Acid-catalysed Rearrangement of Bis-5,6-Dihydro-4*H*-1,3-thiazin-2-yl and Other Disulphides and Related Reactions

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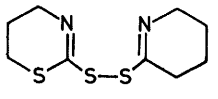
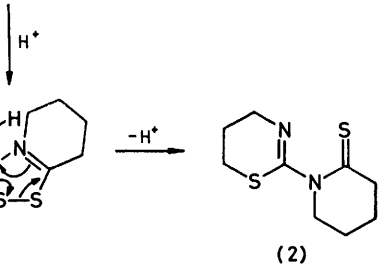
Some dithiocarbamates, thiocarbamates, and thiourea derivatives have been oxidised to the disulphides $[R^1X(R^2N{=})C]_2S_2$ with iodine. In the presence of trifluoroacetic acid, these lost sulphur giving the thiocarbonyl derivatives $R^1X(R^2N{=})C{-}N(R^2)CSR^1$ (R^1, R^2, X = $[CH_2]_3$, S; $[CH_2]_2$, S; Me, Me, S; Et, $PhCH_2$, O; 5α-cholestan-3β-yl, Et, O; and Me, Ph, NMe). These rearrangements were most plausibly intramolecular, but proceeded by varying extents of intermolecular scrambling.

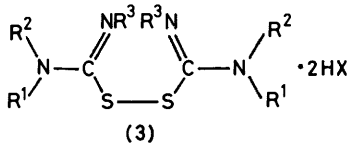
RECENTLY we reported the acid-catalysed conversion of bis-5,6-dihydro-4*H*-1,3-thiazin-2-yl disulphide (1) into 1-(5,6-dihydro-4*H*-1,3-thiazin-2-yl)-1,3-thiazine-2-thione (2).[1] This can be envisaged as proceeding intramolecularly with loss of sulphur (Scheme). Prior to our



(1)



(2)



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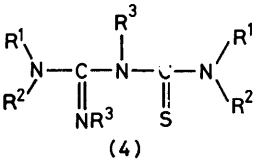
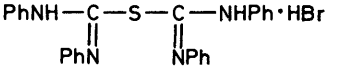


(4)

a; R^1 = Me, R^2 = H, R^3 = Ph, X = Cl
b; R^1 = Et, R^2 = H, R^3 = Ph, X = Cl
c; R^1 = R^2 = Me, R^3 = Ph, X = Cl
d; R^1 = Ph, R^2 = Me, R^3 = H, X = Cl
e; R^1 = Ph, R^2 = Et, R^3 = H, X = Cl
f; R^1 = R^3 = Ph, R^2 = H, X = Br



(5)

work, Srivastava reported the formation of the guanidine derivatives (4) on dissolution of the disulphide salts (3) in water.[2] Lacking any spectral data and acceptable standards in microanalysis these results require confirmation. More recently,[3] Srivastava and Saleem state (without data) that *NN'*-diphenylthiourea gave the disulphide (3f) with bromine. This in ethanol lost sulphur, giving initially monosulphide (5) and finally the guanidine derivative (4f). Held and Gross [4] oxidised *NN*-dimethyl-*N'*-phenylthiourea and fully characterised the product (4c). Schaeffer *et al.*[5] reported that disulphide (7a) and thioacetanilide (6a) reacted at room temperature to give the amidine derivative (8a) (4%). Here we describe further studies on this unusual reaction which more clearly define the mechanism of rearrangement.

RESULTS AND DISCUSSION

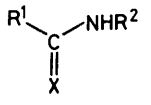
Initially, the oxidations of a series of dithiocarbamates, thioamides, thiohydrazides, *O*-alkyl thiocarbamates, and thioureas were examined. Iodine was chosen as reagent [5] since it is convenient (being self indicating) and usually provides high yields of disulphides. *S*-Methyl *N*-dithiocarbamate (9a) readily decolourised iodine in the presence of triethylamine giving an unstable oil. This lacked the N–H (i.r.) and was the disulphide (10a) (C=N, 1 600 cm^{-1}). On treatment with trifluoroacetic acid in chloroform the product lost sulphur and gave an impure oil. The oil was probably the rearranged product (11a) as a *syn*/*anti*-mixture (M^+ 208). The n.m.r. (eight singlets), i.r. (1 635 cm^{-1}), and u.v. [$\lambda_{max.}$ 248 (ε 9 100) and 269 nm (ε 9 000)] spectra were inconsistent with the isomeric sulphide (10b). In the absence of microanalysis, the assignment is tentative. Although both dithiocarbamates (9b and c) decolourised iodine and triethylamine, the unstable products [presumably (10c and d)] gave complex mixtures with trifluoroacetic acid.

Thiazolidine-2-thione (9d), iodine, and triethylamine gave the disulphide (10e) as a pure crystalline solid. On subsequent reaction with trifluoroacetic acid in chloroform, a new product ($C_6H_8N_2S_3$) was formed. This was assigned the rearranged structure (11b). The presence in the n.m.r. spectrum of four triplets ruled out the alternative sulphide (10f). Also of note was the u.v. chromophore at 277 and 307 nm.

N-Phenylthiobenzamide (6b) gave the known [5] disulphide (7b) on iodine oxidation. On attempted acid-catalysed rearrangement, only the known [5] sulphide (7c) was produced. Since the only chromophore in the u.v. spectrum was at 230 nm (ε 20 100) formulation as the alternative product (8b) was ruled out. In addition, on prolonged storage with trifluoroacetic acid, the sulphide (7c) gave the amide (6c) (100%) and the thioamide

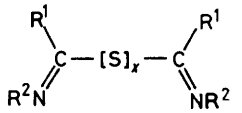
(6b) (76%), both presumably formed *via* hydrolysis by adventitious water.

