equilibrating helical substates. We term such helices "frayed".

Acknowledgment. Financial support from Pfizer Research and from the National Science Foundation (Grant 8813429-CHE) is gratefully acknowledged. Mass specral data were provided by the MIT Mass Spectrometry Facility, which is supported by NIH Grant No. RR00317 (to K. Biemann).

Registry No. Ac-Hel$_1$-OH, 120980-87-2; H-Ala-OBu-*t*, 21691-50-9; Ac-Hel$_1$-Ala-OBu-*t*, 120980-91-8; Ac-Hel$_1$-Ala-OH, 119888-30-1; Ac-Hel$_1$-(Ala)$_2$-OBu-*t*, 119872-62-7; Ac-Hel$_1$-(Ala)$_2$-OH, 120980-92-9; Ac-Hel$_1$-(Ala)$_3$-OBu-*t*, 119872-63-8; Z-(Ala)$_2$-OBu-*t*, 13883-50-6; H-(Ala)$_3$-OBu-*t*, 65356-57-2; Ac-Hel$_1$-(Ala)$_4$-OBu-*t*, 119872-64-9; Z-(Ala)$_4$-OBu-*t*, 13883-53-9; H-(Ala)$_4$-OBu-*t*, 136088-66-9; Ac-Hel$_1$-(Ala)$_5$-OBu-*t*, 136088-67-0; Ac-Hel$_1$-(Ala)$_6$-OBu-*t*, 136088-68-1; H-Sar-OBu-*t*-HCl, 136088-69-2; Ac-Hel$_1$-Sar-OBu-*t*, 136088-70-5; Ac-Hel$_1$-Sar-OH, 136088-71-6; H-Ala-OBu-*t*-HCl, 13404-22-3; Ac-Hel$_1$-Sar-Ala-OBu-*t*, 136088-72-7; Ac-Hel$_1$HSar-(Ala)$_4$-OBu-*t*, 136088-73-8; Ac-Hel$_1$-OMe, 119888-29-8; Ac-Hel$_1$-OBu-*t*, 136088-74-9; Ac-Hel$_1$-(Ala)$_3$-NHMe, 136088-75-0; Ac-Hel$_1$-(Ala-d_3)-(Ala-d_4)$_2$-Ala-OBu-*t*, 136088-76-1; Ac-Hel$_1$-(Ala)$_2$-NHMe, 136088-77-2; Ac-Hel$_1$-(Ala)$_6$-NHMe, 136088-78-3.

Supplementary Material Available: Details of solvent purification, synthesis and characterization of higher alanine homologues of Ac-Hel$_1$-L-Ala-OH, and sarcosine conjugates (9 pages). Ordering information is given on any current masthead page.

A New Procedure for the Conversion of Thiols into Reactive Sulfenylating Agents[1]

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Thiols may be converted in high yield into unsymmetrical 2-pyridyl disulfides **3**. Treatment of these with alkylating agents (e.g., alkyl fluorosulfonates or oxonium salts) affords the corresponding *N*-alkylpyridyl disulfides **4**, which are potent sulfenylating agents (Scheme II) and react smoothly with a variety of sulfur nucleophiles (e.g., thiols, thiones, thioamides, dithiocarbamates, thiocyanate, etc.) to afford disulfides, with amines to afford sulfenamides, and with β-diketones to afford sulfides. This new method is particularly well-suited to the preparation of unsymmetrical disulfides and sulfenamides from complex and otherwise reactive thiols.

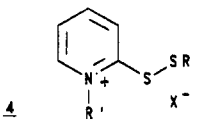
We were interested in the possibility that unsymmetrical disulfides derived from sulfur-containing drugs might serve as useful "prodrugs". There is, however, currently no convenient *general* method for the conversion of a thiol into a *reactive* sulfenylating agent as a prelude to formation of unsymmetrical disulfides,[2] sulfenamides, sulfides, etc., and thus such sulfenylating agents are normally secured through a variety of indirect methods.[3] The crucial limitation upon the direct approach stems from the tendency of unreacted thiol to react with the sulfenylating agent as it is formed, affording symmetrical disulfide (Scheme I).

Scheme I

$$\mathrm{RSH} \xrightarrow[\text{slow}]{} \mathrm{RSX} \xrightarrow[\text{fast}]{\mathrm{RSH}} \mathrm{RSSR}$$

We now report a rather general procedure for conversion of thiols into reactive sulfenylating agents that skirts the above limitation through conversion of the thiol into a *latent* sulfenylating agent that is then "activated" in a second step *in the absence of thiol*. Specifically, the thiol is converted into an unsymmetrical 2-pyridyl disulfide (Scheme IIa) **3**, which is activated through N-alkylation into **4** (Scheme IIb).

The *N*-alkylpyridinium disulfides **4** are potent sulfenylating agents and react at sulfur with various nucleophiles (Scheme IIc) driven by extrusioon of 1-alkyl-2-thiopyridone (**5**). (The reactivity of **5** as a leaving group has been



4

	R	R'	X
a)	R_C	Me	FSO_3^-
b)	"	Et	PF_6^-
c)	"	Me	$CF_3SO_3^-$
d)	Me	Et	BPh_4^-
e)	"	Et	FSO_3^-

(R_C = cholest-5-en-3β-yl)

foreshadowed by the various reactions driven through the departure of 1-alkyl-2-pyridone.[4]) The unsymmetrical disulfides **3** can be made quite simply through reaction of a thiol with 2,2′-dipyridyl disulfide (**2**, X = 2-thiopyridyl), a reagent that is commercially available[5] and that has been

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† Present address: Ciba-Geigy AG, 4002 Basel, Switzerland.

