Studies on Heterocyclic Chemistry. Part 24.[1] Syntheses of the 4-Aryl-isothiazol-3-yl *O*-Thioesters utilising the *S*-Thioester ⟶ *O*-Thioester Rearrangements of the 4-Aryl-5-thioxo-3-isothiazolin-3-yl *S*-Thioesters induced by Acylation Reagents, Peracid, or *N*-Bromosuccinimide

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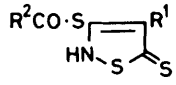
A number of 4-arylisothiazol-3-yl *O*-thioesters have been prepared utilising the *S*-thioester ⟶ *O*-thioester rearrangements of the 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thioesters (1). Reactions of the isothiazolines with acylation reagents (*e.g.* acyl chloride or acid anhydride) in the presence of boron trifluoride afforded the 5-acylthio-4-arylisothiazol-3-yl *O*-thioesters (2), which were also prepared by the reactions of the thallium(I) 4-aryl-5-sulphidoisothiazol-3-yl *O*-thioesters (3) with acyl chloride. Reactions of the isothiazolines with *m*-chloroperbenzoic acid gave the 5,5′-dithiobis(4-arylisothiazol-3-yl *O*-thioesters) (5) and the 4-arylisothiazol-3-yl *O*-thioesters (6). The disulphides (5) were also accessible by the reaction of the isothiazolines with *N*-bromosuccinimide.

O-Thioesters (thioxo-esters) rearrange into *S*-thioesters not only by reaction with chemical reagents (*e.g.* protic acids,[2] triethyloxonium tetrafluoroborate,[3] and boron trifluoride–diethyl ether [4]), but also by pyrolysis [5] and electron impact.[6] These rearrangements are considered to occur because of the nucleophilic character of the C=S group. However, the reverse processes, namely, the rearrangement of *S*-thioesters into *O*-thioesters had not been studied before we reported the reactions of the 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thioesters (1) with alkylation reagents (*e.g.* diazomethane, methyl iodide, and triethyloxonium tetrafluoroborate) which gave the 5-alkylthio-4-arylisothiazol-3-yl *O*-thioesters.[7] We now report that this type of rearrangement also readily occurs when the isothiazolines (1) are allowed to react with acylation reagents, peracid, *N*-bromosuccinimide, and aluminium chloride. These reactions gave a number of isothiazol-3-yl *O*-thioesters.

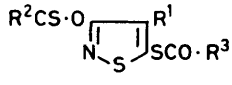
When 4-phenyl-5-thioxo-3-isothiazolin-3-yl *S*-thiobenzoate (1a) was treated with benzoyl chloride in the presence of a boron trifluoride–acetic acid complex or boron trifluoride—diethyl ether, 5-benzoylthio-4-phenylisothioazol-3-yl *O*-thiobenzoate (2a) was obtained. Its structure was established by an independent synthesis from the thallium(I) salt (3a), prepared in high yield from (1a), thallium(I) ethoxide, and benzoyl chloride. The i.r. spectrum of this salt showed no ν(C=O) absorption, indicating that the *S*-thioester ⟶ *O*-thioester rearrangement had occurred during the course of its preparation. Other related 4-aryl-5-benzoylthioisothiazol-3-yl *O*-thioesters (2b)—(2e) and (2g) were similarly prepared by either, or both, of these methods. The reaction seems to be limited to aromatic acyl chlorides since all attempts to acylate the isothiazolines (1) with aliphatic acyl chlorides, including ethyl chloroformate, failed. An ester was also ineffective for acylating (1), as shown by the reaction of (1a) with methyl *p*-chloroformylbenzoate to give (2g). Aluminium chloride is less effective than boron trifluoride, since a substantial amount of (1a) remained unchanged under comparable conditions.

Preparations of the 5-acylthio-4-arylisothiazol-3-yl *O*-thiobenzoates (2h)—(2j) and the *O*-thiocinnamoates (2k) and (2l) were also achieved by using acetic and



(1)

a; $R^1 = R^2 = Ph$
b; $R^1 = p\text{-}MeC_6H_4$, $R^2 = Ph$
c; $R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$
d; $R^1 = Ph$, $R^2 = p\text{-}MeC_6H_4$
e; $R^1 = Ph$, $R^2 = p\text{-}ClC_6H_4$
f; $R^1 = Ph$, $R^2 = p\text{-}MeOC_6H_4$
g; $R^1 = Ph$, $R^2 = p\text{-}NO_2C_6H_4$
h; $R^1 = Ph$, $R^2 = p\text{-}MeO_2CC_6H_4$
i; $R^1 = p\text{-}MeC_6H_4$, $R^2 = p\text{-}ClC_6H_4$
j; $R^1 = Ph$, $R^2 = PhCH{=}CH-$
k; $R^1 = Ph$, $R^2 = Me$
l; $R^1 = p\text{-}ClC_6H_4$, $R^2 = Me$
m; $R^1 = Ph$, $R^2 = Pr^n$