Although both *N*-methylthioacetamide (6d) and piperidine-2-thione (6e) gave tar with iodine and triethylamine, *N*-phenylthioacetamide (6a) gave an unstable product, possibly the disulphide (7a). This on subsequent treatment with trifluoroacetic acid gave tar and



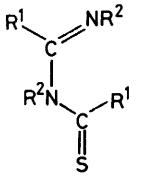
(6)

a; R^1 = Me, R^2 = Ph, X = S
b; R^1 = R^2 = Ph, X = S
c; R^1 = R^2 = Ph, X = O
d; R^1 = R^2 = Me, X = S
e; R^1, R^2 = $[CH_2]_4$, X = S
f; R^1 = Ph, R^2 = $PhCH_2$, X = S
g; R^1 = Ph, R^2 = $PhCH_2$, X = O
h; R^1 = Ph, R^2 = PhNH, X = S



(7)

a; R^1 = Me, R^2 = Ph, x = 2
b; R^1 = R^2 = Ph, x = 2
c; R^1 = R^2 = Ph, x = 1
d; R^1 = Ph, R^2 = $PhCH_2$, x = 2
e; R = Ph, R = PhNH, x = 2



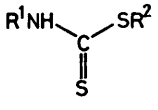
(8)

a; R^1 = Me, R^2 = Ph
b; R^1 = R^2 = Ph

the thioamide (6a). *N*-Benzylthiobenzamide (6f), on reaction with iodine and trifluoroacetic acid in sequence, gave the thioamide (6f) and the amide (6g), both plausibly formed *via* aqueous hydrolysis of the disulphide (7d). Clearly, thioamides are unsatisfactory substrates.

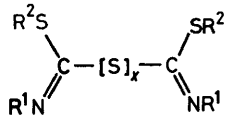
The known [6] disulphide (7e) was inert to chloroform containing a catalytic amount of trifluoroacetic acid; prolonged reaction with an excess of acid gave an intractable mixture.

The steroidal thiocarbamate (12a) did not readily react with iodine and triethylamine. Reaction, however, in the presence of *NNN'N'*-tetramethylguanidine gave the disulphide (13a). On storage in acidic chloroform, loss of sulphur occurred. The crystalline solid ($C_{60}H_{104}N_2O_2S$) obtained was clearly the rearranged product (14a) [$\lambda_{max.}$ 252 nm (ε 14 000); δ 5.43—4.9 (3α-H), 4.8—4.3 (3α-H), 4.0—3.5 (NCH_2), and 3.3—2.7 (NCH_2)]. Analogously, the *O*-ethyl *N*-phenylthiocarbamate (12b) decolourised iodine and *NNN'N'*-tetramethylguanidine giving the disulphide (13b). This, however, was stable to trifluoroacetic acid in chloroform. Presumably, the aryl nitrogen was insufficiently basic or nucleophilic for rearrangement to occur. Consistent with this, *O*-ethyl *N*-benzylthiocarbamate (12c) gave fully characterised acid-sensitive disulphide (13c) on iodine and *NNN'N'*-tetramethylguanidine oxidation. On distillation or acidification, the disulphide (13c) lost



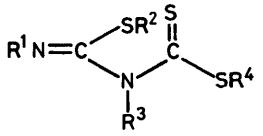
(9)

a; R^1 = R^2 = Me
b; R^1 = Et, R^2 = $PhCH_2$
c; R^1 = $PhCH_2$, R^2 = 4-$O_2NC_6H_4CH_2$
d; R^1, R^2 = $[CH_2]_2$
e; R^1, R^2 = $[CH_2]_3$



(10)

a; R^1 = R^2 = Me, x = 2
b; R^1 = R^2 = Me, x = 1
c; R^1 = Et, R^2 = $PhCH_2$, x = 2
d; R^1 = $PhCH_2$, R^2 = 4-$O_2NC_6H_4CH_2$, x = 2
e; R^1 = R^2 = $[CH_2]_2$, x = 2
f; R^1, R^2 = $[CH_2]_2$, x = 1
g; R^1, R^2 = $[CH_2]_3$, x = 1



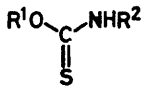
(11)

a; R^1 = R^2 = R^3 = R^4 = Me
b; R^1, R^2 = R^3, R^4 = $[CH_2]_2$
c; R^1, R^2 = $[CH_2]_3$, R^3, R^4 = $[CH_2]_2$
and R^1, R^2 = $[CH_2]_2$, R^3, R^4 = $[CH_2]_3$

sulphur giving a new product. Again, spectral data especially the u.v. [$\lambda_{max.}$ 252 nm (ε 15 400)] and n.m.r. (duplication of OEt and $PhCH_2$ signals) supported formulation as the rearranged product (14b). Although tetrahydro-1,3-oxazine-2-thione (12d) was oxidised by iodine and *NNN'N'*-tetramethylguanidine, the product [presumably the disulphide (13d)] did not rearrange with acid. Instead thione (12d) was re-formed (50%).