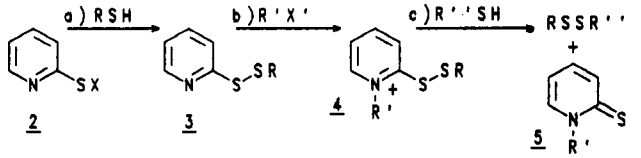
(1) Taken in part from the Ph.D. Thesis (London University) of A. C. O'Sullivan.

(2) Among the various methods, the one promising to be most general lies in conversion of a thiol into a sulfenyl hydrazide through reaction with diethyl azodicarboxylate: Mukalyama, T.; Takahashi, K. *Tetrahedron Lett.* **1968**, 5907. Bockelhelde, V., Mindt, J. L. *Ibid.* **1970**, 1203. However, see: Helmer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 3012. Field, L.; Hanley, W. S.; McVeigh, I. *Ibid.* **1971**, *36*, 2735.

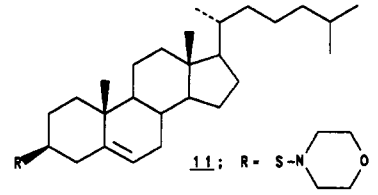
(3) For reviews see: Kühle, E. *The Chemistry of the Sulfenic Acids*; G. Thieme: Stuttgart, 1973. Hogg, D. R. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, pp 261ff. Field, L. In *The Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; Chapter 7, pp 303ff.

0022-3263/91/1956-6697$02.50/0

Scheme II



widely used for the modification of protein thiol groups.[6] Although **3** reacts fairly slowly with thiols (at least under neutral conditions), some competition (as per Scheme I) does take place, and we have found it necessary to employ at least 2 equiv of reagent to suppress formation of symmetrical disulfide and achieve maximum yields of **3** from typical thiols such as thiophenol and 3β-mercaptocholest-5-ene (**6**). As the unreacted dipyridyl disulfide

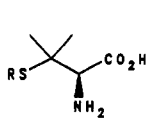


11; R = S-N(morpholinyl)

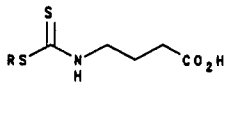
6; R = SH
7; R = SSMe
8; R = SSPh
9; R = SCN
10; R = S-Tosyl
12; R = $SSCH_2CO_2H$
13; R = $SSC(CH_3)_2NPh$
14; R = $SSC(NH_2)=NH$
15; R = SSR_c
16; R = $SS(O)R_c$

(R_c = cholest-5-en-3-β-yl)

must be removed from **3** prior to activation (at best a nuisance), we sought a more efficient procedure. Investigation of derivatives of **2** bearing more reactive leaving groups X led to the observation that the sulfenamide **2** (X = 4-morpholinyl) in the presence of acetic acid reacted stoichiometrically with thiols, for instance, *tert*-butyl thiol or 3β-mercaptocholest-5-ene (**6**) to afford nearly quantitative yields of the desired disulfides **3**. A variety of reactive alkylating agents can be employed to form the pyridinium salts **4**, for instance, $MeOSO_2CF_3$, $EtOSO_2CF_3$, $MeOSO_2F$, Et_3OBF_4, and Et_3OPF_6. Dimethyl sulfate affords **4** only slowly, under forcing conditions, and methyl iodide is unsuitable (because of the thiophilic leaving group). The activated sulfenylating reagents **4** may be employed in situ or may be isolated (evaporation of solvent in vacuo and recrystallization) and stored under normal laboratory conditions. Lower alkyl derivatives of **4** (R = Me, *t*-Bu; X = OSO_2CF_3, BF_4, PF_6) were quite hygroscopic and, thus, difficult to isolate and store. Anion exchange with aqueous tetraphenylborate ($NaBPh_4/H_2O$) gave manageable salts.



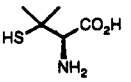
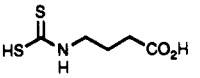
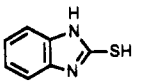
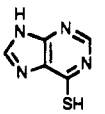
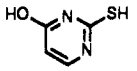
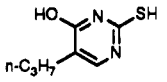
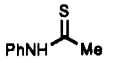
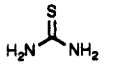
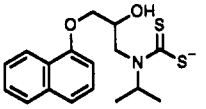
17) a; R = H b; R = SR_c



18) a; R = H b; R = SR_c

Reactions of the sulfenylating agents **4** with simple thiols were, in general, uncomplicated and produced unsymmetrical disulfides in high yield (Table I), provided the strong acid liberated in the reaction was appropriately neutralized. The choice of base for this proved a matter of some importance. Although simple, aqueous workup served in the case of cleanly precipitated products, in general a base stronger than water was required. Triethylamine, 1,8-bis(dimethylamino)naphthalene, DABCO, and DBN reacted too rapidly with **4** and could not be used. Pyridine also reacted, but much more slowly than substrates of interest and thus could often be successfully employed (Table I, entries 1, 5, 10). Pyridine, however, proved an unsuitable base for the neutralization of acid formed during sulfenylation of heterocyclic thiols, as it appeared (Table I, entry 7a) that the pyridinium salt was sufficiently reactive to mobilize an equilibrium among starting thiol, sulfenylating reagent, and products (Scheme III)—a speculation confirmed by the observation that treatment of a mixture of target disulfide **19b** and *N*-methyl-2-thiopyridone (**5**, R = Me) with pyridinium tosylate afforded a similar equilibrium mixture. It was subsequently found that the desired disulfides could be obtained in good yield through quenching the reaction mixture with aqueous sodium hydrogen carbonate (Table I, entries 7b, 8, 9). The reactions are apparently driven to completion through deprotonation. In the course of these experiments, we observed that the hindered base, diisopropylethylamine

