitrogen gas by oxygen gas. (*c*) The studies on the effect of light catalysis were carried out by the complete exclusion of light from the reaction which was effected by wrapping the reaction flask in aluminium foil. (*d*) Inhibition studies with di-t-butyl nitroxide were carried out by addition of di-t-butyl nitroxide at the same time as the anion. The results of these respective studies are shown in Table 1—4.

Reactions between α-Nitrosulphides (**1c**, **e**, and **f**) *and Sodium p-Chlorophenylthiolate in* MeOH–*Water Solution.*—The α-nitrosulphides (**1c**, **e**, and **f**) (1 mmol) were each treated with sodium *p*-chlorophenylthiolate for 5 h in MeOH–water (85:15, v/v) solution using the general procedure. The resulting precipitate was filtered off and recrystallised from ethanol to yield crystals of bis(*p*-chlorophenyl) disulphide which was characterised by m.p. and t.l.c. comparison with authentic material. Work-up of the filtrate did not yield any material. The results are shown in Table 3.

Reaction between α-Nitrosulphides (**1a** *and* **c**) *and* L-*Cysteine in* MeOH–*Water Solution.*—The α-nitrosulphides (**1a** and **c**) (1 mmol) were each treated with L-cysteine (0.242 g, 2 mmol) for 12 h, and 5 and 18 h, respectively in MeOH–H_2O (50:50, v/v) using the general procedure. At the end of the reaction time the pH was adjusted to 5.5 and the precipitate was filtered off and washed with MeOH–water (50:50, v/v) to yield crystals of L,L-cystine. The cystine was identified by its m.p. The filtrate was extracted with dichloromethane (3 × 50 ml), the combined extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield the respective unchanged α-nitrosulphides. The α-nitrosulphides were recrystallised from acetone–water and characterised by m.p. and t.l.c. comparison with authentic material. The results are presented in Table 3.

Reaction between α-Nitrosulphides (**1c**, **d**, **e**, *and* **f**) *and the Anion of 2-Nitropropane.*—The reactions were carried out as detailed in the general procedure for $S_{RN}1$ reactions using DMF or DMSO as solvent with α-nitrosulphide (1 mmol) and the anion of 2-nitropropane (0.17 g, 1.5 mmol) as reactants. The product mixtures were analysed by ^1H n.m.r. spectroscopy using an internal standard. In each reaction (not including the inhibition studies) the semi-crystalline residue, obtained after removal of the solvent under reduced pressure after analysis, was leached with light petroleum (b.p. 40—60 °C) to yield a

crystalline residue. The residue was recrystallised from methanol to yield crystals of 2,3-dimethyl-2,3-dinitropropane. The m.p. agreed closely, in each case, with the literature [1] m.p. of 210—211 °C.

Reactions between α-Nitrosulphides (**1a** *and* **e**) *and Sodium Benzenesulphinate.*—The α-nitrosulphides (**1a** and **e**) (2 mmol) and sodium benzenesulphinate (0.33 g, 2 mmol) were treated in DMSO for 4 h using the general procedure for $S_{RN}1$ reactions. On work-up, only starting materials (α-nitrosulphides) were recovered (50 and 64% respectively).

E.S.R. Spectroscopy of the Radical-anion of 1-*Methyl*-1-*nitroethyl* 2-*Pyrimidyl Sulphide* (**1c**).—Degassed samples of (**1c**) were irradiated as dilute solutions (*ca.* 1% v.v.) in methanol (CD_3OD was used to avoid overlap with solvent radical features) or MeTHF. They were frozen as small beads in liquid nitrogen and irradiated at 77 K in a Vickrad ^{60}Co γ-ray source to doses of up to 1 Mrad. E.s.r. spectra were measured on a Varian E109 spectrometer calibrated with proton resonance. Samples were annealed to *ca.* 140 K and recooled to 77 K for study.

The radical-anion of (**1c**) was identified by an asymmetric triplet characteristic of $Me_2C(X)\dot{N}O_2^-$ species.[17] The e.s.r. parameters used to assign the structure of the radical-anion in both MeTHF and CD_3OD for the ^{14}N nucleus were as follows: *A* values [G (or 10^{-4} T)] were $A_{\parallel}$ 43.5; $A_{\perp}$ 16.0; A_{iso} 25.2; the value for 2*B* was 18.3. A fuller description of the technique and spectral assignments is given in ref. 17.

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