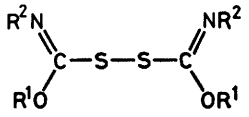
Attention was directed towards the reactions of thiourea derivatives, since in such substrates the rearrange-

ment has precedent.[2-4] Iodine, *NNN'N'*-tetramethylguanidine and 1-methylhexahydropyrimidine-2-thione (15a) gave only polymeric tars. Following the procedure of Held and Gross,[4] *NN*-dimethyl-*N'*-phenylthiourea (15b) was oxidised with thionyl chloride in carbon tetrachloride. Alkali work-up gave directly the known [4] rearranged product (17a). The structural assignment



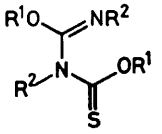
(12)

a; R^1 = 5α-cholestan-3β-yl, R^2=Et
b; R^1 = Et, R^2 = Ph
c; R^1 = Et, R^2 = $PhCH_2$
d; R^1, R^2=$[CH_2]_3$



(13)

a; R^1 = 5α-cholestan-3β-yl, R^2 = Et
b; R^1 = Et, R^2 = Ph
c; R^1 = Et, R^2 = $PhCH_2$
d; R^1, R^2 = $[CH_2]_3$

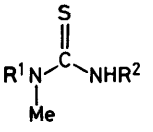


(14)

a; R^1 = 5α-cholestan-3β-yl, R^2=Et
b; R^1 = Et, R^2 = $PhCH_2$

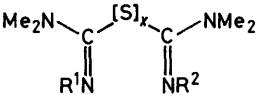
was again in full agreement with analysis and spectral data [$\nu_{max.}$ 1 080 cm^{-1} (C=S); $\lambda_{max.}$ 255 nm (ε 18 800); δ 2.9 and 2.53 (12 H, 2 × s); *m/e* 326 (M^+)]. The thiourea derivative (15b) on oxidation with iodine and triethylamine gave the crystalline and fully authenticated disulphide (16a). This on dissolution in chloroform containing a trace of acid gave the rearranged product (17a), identical with the previous sample. The isomeric monosulphide (16d) was prepared by the condensation of the chloride (18a) and the thiourea (15b) *in situ*, or by desulphurisation of disulphide (16a) with triphenylphosphine. The product (16d) was clearly isomeric with the rearranged compound (17a). Of note, the i.r. spectrum showed the absence of C=S and the n.m.r. spectrum showed all four *N*-methyls to be equivalent (δ 2.68). On acidification (see below) the sulphide (16d) rearranged giving the expected guanidine derivative (17a).

The disulphide (16a), sulphide (16d), and rearranged product (17a) were chosen for further mechanistic study. *NN*-Dimethyl-*N'*-pentadeuteriophenylthiourea (15c) was prepared (53%) from [$^2H_5$]aniline.[7] From this, the [$^2H_{10}$]disulphide (16b), the [$^2H_{10}$]sulphide (16e), and the [$^2H_{10}$]guanidine derivative (17b) were prepared analogously to the non-deuteriated series. Crossover experiments were carried out by the acidification of mixtures of equal quantities of the disulphides (16a and b), the monosulphides (16d and e), and the rearranged products (17a and b). The results are summarised (Table). In addition, the rearrangement of the disulphide (16a) and the monosulphide (16d) were followed by n.m.r. spectroscopy. Clearly, the monosulphide (16d) was *not* an intermediate in the disulphide (16a) rearrangement, and the monosulphide (16d) rearranged intramolecularly. The guanidine derivatives (17a and b) did not scramble in the presence of acid. The disulphides (16a and b) on



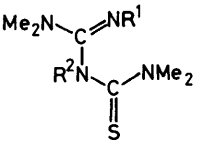
(15)

a; R^1, R^2 = $[CH_2]_3$
b; R^1 = Me, R^2 = Ph
c; R^1 = Me, R^2 = C_6D_5



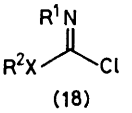
(16)

a; R^1 = R^2 = Ph, x = 2
b; R^1 = R^2 = C_6D_5, x = 2
c; R^1 = Ph, R^2 = C_6D_5, x = 2
d; R^1 = R^2 = Ph, x = 1
e; R^1 = R^2 = C_6D_5, x = 1



(17)

a; R^1 = R^2 = Ph
b; R^1 = R^2 = C_6D_5
c; R^1 = Ph, R^2 = C_6D_5 and R^1 = C_6D_5, R^2 = Ph



(18)

a; R^1 = Ph, R^2X = Me_2N
b; R^1, R^2 = $[CH_2]_3$, X = S

reaction in the presence of acid gave the rearranged product with a ratio of [$^2H_0$] (17a) : [$^2H_5$] (17c) : [$^2H_{10}$] (17b) of 1 : 0.7—2 : 1. This variable and often incomplete scrambling is curious. In addition, under mild

conditions some disulphide was recovered unchanged with a $[^2H_0]$ (16a) : $[^2H_5]$ (16c) : $[^2H_{10}]$ (16b) ratio of 1 : 0.7—2 : 1. In each case the amount of disulphide scrambling was identical with the scrambling of the guanidine derivative. This is consistent with scrambling occurring before intramolecular disulphide rearrangement. Plausibly, scrambling occurred *via* S–S homolysis, possibly also occurring in the mass spectrometer probe.

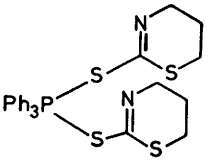
On acidification in chloroform a mixture of the disulphides (1) and (10e) gave a homogeneous (t.l.c.) oil, the mass spectrum of which was consistent with partial scrambling (*m/e* 232 : 218 : 204, 1 : 1.7 : 1). Attempts were made to prepare the sulphides (10g) for mechanistic study. The disulphide (1) and triphenylphosphine gave only the dithiocarbamate (9e) (100%) presumably formed *via* intermediate (19) and water. Alternative phosphorus(III) reagents were also unsuccessful. The chloride (18b) was prepared and fully authenticated. However, this was inert to the dithiocarbamate (9e) under diverse basic conditions. Condensation of chloride (18b) and dithiocarbamate (9e) was successful using triethylamine and stannic chloride; the rearranged product (2) was formed.