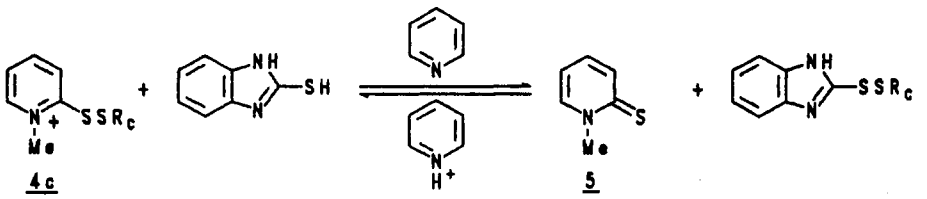
Table I. Reaction of 4 with Sulfur Nucleophiles

expt	4	thiol	product	yield (%)
1a[a,e]	4a	PhSH	8	88
1b[a,e]	4b			84
2[b,f]	4c		17b	87
3[b,h]	4c	$HSCH_2CO_2H$	12	64
4[b,f]	4d	R_cSH (6)[i]	R_cSSMe (7)[i]	72
5[a,e]	4e	PhSH	PhSSMe	97
6[a,h]	4c		18b	86
7a[b,e]	4c		19b	18
7b[b,f]	4c		19b	94
7c[b,g]	4c		19b	100
8[b,f]	4c		20b	72
9a[b,f]	4c		21b	77
9b[b,f]	4c		21d	26
10[c,e]	4c		13	71
11[c,d]	4c		14	100
12[a,d]	4c		22d	88

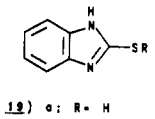
[a] $CHCl_3$ as solvent. [b] DMF as solvent. [c] CH_2Cl_2 as solvent. [d] No base. [e] Pyridine as base. [f] $NaHCO_3$ as base. [g] $EtN(i\text{-}Pr)_2$ as base. [h] H_2O as base. [i] R_c = cholest-5-en-3β-yl.

(4) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *31*, 707.
(5) Aldrithiol-2, Aldrich Chemical Co., Milwaukee, WI.
(6) Brocklehurst, K.; Little, G. *Biochem. J.* **1974**, *139*, 221. Brocklehurst, K. *Ibid.* **1981**, *193*, 819. Brocklehurst, K. *Int. J. Biochem.* **1979**, *10*, 259.

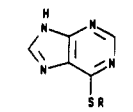
Scheme III



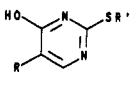
was relatively inert toward the sulfenylating agents 4 and on the basis of preliminary experiments (Table I, entry 7c



19) a; R = H
b; R = SR_c



20) a; R = H
b; R = SR_c



21) a; R = R' = H
b; R = H, R' = SR_c
c; R = n-Pr, R' = H
d; R = n-Pr, R' = SR_c

and Table II, entry 6) may be the most generally useful base for controlling the sulfenylation reactions (we presume that more recently reported hindered bases[7] would serve as well).

The sulfenylating reagents 4 react with nucleophiles other than thiols and a number of examples are collected in Table II. The entries are largely self-explanatory. The disulfide 15 of entry 4 presumably arises from attack of iodide at sulfur followed by the well-known metathesis of sulfenyl iodides[8] and the thiosulfinate 16 (entry 5) from attack at sulfur by water, followed by dimerization and dehydration[9] or by sulfenylation of the resulting sulfenic acid[10] (an α-effect nucleophile).

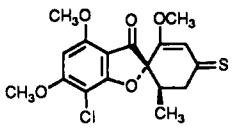
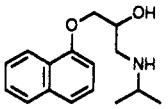
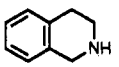
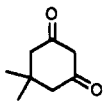
Clearly, unsymmetrical *N*-alkylpyridinium disulfides 4 are convenient and potent sulfenylating agents comparable in utility to sulfenyl chlorides or the heterocyclic sulfenimides[11] (which must generally be prepared from sulfenyl chlorides). The new reagents 4 provide the advantage of formation directly from thiols, including those thiols bearing functions that would react with the SCl group (for instance, alkenyl groups, i.e., **6a**).

Experimental Section

General procedures were as previously reported.[12]

Cholest-5-en-3β-yl Pyridyl Disulfide (3; R = Cholest-5-en-3β-yl). Cholest-5-en-3β-thiol (**6**; 4.0 g, 10 mmol) and 2,2'-dipyridyl disulfide (4.0 g, 18.1 mmol) were dissolved in CH_2Cl_2 (100 mL) and left overnight. The solvent was then removed and the crude product was chromatographed on Florisil. Elution with benzene/hexane (40%) brought down dicholest-5-en-3β-yl disulfide. Further elution with benzene gave the title product **3** (R = cholest-5-en-3β-yl; 4.41 g, 87%). Recrystallization from MeCN/benzene gave 4.30 g (85%): mp 98–100 °C; $[\alpha]_D$ −26° (*c* 1.4, $CHCl_3$); UV λ_{max} (hexane) 284 (4290), 241 nm (10900); NMR δ 5.3 (1 H, H-6), 8.4 (1 H, d, J = 5 Hz, H-6'), 6.83–7.88 (3 H, m, H-3', 4', 5'); MS m/z 512 (M^+ + 1), 430, 402, 369. Anal. Calcd for $C_{32}H_{49}NS_2$: C, 75.08; H, 9.65; N, 2.74; S, 12.53. Found: C, 75.29; H, 9.70; N, 2.73; S, 12.63.

Table II. Reaction of 4c with Various Nucleophiles

expt	nucleophile	product	yield (%)
1		**26**	51
2	Na *p*-toluenesulfinate	**10**	64
3	Na CN	**9**	88
4	$(n\text{-Bu})_4NI$	R_cSSR_c[a] (**15**)	85
5	OH^-	$R_cSS(O)R_c$[a] (**16**)	82
6		**11**	37
7		**22b**	76
8		**23**	76
9		**24**	54

[a] R_c = cholest-5-en-3β-yl.