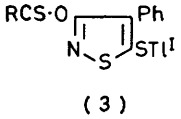
(2)

a; $R^1 = R^2 = R^3 = Ph$
b; $R^1 = R^3 = Ph$, $R^2 = p\text{-}ClC_6H_4$
c; $R^1 = R^3 = Ph$, $R^2 = p\text{-}MeOC_6H_4$
d; $R^1 = R^3 = Ph$, $R^2 = p\text{-}MeC_6H_4$
e; $R^1 = R^3 = Ph$, $R^2 = p\text{-}NO_2C_6H_4$
f; $R^1 = R^3 = Ph$, $R^2 = PhCH{=}CH-$
g; $R^1 = R^2 = Ph$, $R^3 = p\text{-}MeO_2CC_6H_4$
h; $R^1 = R^2 = Ph$, $R^3 = Me$
i; $R^1 = p\text{-}MeC_6H_4$, $R^2 = p\text{-}ClC_6H_4$, $R^3 = Me$
j; $R^1 = R^2 = Ph$, $R^3 = Et$
k; $R^1 = Ph$, $R^2 = PhCH{=}CH-$, $R^3 = Me$
l; $R^1 = Ph$, $R^2 = PhCH{=}CH-$, $R^3 = Et$
m; $R^1 = R^3 = Ph$, $R^2 = Pr^n$

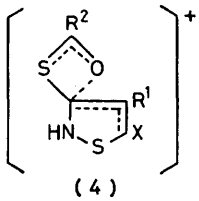
propionic anhydrides in the presence of a boron trifluoride–acetic acid complex. An absorption at ν 1 660—1 670 cm^{-1}, characteristic of the *S*-thioesters of the type ArCO·S–,[8] as observed for the compounds (1a)—(1j) and (2a)—(2g), was absent in the i.r. spectra of (2h)—(2l). Instead, the spectra showed a ν(C=O) band at 1 700 cm^{-1} characteristic of the *S*-thioesters of the

type RCO·S⁻.[8] Acylation with phthalic anhydride was unsuccessful, however.

Acylations of the isothiazolines (1) involves electrophilic attack by the complex of the acid chloride (or acid



(3)

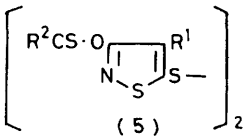


(4)

a; R = Ph
b; R = *p*-ClC$_6$H$_4$
c; R = *p*-NO$_2$C$_6$H$_4$
d; R = PhCH=CH

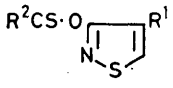
anhydride) with the Lewis acid on the C=S group of (1), accompanied by rearrangement within the C-3 substituent *via* a resonance-stabilised ion (4; X = −S−acyl).

When the isothiazoline (1a) was allowed to react with *m*-chloroperbenzoic acid (1.1 mol equiv.) in methylene chloride at room temperature, a compound, $C_{32}H_{20}N_2O_2S_6$, was obtained in an almost quantitative yield. There was no i.r. absorption in the region >1 600 cm^{-1} and the u.v. spectrum resembled that of 5-methylthio-4-phenylisothiazol-3-yl *O*-thiobenzoate.[7] Reduction of



(5)

a; R^1 = R^2 = Ph
b; R^1 = *p*-MeC$_6$H$_4$, R^2 = Ph
c; R^1 = *p*-ClC$_6$H$_4$, R^2 = Ph
d; R^1 = Ph, R^2 = *p*-MeC$_6$H$_4$
e; R^1 = Ph, R^2 = *p*-ClC$_6$H$_4$
f; R^1 = Ph, R^2 = *p*-MeOC$_6$H$_4$
g; R^1 = Ph, R^2 = *p*-NO$_2$C$_6$H$_4$
h; R^1 = Ph, R^2 = *p*-MeO$_2$CC$_6$H$_4$



(6)

a; R^1 = R^2 = Ph
b; R^1 = Ph, R^2 = *p*-MeC$_6$H$_4$
c; R^1 = Ph, R^2 = *p*-MeOC$_6$H$_4$
d; R^1 = Ph, R^2 = *p*-NO$_2$C$_6$H$_4$
e; R^1 = Ph, R^2 = *p*-MeO$_2$CC$_6$H$_4$
f; R^1 = Ph, R^2 = Me
g; R^1 = *p*-ClC$_6$H$_4$, R^2 = Me
h; R^1 = Ph, R^2 = Pr^n

this compound with a 3 : 1 mixture of sodium borohydride and aluminium chloride [9] gave a high yield of the isothiazoline (1a). From these observations, the structure of 5,5′-dithiobis-(4-phenyl-3-isothiazol-3-yl *O*-thiobenzoate) (5a) was assigned.[10] Similarly, the compounds (1b)—(1e) afforded the corresponding disulphides (5b)—(5e) as the sole isolable product, in good yields.

However, treatment of the isothiazoline (1h) with the peracid under similar conditions yielded 4-phenylisothiazol-3-yl *O*-(*p*-methoxycarbonylthiobenzoate) (6e) in 17% yield along with 55% of the disulphide (5h). The structure of compound (6e) is consistent with its ^{1}H n.m.r. spectrum (CF_3CO_2D), which includes a sharp 1 H singlet at δ 9.69 assigned to a proton on C-5, as well as signals at δ 4.10 (s, 3 H), 7.50—7.83 (m, 5 H), 8.03 (d, *J* 8 Hz, 2 H), and 8.32 (d, *J* 8 Hz, 2 H). The reactions of the isothiazolines (1f) and (1g) with the peracid (1.1 mol equiv.) were also studied. The compound (1f) gave the disulphide (5f) (70%) together with the isothiazole (6c) (14%), whereas separation of the products from the reaction mixture of (1g) in analytically pure states was not possible. When 2 mol equiv. of the peracid were used, the isothiazoles (6a)—(6e) could be isolated more readily and/or in better yields.