TABLE

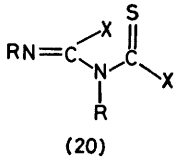
Crossover experiments

No.	Solvent	Reaction conditions *	Product	Ratio $^2H_0 : ^2H_5 : ^2H_{10}$	Mass spec. conditions	Crossover
1	$CHCl_3$	5 min	rearranged product (17a, c, b)	1 : 1.3 : 1	30 °C, 70 eV	partial
2	Benzene	5 min	rearranged product (17a, c, b)	1 : 0.7 : 1	60 °C, 70 eV	partial
3	$CHCl_3$	5 min	rearranged product (17a, c, b)	1 : 1 : 1	30 °C, 70 eV	partial
				1 : 1 : 1	30 °C, 12 eV	partial
4	CCl_4	0 °C, absence of light, 5 min	rearranged product (17a, c, b)	1 : 2 : 1	30 °C, 70 eV	complete
5	Petroleum	Reflux, 1 h, absence of light, no acid	rearranged product (17a, c, b)	1 : 2 : 1	30 °C, 12 eV	complete
6	Petroleum	12 h, irradiated by 500-W external tungsten filament lamp, no acid	rearranged product (17a, c, b)	1 : 2 : 1	30 °C, 12 eV	complete
7	$CHCl_3$	1 min, CF_3CO_2H 0.5 mol %, quenched with an excess of Et_3N	rearranged product (17a, c, b) and disulphide (16a, c, b)	1 : 1.5 : 1	30 °C, 12 eV	partial
				1 : 1.5 : 1	30 °C, 12 eV	partial
8	Petroleum	1 h, no acid, Et_3N (1 drop) added	rearranged product (17a, c, b) (minor) and disulphide (16a, c, b) (major)	1 : 0.7 : 1	30 °C, 12 eV	partial
				1 : 0.7 : 1	30 °C, 12 eV	partial
9	Petroleum	2 d, no acid, Et_3N (1 drop), in the absence of light	rearranged product (17a, c, b) and disulphide (16a, c, b)	1 : 2 : 1	30 °C, 12 eV	complete
				1 : 2 : 1	30 °C, 12 eV	complete
10	$CHCl_3$	−20 °C, absence of light, no acid, Et_3N (a drop) added, 30 min, directly injected into mass spectrometer	rearranged product (17a, c, b) and disulphide (16a, c, b)	1 : 2 : 1	30 °C, 12 eV	complete
				1 : 2 : 1	30 °C, 12 eV	complete
11	$CHCl_3$	Overnight	rearranged product (17a, b)	1 : 0 : 1	55 °C, 70 eV	none
12	$CHCl_3$	5 min	rearranged product (17a, b)	1 : 0 : 1	30 °C, 12 eV	none

* Reactions were carried out at room temperature in the presence of trifluoroacetic acid unless stated to the contrary. Entries 1—10 inclusive are crossover experiments using the disulphide (16a) and the decadeuteriodisulphide (16b) (1 : 1). Entries 11 and 12 refer to crossover experiments using the rearranged products (17a and b) and monosulphides (16d and e) respectively (see text).



(19)



(20)

Although the reaction is not general, disulphides prepared from some dithiocarbamates, thiocarbamates, and thiourea derivatives have been shown to rearrange with acid catalysis, giving the thiocarbonyl derivatives (20) and sulphur.

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage apparatus. I.r. spectra were recorded as Nujol mulls (solids) or as liquid films. U.v. and n.m.r. spectra were recorded on ethanol and deuteriochloroform ($SiMe_4$ reference) solutions, respectively, unless stated to the contrary. Mass spectra were obtained with an A.E.I. MS9 spectrometer. Preparative layer chromatography (p.l.c.) was carried out on Merck Kieselgel GF_{254} (1-mm layers). Organic extracts were dried over anhydrous sodium sulphate. Petroleum and light petroleum refer to the fractions with b.p. 60—80 °C and 40—60 °C respectively. General procedures are described in full in the first instance only.

Preparation of Thioamides, Thiohydrazides, Dithiocarbamates, Thioureas, and Thiocarbamates.—The following compounds were prepared by standard procedures: *N*-phenylthiobenzamide (6b), m.p. 101 °C (lit.,[8] 95.5—96.5 °C); *N*-methylthioacetamide (6d), m.p. 54—55 °C (lit.,[9] 58 °C); *N*-phenylthioacetamide (6a), m.p. 74 °C (lit.,[8] 75—76 °C), *N*-benzylthiobenzamide (6f), m.p. 87—88 °C (lit.,[10] 84—85 °C); piperidine-2-thione (6e), m.p. 92—93 °C (lit.,[11]

95.5—96 °C); *N*-phenyl-*N'*-thiobenzoylhydrazine (6h), m.p. 92 °C (lit.[6] 92 °C); tetrahydro-1,3-thiazine-2-thione (9e), m.p. 133—134 °C (lit.,[12] 129—131 °C); 1,3-thiazolidine-2-thione (9d), m.p. 106—107 °C (lit.,[13] 105—106 °C); *S*-methyl *N*-methyldithiocarbamate (9a), b.p. 156 °C at 20 mmHg (lit.,[14] 155—156 °C); *S*-benzyl *N*-ethyldithiocarbamate (9b), m.p. 114 °C (lit.,[15] oil); *S*-4-nitrobenzyl *N*-benzyldithiocarbamate (9c), m.p. 90—92 °C (lit.,[16] 91 °C); *NN*-dimethyl-*N'*-phenylthiourea (15b), m.p. 134—135 °C (lit.,[17] 134—135 °C); 1-methylhexahydropyrimidine-2-thione (15a), m.p. 120—121 °C (lit.,[18] 130.2 °C); tetrahydro-1,3-oxazine-2-thione (12d), m.p. 125—126 °C (lit.,[19] 125—126 °C), *O*-ethyl *N*-phenylthiocarbamate (12b), m.p. 73 °C (lit.,[17] 71—72 °C); *O*-ethyl *N*-benzylthiocarbamate (12c), b.p. 138—139 °C at 0.5 mmHg (lit.,[17] 125—130 °C at 0.3—0.4 mmHg), and 3β-ethylaminothiocarbonyloxy-5α-cholestane (12a), m.p. 207—208 °C (lit.,[20] 208—210 °C).