Pyridyl Methyl Disulfide (3; R = Me). 2-Mercaptopyridine (1.00 g) was heated under reflux in dimethyl disulfide (20 mL) for 2 h. Most of the disulfide was boiled off and the residue chromatographed on silica (14.0 g), eluting first with hexane and working up to CH_2Cl_2, which eluted the title product **3** (R = Me; 1.40 g, 99%). Purification by fractional distillation instead of chromatography gave 67% yield: bp 82 °C (0.5 Torr); $d_{21°C}$ = 1.18; UV λ_{max} (hexane) 283 (5130) 239 nm (11500); NMR δ 2.63 (3 H, s, Me), 6.8–7.9 (4 H, m, aromatic). Anal. Calcd for $C_6H_7NS_2$: C, 45.32; H, 4.49; N, 8.91; S, 40.78. Found: C, 46.06; H, 4.50; N, 8.94; S, 40.73.

2-Pyridyl Morpholinyl Sulfide (2; X = 4-Morpholinyl). A chloramine solution was prepared by adding 15.7 g of morpholine to excess aqueous sodium hypochlorite solution (500 mL, 0.46 M, Chlorox) and extracting with $CHCl_3$. The chloramine solution was treated with 65 mL of morpholine, and then, after cooling, 2-mercaptopyridine (10.0 g) was added with stirring. The reaction mixture was washed with aqueous Na_2SO_3 (exothermic!), and then the organic solvent was removed and the residue dissolved in hexane. The hexane solution was washed with water, and the solvent was removed to yield the title sulfenamide **2** (X = 4-morpholinyl; 7.3 g, ca. 40%) after recrystallization from ether/hexane. The title compound **2** (X = 4-morpholinyl) had mp 62.5 °C: UV λ_{max} (EtOH), 237 (8589), 291 nm (3905). Anal. Calcd for $C_9H_{12}N_6OS$: C, 55.07; H, 6.16, N, 14.27; S, 16.34. Found: C, 55.05; H, 6.30; N, 14.35; S, 16.09.

Reaction of 2-Pyridyl Morpholinyl Sulfide (2; X = 4-Morpholinyl) with Cholest-5-ene-3β-thiol (6). Cholest-5-ene-3β-thiol (**6**, 1.00 g, 2.49 mmol) and the sulfenamide **2**, (X = 4-morpholinyl; 488 mg, 2.49 mmol) were dissolved in $CHCl_3$ (3 mL) and acetic acid (2 mL). Reaction (monitored by TLC) required a few hours. The reaction mixture was stored overnight. Hexane (50 mL) was then added and the solution washed three times with water. The solvent was evaporated and the residue

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chromatographed on TLC silica starting with hexane and working up to 30% ether in hexane to afford dicholest-5-en-3β-yl disulfide (15; 44 mg, 4%) and the pyridyl disulfide 3 (R = cholest-5-en-3β-yl; 1.23 g, 97%): mp 95–100 °C.

Alkylation of Mixed 2-Pyridyl Disulfides (3 → 4). Methylation of Pyridyl Cholest-5-en-3β-yl Disulfide (3; R = Cholest-5-en-3β-yl) with (A) Methyl Triflate (Preparation of 4c). Pyridyl disulfide (3; R = cholest-5-en-3β-yl; 967 mg, 1.89 mmol) was mixed with hexane, and enough CH_2Cl_2 was added for dissolution. Methyl triflate (310 mg, 1.89 mmol) was then added and the product crystallized out over a period of 15 min. The crystals were filtered off, washed with hexane, and dried to give 4c (1.04 g, 81%): mp 176–182 °C; $[\alpha]_D$ −24° (c 1.16, $CHCl_3$); UV λ_{max} (THF) 239 (5720), 308 nm (9140); NMR δ 4.4 (3 H, s, N-Me), 5.25 (1 H, m, H-6), 7.57–8.87 (3 H, M, 3′, 4′, 5′-H's), 9.18 (1 H, d, J = 6 Hz, H-6′). Anal. Calcd for $C_{34}H_{52}F_3NO_3S_3$: C, 60.41; H, 7.75, N, 2.07; S, 14.23. Found: C, 60.20; H, 7.75; N, 2.11; S, 15.03. **(B). Methyl Fluorosulfate (Preparation of 4a).** The reaction was carried out as for methyl triflate (above) yielding 4a (88%): $[\alpha]_D$ −24° (c 1%, $CHCl_3$); mp undergoes phase transition at 150 °C to a birefringent phase that loses birefringence slowly up to 188 °C; NMR δ 4.42 (3 H, s, N-Me). **(C) Triethyloxonium Hexafluorophosphate (Preparation of 4b).** The reaction was carried out as above in CH_2Cl_2. Hexane was added to precipitate the 4b (92%), mp 195–205 °C. Recrystallization from $CHCl_2$ gave mp 205–207 °C: $[\alpha]_D$ −59° (c 1.1, THF); UV λ_{max} (DME) 309 (8440), 238 nm (6290); NMR δ aromatic (4 H, m); 5.43 (1 H, s, H-6); 4.76 (2 H, q, J = 7 Hz, N-Et). Anal. Calcd for $C_{34}H_{54}F_6NPS_2$: C, 59.54; H, 7.94; N, 2.04; P, 4.52. Found: C, 59.25; H, 7.99; N, 1.98; P, 4.50.

Reaction of Pyridyl Methyl Disulfide (3, R = Me) with Ethyl Fluorosulfate (Preparation of 4e). Equivalent amounts of pyridyl methyl disulfide and ethyl fluorosulfate were dissolved in $CDCl_3$ and the reaction followed by the appearance of the S-Me signal at δ 2.70. It took about 1 h. Removal of the solvent and recrystallization from *tert*-butyl alcohol gave 4e, mp 108–118 °C.