Compared with the *S*-thiobenzoate derivatives, the 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thiocinnamate (1j), *S*-thioacetates (1k) and (1l), and *S*-thiobutyrate (1m) appear to be less effective towards acylation reagents and peracid. Reactions of the compounds (1j) and (1m) with benzoyl chloride afforded low yields of the corresponding rearranged products (2f) and (2m), with substantial amounts of the initial isothiazolines being recovered, whereas treatment of the compounds (1k)—(1m) with the peracid (2 mol equiv.) also left 16—27% of the initial material unchanged, giving moderate yields of the 4-aryl-isothiazol-3-yl *O*-thioesters (6f)—(6h) only.

The structures of the isothiazoles thus prepared were proved by an independent synthesis of (2f) and by the i.r. and ^{1}H n.m.r. spectra for (2m) and (6f)—(6h). The ν(C=O) absorption occurred at 1 670 cm^{-1} for (2m) [8] and the i.r. spectra of (6f)—(6h) showed no ν(C=O). The ^{1}H n.m.r. spectra [$CDCl_3$ or $(CD_3)_2SO$] of compounds (6f)—(6h) displayed a sharp 1 H singlet at δ 8.64 assigned to a proton on C-5 of the isothiazole ring.[11] The Me and CH_2 protons next to the C=S group of (2m) and (6f)—(6h) are seen at δ 2.4 and 2.6—2.7, respectively, *i.e.* shifted down-field compared with those next to the C=O group of (1l) (δ 2.17) and (1m) (δ 2.30). The ^{1}H n.m.r. chemical shifts of the CH_2 group adjacent to the C=S group of *O*-thioesters have been reported to be δ 2.67—3.07.[12]

The hydrogen atom which is incorporated at C-5 of the isothiazole ring appears to arise from the acidic hydrogen of the peracid, since a deuteriated product was not obtained by either of the following experiments: (i) treating the reaction mixture of (1m) with a solution of sodium carbonate in deuterium oxide and (ii) reactions of (1m) in $CDCl_3$. These results were confirmed by ^{1}H n.m.r. spectrometry. It has been reported that treatment of heterocyclic thiones with hydrogen peroxide (3 mol equiv.) in acetic acid produces either heteroaromatic cations or the corresponding oxo-derivatives.[13] Since the 2-alkyl-3-isothiazoline-5-thiones were successfully converted into the corresponding isothiazolium salts,[13b] incorporation of a hydrogen attached to the nitrogen of compounds (1) is unlikely. Although a mechanism whereby the sulphur atom on C-5 is eliminated is, as yet, unknown, desulphurisation may ultimately

lead to the formation of a cation (4; X = H) from which the isothiazoles (6) are produced by a mechanism completely analogous to the one suggested earlier.[7] Formation of the isothiazoles (6) by a further reaction of the disulphides (5) with the peracid is not an important route, since treatment of (5a) with the peracid gave only a 12% yield of (6a). *S*-Thiosulphinate [14] and/or *S*-thiosulphonate,[15] expected from this reaction, were not isolated.

The disulphides (5) are produced from the isothiazolines (1) not only by the treatment with peracid, but also by treatment with *N*-bromosuccinimide and aluminium chloride, but none of these reactions have been mechanistically clarified, as yet.

EXPERIMENTAL

M.p.s were determined in a capillary tube. Molecular weights of the new compounds were determined by field-desorption mass-spectrometry with a Hitachi M-80 spectrometer. ^{1}H N.m.r. spectra were recorded at 60 MHz on a Hitachi R-24-B spectrometer (Me_4Si as internal standard). Kieselgel 60 was used for chromatography. Petroleum E and petroleum L refer to the fractions of boiling ranges 30—70 °C and 70—120 °C, respectively. Recorded yields are based on the material before recrystallisation, unless otherwise stated; in each case the material was a single product (t.l.c.) whose i.r. spectrum was practically identical with that of the material after recrystallisation.

Preparations of the 4-*Aryl*-5-*thioxo*-3-*isothiazolin*-3-*yl* S-*Thioesters* (1d)—(1h), (1j), (1l), *and* (1m).—These thioesters were prepared by a method essentially similar to that in the literature,[7] unless otherwise stated below. The reaction mixture of 3-mercapto-4-phenyl-3-isothiazoline-5-thione (1.125 g) with *p*-nitrobenzoyl chloride (0.928 g) in pyridine (5 ml) was poured into water, acidified, and 4-*phenyl*-5-*thioxo*-3-*isothiazolin*-3-*yl* S-(p-*nitrothiobenzoate*) (1g) (0.94 g) was collected by filtration. The filtrate was extracted with chloroform, the dried ($CaCl_2$) extracts were evaporated off, and the residue was chromatographed with benzene to give an additional quantity of the *S*-thioester (0.06 g). 4-*Phenyl*-5-*thioxo*-3-*isothiazolin*-3-*yl* S-*thiocinnamoate* (1j) was best prepared as follows. The reaction mixture of 3-mercapto-4-phenyl-3-isothiazoline-5-thione (1.125 g) and cinnamoyl chloride (0.833 g) in pyridine (5 ml) was poured into water, acidified, and extracted with chloroform. The extracts were dried ($CaCl_2$), evaporated to dryness, and the residue was dissolved in cold chloroform (15 ml) and stirred for 10 min. The *S*-thioester (1j) crystallised out of the solution and was collected by filtration. Analytical and spectroscopic data of the new 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thioesters (1d)—(1h), (1j), (1h), and (1m) are given in Table 1.