Oxidation of S-*Methyl* N-*Methyldithiocarbamate* (9a).—Iodine (1.27 g) in chloroform (minimum volume) was added dropwise to *S*-methyl *N*-methyldithiocarbamate (1.2 g) and triethylamine (2 ml) in chloroform (40 ml). After washing (water) and drying, the chloroform was evaporated to leave an unstable yellow oil; $\nu_{max.}$ 1 600, 1 430, 1 392, 1 330, 1 310, 1 000, and 900—885 cm^{-1}. Trifluoroacetic acid (1 drop) was added to the oil in chloroform (30 ml). After standing overnight the solution was washed with water, dried, evaporated, and chromatographed on silica to give (eluant ethyl acetate–light petroleum, 1 : 19) an impure oil, possibly the rearranged product (11a) as a *syn*/*anti*-mixture; $\nu_{max.}$ 1 635, 1 510, 1 465, 1 435, 1 335, 1 240, 1 220, 1 108, 1 020, 965, and 945 cm^{-1}; $\lambda_{max.}$ 248 (ε 9 100) and 269 nm (9 000); δ 3.52, 3.43, 3.28, 3.1, 2.63, 2.4, 2.25, and 2.15 (all singlets); *m/e* 208 (M^+), 193, 121 (100%), 88, and 74. Both *S*-benzyl *N*-ethyldithiocarbonate (9b) and *S*-4-nitrobenzyl *N*-benzyldithiocarbonate (9c) decolourised iodine–triethylamine but the products, presumably disulphides (10c and d) were unstable. Neither (10c) nor (10d) and trifluoroacetic acid in chloroform gave readily isolable pure products.

Preparation and Rearrangement of Bis-2,3-thiazolin-2-yl Disulphide (10e).—1,3-Thiazolidine-2-thione (9d) (1.19 g) and triethylamine (1.5 ml) in chloroform (30 ml) were titrated with iodine (1.27 g) in chloroform (50 ml) to a purple end point. The solution was washed with water (3 ×), dried, evaporated, and the residue crystallised from chloroform–diethyl ether to give the *disulphide* (10e) (0.82 g, 70%), m.p. 77—78 °C; $\nu_{max.}$ 1 575, 1 310, 1 190, 990, and 920 cm^{-1}; $\lambda_{max.}$ transparent above 220 nm; δ 4.53—4.27 (2 H, t, *J* 8 Hz) and 3.53—3.27 (2 H, t), *m/e* 236 (M^+), 204 (100%), 176, and 119 (Found: C, 30.5; H, 3.55; N, 11.75. $C_6H_8N_2S_4$ requires C, 30.45; H, 3.4; N, 11.85%). The disulphide (10e) (100 mg) was dissolved in chloroform (5 ml) and trifluoroacetic acid (1 drop) added. After standing overnight, the solution was washed with water, dried, and evaporated. Recrystallisation from methanol gave the *rearranged product* (11b) (73 mg, 85%) as yellow prisms, m.p. 75—76 °C; $\nu_{max.}$ 1 585, 1 390, 1 318, 1 285, 1 255, and 1 030 cm^{-1}; $\lambda_{max.}$ 277 (ε 12 500) and 307 nm (9 900); δ 4.8—4.57 (2 H, t, *J* 8 Hz), 4.3—3.85 (2 H, t, *J* 8 Hz) and 3.52—3.2 (4 H, 2 × t, *J* 8 Hz); *m/e* 204 (M^+, 100%) 176, and 60 (Found: C, 35.35; H, 3.95; N, 13.6. $C_6H_8N_2S_3$ requires C, 35.25; H, 3.95; N, 13.7%).

Oxidation of N-*Phenylthiobenzamide* (6b).—Oxidation of *N*-phenylthiobenzamide (6b) with iodine in triethylamine and chloroform gave the disulphide (7b) (73%), m.p. 105—106 °C (lit.,[5] 102—104 °C); $\nu_{max.}$ 1 610, 1 590, 1 165, 930, 915, 760, 755, and 690 cm^{-1}; $\lambda_{max.}$ 235 nm br (ε 31 300), δ 7.7—6.2 (m); *m/e* 424 (M^+, weak), 392, and 180 (100%) (Found: C, 73.65; H, 4.8; N, 6.55. Calc. for $C_{26}H_{20}N_2S_2$: C, 73.55; H, 4.75; N, 6.6%). Trifluoroacetic acid (1 drop) was added to the disulphide (7b) (0.71 g) in chloroform (30 ml). After 2 d, the solution was washed with water, dried, and evaporated. The residue crystallised from chloroform and diethyl ether to give the monosulphide (7c) (0.5 g, 76%), m.p. 208—210 °C (lit.,[5] 202—204 °C); $\nu_{max.}$ 1 630, 1 600, 1 580, 1 485, 1 450, 1 350, 775, 762, 697, and 690 cm^{-1}; $\lambda_{max.}$ 230 br nm (ε 20 100); δ 8.3—6.3 (aryl-H); *m/e* 392 (M^+), 213, 212, 197, 180 (100%), 105, and 77. Further reaction of the monosulphide (7c) and trifluoroacetic acid in chloroform for 2 d gave *N*-phenylthiobenzamide (7b) (76%) and *N*-phenylbenzamide (7c) (100%) both identical (m.p., i.r.) with authentic samples.