1-Ethyl-2-(methyldithio)pyridinium Tetraphenylborate (4d). 1-Ethyl-2-(methyldithio)pyridinium fluorosulfate (4e, 1.01 g, 3.53 mmol) was dissolved in water and mixed with a solution of sodium tetraphenylborate (1.20 g, 3.53 mmol) in water. The white precipitate that formed was filtered off, washed with water, and recrystallized from $MeCN/H_2O$ to give 4d (665 mg, 37%): mp 103–120 °C. Anal. Calcd for $C_{32}H_{32}BNS_2$: C, 76.03; H, 6.38; N, 2.77; S, 12.68; B, 2.14. Found: C, 75.78; H, 6.37; N, 2.74; S, 12.57; B, 2.44.

Reaction of 1-Ethyl-2-(methyldithio)pyridinium Tetraphenylborate with Cholest-5-ene-3β-thiol To Give 7. A solution of the title sulfenylating agent 4d (277 mg, 0.547 mmol) in DMF (2 mL) was added to a solution of cholest-5-en-3β-thiol (6, 220 mg, 0.547 mmol) in CH_2Cl_2 (1 mL). Hexane was added, and the solution was washed with 5% aqueous sodium bicarbonate, water (twice), and then MeCN (twice). Removal of the solvent gave 217 mg of solid that was recrystallized from ethyl acetate to yield 7 (177 mg): mp 125–132 °C; NMR δ 5.3 (1 H, m, H-6), 2.40 (3 H, s, SMe). The disulfide thus prepared was identical with an authentic sample of the compound prepared by treating cholest-5-en-3β-thiol with a large excess of dimethyl disulfide and triethylamine, mp 129–134 °C.

In Situ Methylation and Sulfenylation (Preparation of Phenyl Methyl Disulfide). Methyl fluorosulfate (0.264 mL, 372 mg, 3.18 mmol) was added to a solution of pyridyl methyl disulfide (3; R = Me; 0.420 mL, 500 mg, 3.18 mmol) in $CHCl_3$ (10 mL), and after 10 min thiophenol (0.327 mL, 350 mg, 3.18 mmol) was added to give a yellow color. Pyridine (0.290 mL, 283 mg, 3.58 mmol) was added to give a precipitate. The crude product was chromatographed on a column of silica (10 g) starting with 50% $CHCl_3$/hexane and working up to ethyl acetate to yield phenyl methyl disulfide (484 mg, 97%, NMR), uncontaminated by either symmetrical disulfide (by TLC developed in hexane or in carbon tetrachloride), pyridyl methyl disulfide (starting material; 15 mg, 3%; NMR), *N*-methyl-2-thiopyridone (248 mg, 62%; NMR), and 2-mercaptopyridine (54 mg, 15%; NMR).

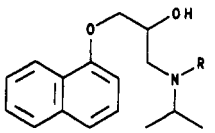
Reaction of the Cholest-5-en-3β-yl Sulfenylating Agents (4a and 4b) with Thiophenol To Give 8. The steroidal sulfenylating agent (4a; 209 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (ca. 1 mL) and pyridine (ca 0.5 mL), and thiophenol (34 mg, 0.31 mmol) in CH_2Cl_2 (ca. 1 mL) was added. The crude product was chromatographed on Florisil, eluting first with 40% benzene/hexane and working up to 5% EtOAc/benzene to give 8 (139 mg, 88%), mp 116–118 °C. When DMF was used as solvent, the yield was 90%, mp 104–108 °C. The ethylated reagent 4b in CH_2Cl_2 as above yielded 84%. A sample of 8 crystallized from CH_3CN/benzene had mp 114–118 °C: UV λ_{max} (hexane) 242 nm (8990); $[\alpha]_D$ −37° (c 1.63, $CHCl_3$); NMR δ 5.38 (1 H, d, H-6) and 5 aromatic protons; MS 510 (M^+), 402, 369.

Reaction of 4c with D-(−)-Penicillamine (17a) To Give 17b. The cholest-5-en-3β-yl sulfenylating agent 4c (1.005 g, 1.467 mmol) and D-(−)-penicillamine (17a; 219 mg, 1.467 mmol) were stirred in DMF solution (ca. 10 mL). The penicillamine was initially insoluble but most of it had dissolved and reacted within 15 min. The residue was filtered off and the filtrate treated with aqueous sodium bicarbonate as above. The resulting precipitate was filtered off, washed with water and hexane in the usual way, and dried in vacuo to yield crude 17b (704 mg, 87%), mp 173 °C (gas evolution). This compound was highly insoluble in nearly all solvents tried, but an analytical sample was recrystallized from DMF. The acid salt, soluble but unstable, was sufficiently long lived to obtain an NMR: NMR (of TFA salt, $CDCl_3$ + TFA) δ 5.31 (1 H, s, H-6), 3.83 (1 H, s, H-2′), 1.52 (3 H, s, H-Me), 1.42 (3 H, s, Me). Anal. Calcd for $C_{32}H_{55}NOS_2$: C, 69.57; H, 10.15; N, 2.51; S, 12.05. Found: C, 69.89; H, 10.08; N, 2.55; S, 11.66.

Reaction of 4c with 2-Mercaptoacetic Acid To Give 12. The sulfenylating agent 4c (3.0 g, 4.4 mmol) was dissolved in DMF (approximately 15 mL), and 2-mercaptoacetic acid (0.31 mL, 410 mg, 4.4 mmol) was added. Water (20 mL) was added to the yellow solution and the product separated as a gum. The liquid was decanted off, and the crude product was washed with water (addition and decantation) a few times. The gum was then dissolved in CH_2Cl_2 and separated from the water by filtration through a Whatman phase-separator paper. The solvent was removed in vacuo and the product recrystallized from MeCN to give 12 (1.41 g, 64%): mp 103–106 °C; $[\alpha]_D$ −29° (c 1.25, $CHCl_3$); NMR δ 5.33 (1 H, s, H-6), 3.48 (2 H, s, H-2′), 8.80 (1 H, s, COOH). Anal. Calcd for $C_{29}H_{48}O_2S_2$: C, 70.68; H, 9.82; S, 13.01. Found: C, 70.75; H, 9.88; S, 12.83.