Preparations of the 5-*Acylthio*-4-*arylisothiazol*-3-*yl* O-*Thioesters* (2a)—(2m).—(a) A solution of the 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thioester (0.25 mmol) [(1a), (1d)—(1g), (1j), and (1m)] were used, benzoyl chloride (0.1 ml) [or methyl *p*-chloroformylbenzoate (0.3 mmol)], and a boron trifluoride–acetic acid complex (or boron trifluoride–diethyl ether) (0.2 ml) in methylene chloride (20 ml) was set aside at room temperature for 24 h and then poured into water. The organic layer was separated, dried ($CaCl_2$), and evaporated to dryness. Trituration of the residue with ethanol gave a solid which was filtered off. Two recrystallisations afforded the 4-*aryl*-5-*benzoylthioisothiazol*-3-*yl* O-*thioesters* (2a)—(2g) and (2m), whose analytical and spectroscopic data are given in Table 2. The filtrates of the compounds (2f) and (2m) were evaporated to dryness and the residue was chromatographed with benzene or chloroform to give the initial *S*-thioesters (1j) (10%) and (1m) (34%), respectively.

(b) Thallium(I) ethoxide (0.1 ml) was added to a stirred solution of the *S*-thioesters (0.5 mmol) [(1a), (1e), (1g), and (1j) were used] in dry tetrahydrofuran (THF) (20 ml) to form immediately the corresponding *thallium*(I) 4-*aryl*-5-*sulphidoisothiazol*-3-*yl* O-*thiobenzoates* (3), which was filtered off, washed well with dry THF, and dried under reduced pressure. The salts gave no ν(C=O) absorption in their i.r. spectra and were obtained in yields of 88—100%. Benzoyl chloride (0.1 ml) was added to a mixture of the salt in dry THF (20 ml) and stirred at room temperature for 1 h, during which time the colour of the mixture changed from brown to bright yellow. Thallium(I) chloride was filtered off and the filtrate was evaporated to dryness to leave the corresponding 4-*aryl*-5-*benzoylthioisothiazol*-3-*yl* O-*thioesters* (2a)—(2b), (2e), and (2f), whose overall yields are given in Table 2.

(c) A boron trifluoride–diacetic acid complex (0.2 ml) was added to a stirred mixture of the *S*-thioesters (0.5 mmol) [(1a), (1i), and (1j) were used] and acetic or propionic anhydride (5 ml). A homogeneous solution was formed within a few minutes, which was poured into water after 1 h. Pale orange precipitates were filtered off and recrystallised twice to give the 5-*acylthio*-4-*arylisothiazol*-3-*yl* O-*thioesters* (2h)—(2l), whose analytical and spectroscopic data are given in Table 2.

(d) A mixture of the *S*-thioester (1a) (0.164 g, 0.5 mmol), aluminium chloride (0.07 g, 0.5 mmol), and benzoyl chloride (0.1 ml) in carbon disulphide (20 ml) was stirred at room temperature for 24 h and worked up as in (a). Chromatography of the reaction mixture with benzene gave 5-benzoylthio-4-phenylisothiazol-3-yl *O*-thiobenzoate (2a), 0.04 g (17%) (after recrystallisations) followed by the unchanged *S*-thioester (0.07 g, 44%).

Reactions of the 4-*Aryl*-5-*thioxo*-3-*isothiazolin*-3-*yl* S-*Thioesters with* m-*Chloroperbenzoic Acid*.—(a) *m*-Chloroperbenzoic acid (80% purity) (1.1 mmol) was added to a solution of the *S*-thioesters (1 mmol) [(1a)—(1f) and (1h) were used] in methylene chloride (20 ml). The colour of the solution intensified and then cleared within a few minutes. The mixture was stirred at room temperature for 1 h and then washed with aqueous sodium hydrogencarbonate. The organic layer was separated, dried ($CaCl_2$), and evaporated off. Chromatography of the residue with benzene gave the corresponding 4-*arylisothiazol*-3-*yl* O-*thioesters* (6), 5,5′-*dithiobis*-(4-*arylisothiazol*-3-*yl* O-*thioesters*) (5), and the initial *S*-thioesters (1), successively. The disulphides (5b)—(5d) and (5f) crystallised out of the solution during the course of the reactions. They were filtered off and washed well with aqueous sodium hydrogencarbonate. The filtrate was worked up to give an additional quantity of the disulphide. The reactions of the *S*-thioesters (1a)—(1c) and (1e) gave the disulphides (5a)—(5c) and (5e) only. The reaction of the *S*-thioester (1d) gave the disulphide (5d) and the initial *S*-thioester (2%) was also recovered. The reactions of the *S*-thioesters (1f) and (1h) yielded not only the disulphides (5f) and (5h), but also 4-*phenylisothiazol*-3-*yl* O-(p-*methoxythiobenzoate*) (6c) (14%) and 4-*phenylisothiazol*-3-*yl* O-(p-*methoxycarbonylbenzoate*) (6e) (17%). Analytical and spectroscopic data of the disulphides (5a)—(5f) and (5h)

TABLE 1

Analytical and spectroscopic data of the 4-aryl-3-isothiazolin-3-yl *S*-thioesters (1d)—(1h), (1j), and (1l)—(1m) [a]