Oxidation of N-*Phenylthioacetamide* (6a).—Iodine, triethylamine, and *N*-phenylthioacetamide (6a) at 0—5 °C gave a dark oil, presumably [5] the disulphide (7a); $\nu_{max.}$ 1 640, 1 592, 1 485, 1 215, 1 120, 805, 755, and 695 cm^{-1}; δ 7.6—6.6 (10 H, m) and 2.45 (br, 6 H, m). Reaction of the disulphide (7a) (300 mg) and trifluoroacetic acid (77 μl) in chloroform (15 ml) for 15 h at 5 °C gave tar and *N*-phenylthioacetamide (6a) (100 mg, 33%).

Oxidation of 3β-*Ethylaminothiocarbonyloxy*-5α-*cholestane* (12a).—Iodine (260 mg) in chloroform (20 ml) was added to the thiocarbamate (12a) (475 mg) and *NNN'N'*-tetramethylguanidine (230 mg) in chloroform (10 ml). The usual work-up and crystallisation from ethyl acetate gave the *disulphide* (13a) (400 mg, 84%) m.p. 170—172 °C; $\nu_{max.}$ 1 650, 1 210, 1 052, and 935 cm^{-1} (Found: C, 75.55; H, 11.15; N, 2.95; S, 7.1. $C_{60}H_{104}N_2O_2S_2$ requires C, 75.85; H, 11.05, N, 2.95; S, 6.75%). To the disulphide (13a) (400 mg) in chloroform (10 ml) was added trifluoroacetic acid (1 drop). After 12 h, the usual work-up and crystallisation from ethyl acetate gave the *rearranged product* (14a) m.p. 190 °C; $[\alpha]_D^{20}$ +19.8° (*c* 1.84 in $CHCl_3$); $\nu_{max.}$ 1 590 cm^{-1}; $\lambda_{max.}$ (dioxan) 252 nm (ε 14 000); δ 5.43—4.9 (1 H, m, 3α-H), 4.8—4.3 br (1 H, m, 3α-H), 4.0—3.5 (2 H, q, *J* 7 Hz, NCH_2), and 3.3—2.7 (2 H, q, *J* 7 Hz, NCH_2); *m/e*, M^+ absent, 374, 253, 247, and 188 (Found: C, 78.4; H, 11.45; N, 3.0. $C_{60}H_{104}N_2O_2S$ requires C, 78.55; H, 11.45; N, 3.05%). Thiocarbamate (12a) was stable to iodine and triethylamine.

Oxidation of O-*Ethyl* N-*Phenylthiocarbamate* (12b).—Thiocarbamate (12b) (1.0 g), iodine (0.7 g), and *NNN'N'*-tetramethylguanidine (0.7 ml) in chloroform gave disulphide (13b) (0.84 g, 84%), m.p. 97—98 °C (from cyclohexane); $\nu_{max.}$ 1 635, 1 590, 1 270, 1 180—1 150, 1 012, 890, 765, 720, and 700 cm^{-1}; $\lambda_{max.}$ 225 sh nm (ε 25 500); δ 7.39—6.63 (10 H, m), 4.6—4.13 (4 H, q, *J* 7 Hz), and 1.5—1.25 (6 H, t, *J* 7 Hz); *m/e* 360 (M^+), 181, 148 (100%), 120, and 77 (Found: C, 60.1; H, 5.6; N, 7.75; S, 17.9. $C_{18}H_{20}N_2O_2S_2$ requires C, 59.95; H, 5.6; N, 7.75; S, 17.8%). The disulphide (13b) was stable to trifluoroacetic acid in chloroform.

Oxidation of O-*Ethyl* N-*Benzylthiocarbamate* (12c).—Iodine (6.2 g), *NNN'N'*-tetramethylguanidine (6.12 ml), and the thiocarbamate (12c) (8 g) gave, on usual reaction, washing with dilute aqueous hydrochloric acid, and work-up, the *disulphide* (13c) as a yellow oil; $\nu_{max.}$ 1 640, 1 175, 1 040, 730, and 695 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 24 700); δ 7.26 (10 H, s, aryl-H), 4.6 (4 H, s, aryl-CH_2), 4.43—4.1 (4 H, q, *J* 7 Hz, OCH_2), and 1.37—1.17 (6 H, t, *J* 7 Hz, Me); *m/e*,

M^+ absent, 339, 266, 195 (100%), 166, 123, 106, and 91 (Found: C, 62.1; H, 6.2; N, 7.25. $C_{20}H_{24}N_2O_2S_2$ requires C, 61.8; H, 6.25; N, 7.2%). On storage in chloroform containing trifluoroacetic acid (catalytic), or on distillation at 150 °C and 10^{-4} mmHg, the disulphide (13c) gave the rearranged product (14b). This was isolated (71, 82% respectively) by chromatography on Kieselgel H (eluant diethyl ether–light petroleum, 0 : 1—1 : 19); $\nu_{max.}$ 1 690, 1 400, 1 270—1 190, 1 032, 730, and 700 cm^{-1}; $\lambda_{max.}$ 252 nm (ε 15 400); δ 7.43—6.58 (10 H, m, aryl-H), 4.63—4.27, 4.3—3.95 (4 H, 2 q, *J* 7 Hz, OCH_2), 4.06, 3.95 (4 H, 2 × s, aryl-CH_2), and 1.38—1.08 (6 H, 2 × t, *J* 7 Hz, Me); *m/e* 356 (M^+), 327, 323, 312, 283, 267, 265, 222, 194, 177, 162, 134, 132, and 91 (100%) (Found: C, 67.65; H, 6.9; N, 7.75. $C_{20}H_{24}N_2O_2S$ requires C, 67.35; H, 6.8; N, 7.85%).