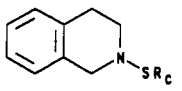
Reaction of 4c with the *O*-TMS Ester of Triethylammonium 4-Aminobutyric Acid Dithiocarbamate (18a) To Give 18b. A suspension of 4-aminobutyric acid (5.16 g, 50 mmol) and chlorotrimethyl silane (6.34 mL, 50 mmol) was heated under reflux in a mixture of dry $CHCl_3$ (70 mL) and dry MeCN (13 mL) for 2 h with stirring. The suspension was cooled to −20 °C and a mixture of triethylamine (13.0 mL, 100 mmol) and carbon disulfide (3.10 mL, 50 mmol) added. The mixture was allowed to warm slowly to room temperature and then transferred (with washing) to a measuring cylinder and the volume adjusted to 110 mL (0.455 M). (The above operations were carried out under argon.) The cholest-5-en-3β-yl sulfenylating agent 4 (2.0 g, 3.2 mmol) was added to 7.1 mL (3.2 mmol) of the above solution of 18a (diluted with $CHCl_3$ (50 mL)) to give an instantaneous yellow color. The solution was then washed with 10% aqueous citric acid. The organic solvent was evaporated and the residue recrystallized from MeCN (with some decomposition) to give crude 18b (1.6 g, 86%). A sample of 18b was recrystalllized from $MeCN/CHCl_3$ to give: mp 149–154 °C, $[\alpha]_D$ −14° (c 1.2, CH_2Cl_2); UV λ_{max} (EtOH) 282 (6400), 235 nm (16 590); NMR δ 10.33 (1 H, br, s, COOH), 8.73 (1 H, br t, J = 6 Hz, NH), 5.33 (1 H, br s, 6-H), 3.70 (2 H, dt, J = 6, 6 Hz, 4′-H). Anal. Calcd for $C_{32}H_{53}NO_2S_3$: C, 66.27; H, 9.21; N, 2.42; O, 5.52; S, 16.59. Found: C, 65.97; H, 9.19; N, 2.44; O, 5.70; S, 16.68.

Reaction of 4c with Triethylammonium Propranolol Dithiocarbamate To Give 22d. A solution of propranolol 22a (1.00 g, 3.9 mmol), triethylamine (0.54 mL, 3.9 mmol), and carbon disulfide (0.24 mL, 3.9 mmol) in CH_2Cl_2 (10 mL) was left overnight to form the dithiocarbamate salt. This mixture was added to a solution of the sulfenylating agent 4c (2.91 g, 3.9 mmol) in CH_2Cl_2 (30 mL), producing an instantaneous yellow color. The solvent was removed, and the residue was chromatographed on TLC silica (benzene as eluent) to yield 22d (2.5 g, 88%): $[\alpha]_D$ −48° (c 1, $CHCl_3$); UV λ_{max} (EtOH) 230 (37 600) 289 (12 200) 320 nm (2300); NMR δ aromatic (7 H, m), 5.4 (1 H, s, H-6). Anal. Calcd for $C_{44}H_{65}NO_2S_3$: C, 71.78; H, 8.90; N, 1.90; O, 4.35; S, 13.06. Found: C, 71.98; H, 8.81; N, 1.65; O, 4.62; S, 13.07.



22) a; R- H b; R- SR_c
c; R- C(S)SH
d; R- C(S)SSR_c

Reaction of 4c with Thioacetanilide To Give 13. The sulfenylating agent **4c** (254 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (2 mL). Thioacetanilide (57 mg, 0.38 mol) was added and the mixture swirled until dissolution was complete. Pyridine (3 drops) was added and the solvent removed. The mixture was separated by TLC (CH_2Cl_2 eluant) to give product **13** (147 mg, 71%), which on recrystallization from MeCN gave 126 mg (61%), mp 89–93 °C (most crystals dissolve, some rods left). Liquid crystallized as rods at 95–96 °C, remelting at 96–97 °C: $[\alpha]_D$ −27° (*c* 1.1, $CHCl_3$); UV λ_{max} (hexane) 232 nm (16 100) shoulder from 265–205; NMR δ (aromatic region, 5 H, m) 5.33 (1 H, s, H-6). Anal. Calcd for $C_{35}H_{53}NS_2$: C, 76.16; H, 9.68; N, 2.54; S, 11.62. Found: C, 76.02; H, 9.77; N, 2.55; S, 11.55.



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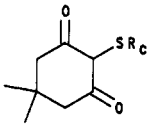

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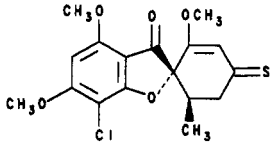
Reaction of 4c with Thiourea To Give 14. The sulfenylating agent **4c** (849 mg, 1.26 mmol) was dissolved in CH_2Cl_2 and stirred with thiourea (129 mg, 1.69 mmol) for about 15 min. The excess thiourea was filtered off. Hexane was added to the filtrate and the product separated as a crystalline solid. It was filtered off, washed thoroughly with hexane, and dried, giving triflate salt **14** (804 mg, 105%), some of which was recrystallized from MeCN/CH_2Cl_2 to give: mp 173–173.5 °C; $[\alpha]_D$ −7.5° (*c* 1.1, EtOH); NMR δ 9.05 (4 H, br s, 2xNH_2), 5.40 (1 H, br s, H-6). Anal. Calcd for $C_{28}H_{48}N_2S_2{\cdot}HSO_3CF_3$: C, 55.59; H, 7.83; N, 4.47; S, 15.34. Found: C, 55.68; H, 7.90; N, 4.40; S, 16.19. (Fluorine interferes with S analysis.)