Compound (formula)	Yield (%)	M.p. (°C) (decomp.)	Found (%) [Required (%)] C	H	N	$\lambda_{max.}$ (nm) [j] (log ϵ)	$\nu_{max.}$ (cm^{-1})	δ_H
(1d) [b] ($C_{17}H_{13}NOS_3$)	69	189—190	59.7 [59.4]	4.0 [3.8]	3.9 [4.1]	265sh (4.27) 320 (4.29) 420 (4.16)	3 350 [j] 1 665	2.40 (s, 3 H) [l] 7.17—7.67 (m, 9 H) 8.76 (s,br, 1 H)
(1e) [c] ($C_{16}H_{10}ClNOS_3$)	76	210—212	53.1 [52.8]	3.0 [2.8]	3.8 [3.85]	255 (4.45) 317 (4.41) 422 (4.27)	3 360 [j] 1 670	7.43—7.90 (m, 9 H) [m, n]
(1f) [d] ($C_7H_{13}NO_2S_3$)	61	200—202	57.1 [56.8]	3.95 [3.65]	4.0 [3.9]	285 (4.10) 325 (4.30) 420 (4.04)	3 360 [j] 1 660	3.81 (s, 3 H) [l] 6.88 (d, J 9 Hz, 2 H) 7.32—7.60 (m, 7 H) 8.62 (s,br, 1 H)
(1g) [e] ($C_{16}H_{10}N_2O_3S_3$)	57	243—244	51.6 [51.3]	2.6 [3.2]	7.4 [7.5]	318 (4.16) 431 (3.93)	3 300 [k] 1 670	7.43 (s, 5 H) [n, o] 7.86 (d, J 9 Hz, 2 H) 9.27 (d, J 9 Hz, 2 H)
(1h) [f] ($C_{18}H_{13}NO_3S_3$)	49	185—187	55.85 [55.8]	3.3 [3.4]	3.6 [3.6]	316 (4.50) 423 (4.33)	3 360 [j] 1 725 1 675	3.97 (s, 3 H) [l] 7.30—7.73 (m, 5 H) 7.69 (d, J 9 Hz, 2 H) 8.19 (d, J 9 Hz, 2 H) 8.86 (s, br, 1 H)
(1j) [g] ($C_{18}H_{13}NOS_3.\frac{1}{2}MeCN$)	56	227—229	60.6 [60.7]	3.9 [3.9]	5.6 [5.6]	332 (4.46) 425 (4.11)	3 230 [k] 1 665	2.08 (s, 1.5 H) [m, n] 6.72 (d, J 15 Hz, 1 H) 7.50 (s, 7 H) 7.78 (m, 3 H) 8.14 (d, J 15 Hz, 1 H)
(1l) [h] ($C_{11}H_8ClNOS_3$)	92	244—246	43.9 [43.8]	2.6 [2.7]	4.5 [4.6]	308 (4.19) 413 (4.23)	3 370 [j] 1 705	2.17 (s, 3 H) [n, o] 7.20 (d, J 8 Hz, 2 H) 7.50 (d, J 8 Hz, 2 H)
(1m) [i] ($C_{13}H_{13}NOS_3$)	84	168—170	52.6 [52.85]	4.35 [4.4]	4.7 [4.7]	308 (4.11) 413 (4.15)	3 370 [j] 1 690	0.93 (t, J 7 Hz, 3 H) [n, o] 1.66 (sext, J 7 Hz, 2 H) 2.30 (t, J 7 Hz, 2 H) 7.25 (m, 2 H) 7.53 (m, 3 H) 7.97 (s, br, 1 H)

[a] Recrystallisation solvents: EtOH for (1d) and (1e); MeOH for (1f); CH_2Cl_2 for (1g) and (1l); MeCN for (1h) and (1j); and CCl_4 for (1m). [b] Yellowish orange rods. [c] Reddish orange rods. [d] Yellow needles. [e] Reddish brown prisms. [f] Orange needles. [g] Orange cubes. [h] Yellow prisms. [i] Yellow rods. [j] Taken for $CHCl_3$ solutions. [k] Taken as Nujol mulls. [l] Taken for $CDCl_3$ solutions. [m] Taken for CF_3CO_2D solutions. [n] An NH proton was not visible. [o] Taken for $[(CD_3)_2SO]$.

TABLE 2

Analytical and spectroscopic data of 5-acylthio-4-arylisothiazol-3-yl *O*-thioesters (2a)—(2l) [a]

Compound (formula)	Yield [i, j] (%) A	B	C	M.p. (°C)	Found (%) [Required (%)] C	H	N	$\lambda_{max.}$ (nm) [k] (log ϵ)	$\nu_{max.}$ [l] (cm^{-1})
(2a) [b] ($C_{23}H_{15}NO_2S_2$)	60	38		171—172	64.0 [63.7]	3.7 [3.5]	3.1 [3.2]	256 (4.54) 407 (4.49)	1 665
(2b) [c] ($C_{23}H_{14}ClNO_2S_3$)	62	47		181—182	58.85 [59.0]	2.7 [3.0]	2.9 [3.0]	275 (4.43) 407 (4.46)	1 660
(2c) [c] ($C_{24}H_{17}NO_3S_3$)	42			205—206	62.15 [62.2]	3.7 [3.7]	2.85 [3.0]	300 (4.35) 411 (4.53)	1 665
(2d) [b] ($C_{24}H_{17}NO_2S_3$)	57			170	64.55 [64.4]	3.6 [3.8]	3.0 [3.1]	278 (4.38) 408 (4.42)	1 665
(2e) [c] ($C_{23}H_{14}N_2O_4S_3$)	59	41		183—185 (decomp.)	57.5 [57.7]	2.9 [2.95]	5.75 [5.9]	269 (4.58) 413 (4.54)	1 670
(2f) [c] ($C_{25}H_{17}NO_2S_3$)	19	25		191—192 (decomp.)	65.1 [65.3]	3.6 [3.7]	3.1 [3.05]	304 (4.33) 417 (4.44)	1 660
(2g) [d] ($C_{25}H_{17}NO_4S_3$)	57			180—181	61.1 [61.1]	3.5 [3.5]	2.8 [2.85]	262 (4.53) 408 (4.35)	1 730 1 660
(2h) [e] ($C_{18}H_{13}NO_2S_3$)			67	175—176	58.1 [58.2]	3.6 [3.5]	3.7 [3.8]	270 (4.57) 401 (4.60)	1 700
(2i) [d] ($C_{19}H_{14}ClNO_2S_3$)			63	164—166	54.3 [54.3]	3.3 [3.4]	3.4 [3.3]	275 (4.50) 403 (4.56)	1 700
(2j) [e] ($C_{19}H_{15}NO_2S_3$)			70	143—144	59.15 [59.2]	3.7 [3.9]	3.5 [3.6]	268 (4.25) 402 (4.34)	1 700
(2k) [b, f] ($C_{20}H_{15}NO_2S_3$)			57	183—185 (decomp.)	60.3 [60.4]	3.7 [3.8]	3.3 [3.5]	297 (4.36) 414 (4.54)	1 705
(2l) [b, g] ($C_{21}H_{17}NO_2S_3$)			57	134—136 (decomp.)	61.4 [61.3]	4.1 [4.2]	3.3 [3.4]	296 (4.30) 414 (4.50)	1 705
(2m) [b, h] ($C_{20}H_{17}NO_2S_3$)			27	139—140	60.3 [60.1]	4.5 [4.3]	3.3 [3.5]	252 (4.37) 305sh (3.88) 390 (4.12)	1 670