Oxidation of Tetrahydro-1,3-oxazine-2-thione (12d).—The thiocarbamate (12d), iodine, and *NNN'N'*-tetramethylguanidine readily gave the crude unstable disulphide (13d); $\nu_{max.}$ 1 650, 1 460, 1 325, 1 225, 1 110, 1 040, 915, 840, and 800 cm^{-1}; δ 4.4—4.1 (4 H, t, *J* 6 Hz, OCH_2), 3.55—3.3 (4 H, t, *J* 6 Hz, NCH_2), and 2.2—1.6 (4 H, m, C–CH_2–C). Attempted rearrangement of the disulphide (13d) catalysed by trifluoroacetic acid gave tetrahydro-1,3-oxazine-2-thione (12d) (50%) and a mixture of by-products.

Reaction of NN-*Dimethyl*-N'-*phenylthiourea* (15b) *with Thionyl Chloride*.—Thionyl chloride (0.81 ml) in carbon tetrachloride (5 ml) was added dropwise (30 min) to the thiourea derivative (15b) (4 g) in chloroform (25 ml) at 0 °C. The yellow suspension was evaporated and the residue partitioned between chloroform and 10% aqueous sodium hydroxide. After thorough phase mixing, the chloroform solution was dried, and evaporated to leave the rearranged product (17a) (3.15 g, 87%). Crystallisation from aqueous ethanol and subsequently from light petroleum gave material with m.p. 119—120 °C (lit.,[4] 119—121 °C); $\nu_{max.}$ 1 625, 1 580, 1 300, 1 080, 765, and 695 cm^{-1}; $\lambda_{max.}$ 255 nm (ε 18 800); δ 7.53—6.6 (10 H, m), 2.9 (6 H, s), and 2.53 (6 H, br s); *m/e* 326 (M^+), 147 (100%), and 88 (Found: C, 66.55; H, 6.85; N, 17.2. Calc. for $C_{18}H_{22}N_4S$ C, 66.2; H, 6.8; N, 17.15%).

Reaction of NN-*Dimethyl*-N'-*phenylthiourea* (15b) *with Iodine*.—The thiourea derivative (15b) gave the *disulphide* (16a) (80%) on oxidation with iodine (1.5 equiv.) and triethylamine (2 equiv.) in chloroform. Crystallisation from light petroleum gave material with m.p. 56—60 °C; $\nu_{max.}$ 1 610, 1 585, 1 260, 1 100, 920, 830, 765, and 698 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 23 300); δ 7.44—6.46 (10 H, m) and 2.9 (12 H, s); *m/e* 358 (M^+), 326, 180, 163, 147 (100%), 135, and 88 (Found: C, 60.45; H, 6.2; N, 15.65. $C_{18}H_{22}N_4S_2$ requires C, 60.3; H, 6.2; N, 15.65%).

Rearrangement of the Disulphide (16a).—Trifluoroacetic acid (1 drop) was added to the disulphide (16a) (200 mg) in chloroform (2 ml). After standing overnight, the normal work-up gave the rearranged product (17a) (130 mg, 71%), m.p. 120—121 °C, identical (i.r., n.m.r. and mass spectrum) with that previously described.

Preparation of the Sulphide (16d).—(*a*) *NN*-Dimethyl-*N'*-phenylthiourea (15b) (0.9 g) in phosgene (2 g) and dichloromethane (10 ml) was left overnight, the solution evaporated, the residue suspended in dry dichloromethane (20 ml), and triethylamine (0.7 ml) added. *NN*-Dimethyl-*N'*-phenylthiourea (15b) (0.9 g) and *NNN'N'*-tetramethylguanidine (0.93 ml) in dichloromethane (20 ml) were added dropwise. After stirring overnight the solution was washed with water, dried, evaporated, and the residue crystallised from petroleum to give the sulphide (16d) (0.9 g, 55%). Second-crop material (0.5 g, 31%) was contaminated by traces of the rearranged product (17a). The pure *sulphide* (16d) had m.p. 100—102 °C, $\nu_{max.}$ 1 620, 1 585, 1 300, 750, and 690 cm^{-1}; $\lambda_{max.}$ 252 nm (ε 17 900); δ 7.4—6.6 (10 H, m) and 2.68 (13 H, s); *m/e* 326 (M^+), 294, 147 (100%), and 88 (Found: C, 66.2; H, 6.8; N, 17.25. $C_{18}H_{22}N_4S$ requires C, 66.2; H, 6.8; N, 17.15%). Omission of the triethylamine resulted in the formation of a mixture of sulphide (16d) and rearranged product (17a).

(*b*) Triphenylphosphine (256 mg) was added to the disulphide (16a) (350 mg) in deuteriochloroform (2 ml). After complete reaction (3 h, n.m.r.) the mixture was evaporated and the residue leached with diethyl ether–chloroform leaving triphenylphosphine sulphide. The evaporated filtrate in hot petroleum was filtered free from additional triphenylphosphine sulphide and cooled to deposit the sulphide (16d) (112 mg, 35%), m.p. 98—100 °C identical (n.m.r., i.r.) with that previously obtained.