Reaction of 4c with Griseofulvin 4′-Thione To Give 26. Griseofulvin 4′-thione (**25**;[13] 354 mg, 0.96 mmol) was added to a solution of the sulfenylating agent **4c** (640 mg, 0.95 mmol) and pyridine (0.1 mL) in $CHCl_3$ (15 mL). The red color of the thione was immediately replaced by a yellow color. After evaporation of the solvent, preparative TLC yielded **26** (373 mg, 51%), which was recrystallized from CH_2Cl_2 and hexane: mp 218–220 °C; $[\alpha]_D$ +88° (*c* 1.15, $CHCl_3$); UV λ_{max} (THF) 292 (44 800) 320 (shoulder), 223 nm (shoulder); NMR δ 6.62 (1 H, s, H-5′), 6.10 (1 H, s, H-3′), 5.40 (1 H, s, H-6), 4.02 (3 H, s, OMe), 3.90 (3 H, s, OMe). Anal. Calcd for $C_{43}H_{59}ClO_5S_2$: C, 68.36; H, 7.87; Cl, 4.69. Found: C, 68.32; H, 8.00; Cl, 5.01.



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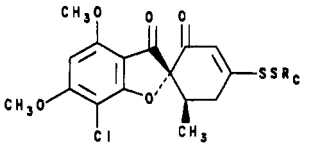

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Reaction of Cholest-5-en-3β-yl Sulfenylating Agent (4c) with 2-Mercaptobenzimidazole (19a) To Give 19b: Method A, in the Presence of Pyridine. The sulfenylating agent **4c** (402 mg, 0.596 mmol) was dissolved in DMF (ca. 5 mL) and pyridine (ca. 0.5 mL). 2-Mercaptobenzimidazole (**19a**; 89.4 mg, 0.596 mmol) was added and stirring continued until it had dissolved. As the thiol dissolved some material precipitated. Stirring was continued for a further 10 or 15 min. The mixture was then worked up and the crude product chromatographed, eluting first with $CHCl_3$ and working up to 4% methanol/$CHCl_3$ to give benzimidazol-2-yl cholest-5-en-3β-yl disulfide (**19b**; 60 mg, 18%; IR and NMR), starting 2-mercaptobenimidazole (**19a**; 41 mg, 46%; NMR, IR, TLC) and starting sulfenylating agent **4c** (140 mg, 35%; IR and UV) along with other products in smaller quantities. **Method B, with Sodium Bicarbonate Workup.** The sulfenylating agent **4c** (252 mg, 0.37 mmol) was dissolved in DMF (2 mL) and 2-mercaptobenzimidazole (**19a**; 56 mg, 0.37 mmol) added with stirring. A solution of sodium bicarbonate (80 mg, 0.95 mmol) in water (2 mL) was added to the yellow reaction mixture causing slight warming and a white precipitate. More water (4 mL) was added, and the precipitate was filtered off and washed with a large volume of water and then a large volume of hexane (removing the thiopyridone). After drying, the yield of **19b** was 193 mg (94%): mp 201–218 °C. Recrystallization yielded 142 mg (69%): mp 214–216 °C; NMR δ 5.33 (1 H, br s, H-6), 7.2 (4 H, br m, Ar). Anal. Calcd for $C_{34}H_{50}N_2S_2$: C, 74.1; H, 9.1; N, 5.1; S, 11.6. Found: C, 74.6; H, 9.4; N, 4.9; S, 11.4. **Method C, with Diisopropylethylamine Workup.** A reaction carried out as above but worked up by adding first diisopropylethylamine then water rather than aqueous sodium bicarbonate afforded 100% crude **19b**: mp 213–216 °C, with some material solidifying then remelting at 221–232 °C.

Reaction of 4c with 6-Mercaptopurine (20a) To Give 20b. A reaction carried out as for 2-mercaptobenzimidazole (method B) gave 81% crude **20b** (72% after recrystallization from MeCN/$CHCl_3$): mp 218 °C; $[\alpha]_D$ −65° (*c* 1.08, THF); UV λ_{max} 280 (12 800) 285 nm (shoulder); NMR δ ($CDCl_3$ + Polysol) 8.25 (1 H, s, purine), 7.83 (1 H, s, purine), 5.26 (1 H, s, H-6). Anal. Calcd for $C_{32}H_{48}N_4S_2$: C, 69.52; H, 8.75; N, 10.14; S, 11.60. Found: C, 69.61; H, 8.95; N, 9.99; S, 11.71.

Reaction of 4c with 2-Thiouracil (21a) To Give 21b. A reaction carried out as for 2-mercaptobenzimidazole (method B) above gave 92% crude **21b** (78% after recrystallization from MeCN/$CHCl_3$): mp 164–166 °C; $[\alpha]_D$ −32° (*c* 0.98, $CHCl_3$); UV (THF) λ_{max} 227 (9357), 279 (5670), 290 nm (shoulder); NMR δ 7.87 (1 H, d, *J* = 6 Hz, 4-H′), 6.27 (1 H, d, *J* = 6 Hz, 5-H′), 5.40 (1 H, s, 6-H). Anal. Calcd for $C_{31}H_{48}N_2OS_2$: C, 70.44; H, 9.15; N, 5.30; S, 12.12. Found: C, 70.28; H, 9.22; N, 5.24; S, 12.29.

Reaction of 4c with 5-Propyl-2-thiouracil (21c) To Give 21d. The reaction was carried out as for 2-mercaptobenzimidazole (method B) but without the hexane wash (the product was too soluble). The product was isolated by chromatography on Florisil and recrystallized from hexane to give **21d** (26%): mp 150–152 °C; $[\alpha]_D$ −43° (*c* 1.21, $CHCl_3$); UV (hexane) λ_{max} 229 (10 153), 290 nm (6666); NMR δ 5.97 (1 H, s, H-6 (pyrimidine ring)), 5.30 (1 H, s, H-6). Anal. Calcd for $C_{34}H_{54}N_2OS_2$: C, 71.52; H, 9.53; N, 4.90; S, 11.21. Found: C, 71.72; H, 9.60; N, 4.92; S, 11.23.