[a] Recrystallisation solvents: EtOH for (2a)—(2d), (2f), and (2i); Me_2CO for (2e) and (2k)—(2l); AcOEt for (2h); MeCN for (2g); petroleum L for (2j); and aq. Me_2CO for (2m). [b] Yellow needles. [c] Yellow rods. [d] Orange needles. [e] Orange prisms. [f] δ_H (CF_3CO_2D) 2.65 (s, 3 H), 6.75 (d, J 16 Hz, 1 H), 7.38—7.58 (m, 7 H), 7.75—7.85 (m, 3 H), and 8.23 (d, J 16 Hz, 1 H). [g] δ_H (CF_3CO_2D) 1.35 (t, J 7 Hz, 3 H), 2.92 (q, J 7 Hz, 2 H), 6.73 (d, J 16 Hz, 1 H), 7.33—7.60 (m, 7 H), 7.73—7.83 (m, 3 H), and 8.17 (d, J 16 Hz, 1 H). [h] δ_H ($CDCl_3$) 0.92 (t, J 7 Hz, 3 H), 1.50—1.90 (m, 2 H), 2.60 (t, J 7 Hz, 2 H), 7.23—7.63 (m, 8 H), and 7.76—7.95 (m, 2 H). [i] A boron trifluoride–acetic acid complex was used. [j] Refers to the yields of the product after two recrystallisations. [k] Taken for $CHCl_3$ solutions. [l] Taken as Nujol mulls.

TABLE 3

Analytical and spectroscopic data of 5,5′-dithiobis-(4-arylisothiazol-3-yl *O*-thioesters) (5a)—(5h) [a]

Compound (formula)	Yield [c] (%)	M.p. (°C) (decomp.)	Found (%) [Required (%)] C	H	N	S	$\lambda_{max.}$ (nm) [f] (log ε)	$\nu_{max.}$ [g] (cm^{-1})	δ_H
(5a) [b] ($C_{32}H_{20}N_2O_2S_6$)	94	209—210	58.7 [58.5]	3.15 [3.1]	4.3 [4.3]	29.05 [29.3]	269 (4.44) 320sh (3.82) 402 (4.58)	1 260	7.53—8.00 (m, 20 H) [h]
(5b) [b] ($C_{34}H_{24}N_2O_2S_6$)	83	232—233	59.8 [59.6]	3.5 [3.5]	4.0 [4.1]		267 (4.56) 320sh (3.82) 403 (4.65)	1 260	2.58 (s, 6 H) [h] 7.40—7.93 (m, 18 H)
(5c) [c] ($C_{32}H_{18}Cl_2N_2O_2S_6$)	77	264—266	52.8 [53.0]	2.7 [2.5]	3.8 [3.9]	26.3 [26.5]	269 (4.62) 320sh (3.97) 402 (4.70)	1 260	7.53—8.00 (m, 18 H) [h]
(5d) [b] ($C_{34}H_{24}N_2O_2S_6$)	73	217—219	59.4 [59.6]	3.3 [3.5]	4.3 [4.1]		275 (4.54) 402 (4.76)	1 270	2.36 (s, 6 H) [i] 7.16 (d, *J* 8 Hz, 4 H) 7.53 (s, 10 H) 8.03 (d, *J* 8 Hz, 4 H)
(5e) [d] ($C_{32}H_{18}Cl_2N_2O_2S_6$)	94	236—237	52.9 [52.95]	2.5 [2.5]	3.9 [3.9]	26.4 [26.5]	274 (4.62) 403 (4.80)	1 265	7.50 (d, *J* 9 Hz, 4 H) [h] 7.63—7.90 (m, 10 H) 7.80 (d, *J* 9 Hz, 4 H)
(5f) [b] ($C_{34}H_{24}N_2O_4S_6 \cdot \frac{1}{5}CH_2Cl_2$)	70	221—223	56.2 [56.0]	3.5 [3.35]	3.8 [3.8]	26.0 [26.2]	298 (4.51) 407 (4.89)	1 260	3.98 (s, 6 H) [h] 5.23 (s, 0.4 H) 7.12 (d, *J* 9 Hz, 4 H) 7.65—7.95 (m, 14 H)
(5g) [b] ($C_{32}H_{18}N_4O_6S_6$)	23	218—220	51.2 [51.45]	2.35 [2.4]	7.3 [7.5]		272 (4.81) 413 (4.87)	1 265	
(5h) [e] ($C_{36}H_{24}N_2O_6S_6$)	55	247—248	56.2 [55.9]	2.95 [3.1]	3.8 [3.6]		270 (4.81) 407 (4.83)	1 725 1 260	4.12 (s, 6 H) [h] 7.55—7.95 (m, 10 H) 7.95 (d, *J* 9 Hz, 4 H) 8.28 (d, *J* 9 Hz, 4 H)