Preparation of NN-*Dimethyl*-N'-*pentadeuteriophenylthiourea* (15c).—Pentadeuterioaniline [7] (1 g) was added with stirring to carbon disulphide (0.77 ml) and aqueous ammonia (33%, 1.6 ml). After 15 min, water (15 ml) and lead nitrate (3.57 g) in water (7 ml) were added. The mixture was steam-distilled into dilute sulphuric acid and extracted with diethyl ether. Evaporation of the organic phase gave crude pentadeuteriophenyl isothiocyanate. This in ethanol (30 ml) was treated with aqueous dimethylamine (60%; 5 ml). After 30 min evaporation and crystallisation from ethanol gave *NN*-dimethyl-*N'*-pentadeuteriophenylthiourea (15c) (1 g, 53%), m.p. 134—135 °C; δ 7.28 (1 H, br s, NH) and 3.23 (6 H, s, NMe_2); *m/e* 185 (M^+) and 80.

Decadeuteriodisulphide (16b), *Decadeuteriosulphide* (16e), *and Decadeuterio-rearranged Product* (17b).—These were prepared as for the protio-analogues. Decadeuteriodisulphide (16b) had δ 2.93 (s, NMe_2); *m/e* 368 (M^+), 336, 185, 182, 180, 153, 152, 151, 140, 137, 136, and 88. Decadeuteriosulphide (16e) had $\nu_{max.}$ 1 620—1 600, and 1 290 cm^{-1}; δ 2.7 (s, NMe_2); *m/e* 336 (M^+), 152 (100%), and 88. The decadeuterio-rearranged product (17b) had *m/e* 336 (M^+), 258, 256, 214, 185, 152, and 88 (100%).

Crossover Experiments.—The disulphide (16a) (50—100 mg) was mixed with the decadeuteriodisulphide (16b) (1.0 equiv.) in a solvent (2 ml). Trifluoroacetic acid (1 drop) was added and after standing the solution was washed with saturated aqueous sodium hydrogen carbonate and evaporated, and the residue crystallised from petroleum to give the rearranged product. The ratio of $[^2H_0]$-(17a) : $[^2H_5]$-(17c) : $[^2H_{10}]$-(17b) compounds was determined by mass spectra. The experiment was repeated using the rearranged products (17a and b) and the monosulphides (16d and e) (see Table). N.m.r. studies indicated that the monosulphide (16d) was not an intermediate in the formation of the rearranged product (17a) from the disulphide (16a). Although monosulphide (16d) was slow to react, the disulphide (16a) rearranged rapidly with 0.1 mole % trifluoroacetic acid giving only product (17a).

Reaction of the Disulphides (1) *and* (10e) *with Acid*.—Trifluoroacetic acid (1 drop) was added to a mixture of disulphides (1) and (10e) (120 mg each) in chloroform (2 ml). Normal work-up gave a homogeneous oil, *m/e* 232 [M^+ (2)], 218 [M^+ (11c)], and 204 [M^+ (11b)] (ratio 1 : 1.7 : 1).

Attempted Preparation of the Sulphide (10g).—(*a*) The disulphide (1) (100 mg), triphenylphosphine (99 mg), and deuteriochloroform (5 ml) were allowed to stand at room

temperature for 12 h, and then heated to reflux for 30 min. Leaching with hot diethyl ether gave, in the filtrate, dithiocarbamate (9e) (100%). The disulphide (1) also readily reacted with hexamethylphosphorus triamide, triphenyl phosphite, triethyl phosphite, and tri-n-butylphosphine but these gave either dithiocarbamate (9e) or complex mixtures.

(*b*) Dithiocarbamate (9e) (10 g) was added to phosgene (20 g) in dichloromethane (100 ml) at −40 °C. After 4 h, a white solid precipitated; after stirring overnight this was filtered off. The solid was dried under vacuum, suspended in dry diethyl ether (50 ml), and triethylamine (8 ml) added. After stirring for 30 min, triethylammonium chloride was filtered off and the filtrate evaporated and distilled to give 2-*chloro*-5,6-*dihydro*-4H-1,3-*thiazine* (18b) (6.2 g, 61%), b.p. 58—60 °C at 1 mmHg; $\nu_{max.}$ 1 625, 1 430, 1 340, 1 285, 1 060, 995, 948, 866, and 830 cm^{-1}; $\lambda_{max.}$ 233 nm (ε 3 700); δ 3.93—3.73 (2 H, t, *J* 6 Hz), and 2.17—1.75 (2 H, m); *m/e* 137, 135 (M^+), 109, 107, and 100 (Found: C, 35.7; H, 4.5; N, 10.3. C_4H_6ClNS requires C, 35.4; H, 4.45; N, 10.35%). The chloride (18b) and the dithiocarbamate (9e) were recovered unchanged on attempted condensation using triethylamine or *NNN'N'*-tetramethylguanidine in chloroform at 25°C or reflux, sodium hydride in THF, *NNN'N'*-tetramethylguanidine and potassium iodide in DMF at 100°C, pyridine and zinc dust (catalytic) at reflux, or potassium hydride and 18-crown-6 in THF at 25 °C or xylene at 100 °C. Prolonged drastic reactions give tar.

(c) Tin(IV) chloride (1 drop) was added to the chloride (18b) (0.55 ml), the dithiocarbamate (9e) (0.7 g), and triethylamine (1.44 ml) in dry THF (5 ml). After stirring overnight, the mixture was poured into water, dried, and evaporated (50—60°C). The residue on crystallisation from chloroform-diethyl ether gave the rearranged product (2) (0.85 g, 70%), identical with that previously described.[1]

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