[a] Recrystallisation solvents: methylene chloride–petroleum L for (5a)—(5c) and (5h); methylene chloride for (5d)—(5f); and MeCN for (5g). [b] Bright yellow needles. [c] Yellow powders. [d] Yellow prisms. [e] 1.1 Mol equiv. of *m*-chloroperbenzoic acid was used for (5a)—(5f) and (5h) and 2 mol equiv. of the peracid for (5g). [f] Taken for $CHCl_3$ solutions. [g] Taken as Nujol mulls. [h] Taken for CF_3CO_2D solutions. [i] Taken for $CDCl_3$ solutions.

TABLE 4

Analytical and spectroscopic data of 4-arylisothiazol-3-yl *O*-thioesters (6a)—(6h) [a]

Compound (formula)	M.p. (°C)	Found (%) [Required (%)] C	H	N	S	$\lambda_{max.}$ (nm) [d] (log ε)	$\nu_{max.}$ [e] (cm^{-1})	δ_H
(6a) [b] ($C_{16}H_{11}NO_2S_2$)	141—143	64.5 [64.6]	3.7 [3.7]	4.6 [4.7]	22.0 [21.6]	267 (4.14) 396 (4.27)	1 270	7.48—8.05 (m, 10 H) [f] 9.66 (s, 1 H)
(6b) [b] ($C_{17}H_{13}NOS_2$)	176—177	65.3 [65.6]	4.4 [4.2]	4.3 [4.5]	20.4 [20.6]	274 (4.18) 395 (4.41)	1 275	2.50 (s, 3 H) [f] 7.46 (d, *J* 9 Hz, 2 H) 7.67—7.93 (m, 7 H) 9.67 (s, 1 H)
(6c) [b] ($C_{17}H_{13}NO_2S_2$)	167—169	62.6 [62.4]	4.0 [4.0]	4.35 [4.3]		273 (4.18) 302 (4.13) 399 (4.55)	1 260	3.96 (s, 3 H) [f] 7.12 (d, *J* 9 Hz, 2 H) 7.60—7.80 (m, 5 H) 7.91 (d, *J* 9 Hz, 2 H) 9.60 (s, 1 H)
(6d) [c] ($C_{16}H_{10}N_2O_3S_2$)	229—231	56.3 [56.1]	2.8 [2.9]	8.0 [8.2]	18.5 [18.7]	263 (4.23) 300sh (3.78) 406 (4.23)	1 270	7.57—7.86 (m, 5 H) [f] 8.17 (d, *J* 8 Hz, 2 H) 8.48 (d, *J* 8 Hz, 2 H) 9.73 (s, 1 H)
(6e) [c] ($C_{16}H_{13}NO_3S_2 \cdot \frac{1}{5}CH_2Cl_2$)	232—233	58.7 [58.7]	3.6 [3.6]	3.6 [3.8]	16.9 [17.2]	265sh (4.38) 401 (4.49)	1 730 1 270	4.10 (s, 3 H) [f] 5.23 (s, 0.4 H) 7.50—7.83 (m, 5 H) 8.03 (d, *J* 8 Hz, 2 H) 8.32 (d, *J* 8 Hz, 2 H) 9.69 (s, 1 H)
(6f) [b] ($C_{11}H_9NOS_2$)	123—124	55.8 [56.1]	3.8 [3.9]	5.7 [5.95]	27.05 [27.25]	377 (3.82)	1 260	2.46 (s, 3 H) [g] 7.40—7.52 (m, 3 H) 7.62—7.72 (m, 2 H) 8.64 (s, 1 H)
(6g) [b] ($C_{11}H_8ClNOS_2$)	126—128	49.25 [49.0]	3.0 [3.0]	5.2 [5.2]	23.9 [23.8]	262 (3.94) 377 (3.90)	1 260	2.43 (s, 3 H) [g] 7.40 (d, *J* 8 Hz, 2 H) 7.67 (d, *J* 8 Hz, 2 H) 8.64 (s, 1 H)
(6h) [b] ($C_{13}H_{13}NOS_2$)	74—75	59.55 [59.3]	4.9 [5.0]	5.2 [5.3]	24.5 [24.35]	258 (3.90) 377 (3.96)	1 190	0.90 (t, *J* 7 Hz, 3 H) [g] 1.79 (sext, *J* 7 Hz, 2 H) 2.70 (t, *J* 7 Hz, 2 H) 7.38—7.55 (m, 3 H) 7.65—7.85 (m, 2 H) 8.64 (s, 1 H)

[a] Recrystallisation solvents: petroleum L for (6a)—(6d); methylene chloride–petroleum L for (6e); EtOH for (6f); and petroleum E for (6g) and (6h). [b] Pale yellow needles. [c] Yellow needles. [d] Taken for $CHCl_3$ solutions. [e] Taken as Nujol mulls. [f] Taken for CF_3CO_2D solutions. [g] Taken for $CDCl_3$ solutions.

are given in Table 3 and those of the isothiazoles (6c) and (6e) in Table 4.

(b) The reaction described above was repeated using 2 mol equiv. of the peracid. The reaction mixtures obtained from the *S*-thioesters (1a) and (1f)—(1h) were chromatographed to give the corresponding *4-arylisothiazol-3-yl O-thioester* (6a) and (6c)—(6e) and *5,5′-dithiobis-(4-arylisothiazol-3-yl O-thioesters*) (5a) and (5f)—(5h), successively. The reaction mixture obtained from the *S*-thioester (1d) was chromatographed with benzene to give a solid, of wide melting range, followed by the initial *S*-thioester (0.01 g, 4%). A mixture of this solid and petroleum L (100 ml) was heated under reflux for 30 min and an insoluble material was filtered off and recrystallised to give *5,5′-dithiobis-(4-phenylisothiazol-3-yl O-thiotoluoate*) (5d) (0.04 g, 12%). The filtrate was filtered off once more and concentrated. A solid precipitated and was recrystallised to give *4-phenylisothiazol-3-yl O-thiotoluoate* (6b) (0.06 g, 19%). The reaction mixtures obtained from 4-aryl-5-thioxo-3-isothiazolin-3-yl *S*-thioacetates and thiobutyrates [(1d), (1l), and (1m), respectively], were chromatographed to afford the corresponding 4-arylisothiazol-3-yl *O*-thioacetates and -thiobutyrates [(6f), (6g), and (6h), respectively] followed by the unchanged *S*-thioesters. The eluants [B, benzene; C, chloroform; BC, benzene–chloroform (5 : 1)] and yields of the isothiazoles (6a) and (6c)—(6h), the disulphides (5a) and (5f)—(5h), and the unchanged *S*-thioesters are given in Table 5. Analytical and spectroscopic data of the isothiazoles (6a), (6b), (6d), and (6f)—(6h) are given in Table 4 and those of the disulphide (5g) in Table 3.

TABLE 5

Isothiazoline	Isothiazole (%)	Disulphide (%)	Uncharged material (%)
(1a)	(6a) 56 (B)	(5a) 13 (B)	
(1f)	(6c) 43 (B)	(5f) 30 (B)	
(1g)	(6d) 46 (B)	(5g) 23 (C)	
(1h)	(6e) 37 (B)	(5h) 29 (B)	
(1k)	(6f) 52 (BC)		(1k) 27 (BC)
(1l)	(6g) 43 (B)		(1l) 24 (C)
(1m)	(6h) 48 (B)		(1m) 16 (BC)

Reduction of 5,5′-Dithiobis-(4-phenylisothiazol-3-yl O-Thiobenzoate) (5a).—To a solution of sodium borohydride (0.023 g, 0.6 mmol) in dry THF (20 ml) was added a solution of the disulphide (5a) (0.39 g, 0.6 mmol) in dry THF (40 ml) followed by a solution of aluminium chloride (0.03 g, 0.2 mmol) in dry THF (2 ml), and the mixture was stirred at room temperature for 2 h and then heated under reflux for 30 min. The mixture was poured onto ice, acidified, and extracted with chloroform. Evaporation of the dried ($CaCl_2$) extracts to dryness and chromatography of the residue with benzene gave a trace amount of an unidentified material followed by 4-phenyl-5-thioxo-3-isothiazolin-3-yl *S*-thiobenzoate (1a) (0.34 g, 86%), identical with an authentic specimen.

Reaction of 5,5-Dithiobis-(4-phenylisothiazol-3-yl O-Thiobenzoate) (5a) *with* m-*Chloroperbenzoic Acid.*—*m*-Chloroperbenzoic acid (80% purity) (0.072 g, 0.33 mmol) was added to a solution of the disulphide (5a) (0.110 g, 0.16 mmol) in methylene chloride (30 ml). The mixture was stirred at room temperature for 1 h and worked up as described for the preparation of (5a). Benzene eluted 4-phenylisothiazol-3-yl *O*-thiobenzoate (6a) (0.012 g, 12%; m.p. 142—144 °C, mixed m.p. 143—144 °C), further identified by mass spectrometry, followed by the initial disulphide (0.062 g, 56%).

Miscellaneous Preparations of 5,5′-Dithiobis-(4-phenylisothiazol-3-yl) O-Thiobenzoate (5a).—(a) *N*-Bromosuccinimide (0.146 g, 0.8 mmol) was added to a stirred mixture of the *S*-thioester (1a) (0.271 g, 0.8 mmol) in acetic acid (20 ml) to form immediately a voluminous, insoluble material; the mixture was then stirred at room temperature for 1 h. The insoluble material was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was combined with the filtered material, washed with aqueous sodium hydroxide, and extracted with chloroform. Evaporation of the extracts to dryness and chromatography of the residue with benzene gave the disulphide (5a) (0.173 g, 64%), identical with an authentic specimen.

(b) A solution of aluminium chloride (0.06 g, 0.44 mmol) in dry THF (4 ml) was added to a solution of the *S*-thioester (1a) (0.16 g, 0.5 mmol) in dry THF (20 ml) and the mixture was stirred at room temperature for 2 h, then heated under reflux for 30 min, and worked up as described for the reduction of the disulphide (5a). Benzene eluted the disulphide (5a) (0.028 g, 18%), followed by the unchanged *S*-thioester (0.119 g, 74%). Use of zinc chloride or a boron trifluoride–diacetic acid complex gave a trace amount of the disulphide (5a) (<1%).

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