Reaction of 4c with Sodium *p*-Toluenesulfinate To Give 10. The sulfenylating agent **4c** (342 mg, 0.51 mmol) was dissolved in CH_2Cl_2 (3 mL), and sodium *p*-toluenesulfinate (90 mg, 0.51 mmol) in trifluoroethanol (1.2 mL) was added. Reaction proceeded over 15 min with formation of a fine precipitate. The product was isolated by TLC (benzene eluant) to give **10** (180 mg, 64%). Recrystallization from MeCN/carbon tetrachloride gave 140 mg (51%): mp 111–112 °C; $[\alpha]_D$ −36° (*c* 0.98, $CHCl_3$); UV λ_{max} 260 (2430) 266 (2400), 277 nm (1700); NMR δ 2.45 (3 H, s, Ph-Me), 5.23 (1 H, m, 6-H), 7.3 (2 H, d, *J* = 8 Hz, 2-H, 3-H of Ts), 7.8 (2 H, d, *J* = 8 Hz, H-3, H-5 of Ts). Anal. Calcd for $C_{34}H_{52}O_2S_2$: C, 73.33; H, 9.41; S, 11.51. Found: C, 73.25; H, 9.44; S, 11.51.

Reaction of 4c with Sodium Cyanide To Give 9. The sulfenylating agent **4c** (259 mg, 0.378 mmol) was dissolved in DMF (95 mL) and NaCN (20 mg, 0.41 mol) added with stirring. A few mg of dicyclohexyl-18-crown-6 was then added to aid solution. After 2 h all the solid had dissolved to produce a yellow solution. The solvent was evaporated, and the residue was chromatographed (TLC, benzene as eluant) to yield the thiocyanate **9**, 142 mg (88%): mp 125–129 °C (lit.[14] 129 °C), identical by IR with authentically prepared material.

Reaction of 4c with Dimedone To Give 24. The sulfenylating agent **4c** (279 mg, 0.407 mmol) and dimedone (57 mg, 0.41 mmol) were dissolved in CH_2Cl_2 (10 mL), and after 1 h pyridine was

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added, giving a yellow color and a precipitate that came down slowly. The crude product was chromatographed (TLC, 20% EtOAc/$CHCl_3$) to yield **24** (119 mg, 54%), which was crystallized from MeOH to give: mp 138–140 °C (solidifying and remelting at 147–148 °C); $[\alpha]_D$ −17° (*c* 1.085, $CHCl_3$); NMR δ 5.26 (s, H-6), 2.45 (s, H-α to carbonyl), 1.12 (s, 2 Me's). Anal. Calcd for $C_{35}H_{56}O_2S$: C, 77.72; H, 10.44; S, 5.93. Found: C, 77.92; H, 10.64; S, 5.95.

Reaction of 4c with Iodide To Give 15. The sulfenylating agent **4c** (252 mg, 0.373 mmol) and Bu_4NI (209 mg, 0.569 mmol) were dissolved in CH_2Cl_2 (3 mL). Iodine was removed by washing with aqueous sodium thiosulfate. The solution was dried and chromatographed (TLC, CH_2Cl_2 eluant) to yield the disulfide **15** (127 mg, 88%), mp 140–143 °C, and thioamide **5** (40 mg, 85%) (by NMR). The ethylated sulfenylating agent **4b** gave 80% of **15**, mp 145–147 °C.

Reaction of 4c with Aqueous Sodium Bicarbonate To Give 16. The sulfenylating agent **4c** (100 mg, 0.148 mmol) was dissolved in DMF (2 mL), and $NaHCO_3$ (29 mg, 0.35 mmol) was added with stirring. No obvious reaction occurred (no color change). Water (5 mL) was added, and the precipitate that formed was filtered off, washed with water, and dried to yield crude **16** (60 mg). Preparative TLC (CH_2Cl_2 as eluant) yielded **16**, 50 mg (82%). Recrystallization ($CHCl_3$/MeCN) yielded 20 mg **16**: mp 170–173 °C, which was identical by mixed mp and spectral data with an authentic specimen (prisms) prepared as follows.

Unambiguous Preparation of 16. Dicholest-5-en-3β-yl disulfide (374 mg, 0.466 mmol) was dissolved in CH_2Cl_2 (5 mL), and *m*-chloroperbenzoic acid (94 mg, 0.55 mmol) was added. Purification of the product by TLC yielded **16** (283 mg, 74%). Recrystallization from $CHCl_3$/MeCN yielded 219 mg comprising two crystalline modifications, needles and prisms. These were separated manually to give 25 mg of needles and 194 mg of prisms. The IR spectra of the two forms were almost identical except for the SO stretch. Needles: mp 188–195 °C; $[\alpha]_D$ 21° (*c* 1.32, $CHCl_3$); IR ν_{max} 1080 s, 1070 s cm^{-1}. Prisms: mp 170–173 °C; $[\alpha]_D$ 3.8° (*c* 1.32, $CHCl_3$); IR 1080 s cm^{-1}. Both: NMR δ 5.43 (1 H, s, H-6); UV λ_{max} (EtOH) 260 nm (2500). Anal. (Prisms, mp 170–173 °C) Calcd for $C_{54}H_{90}OS_2$: C, 79.15; H, 11.07; S, 7.83. Found: C, 78.85; H, 11.33; S, 7.44.

Reaction of 4a with Tetrahydroisoquinoline To Give 23. A solution of the steroidal sulfenylating agent **4a** (200 mg, 0.320 mmol) was dissolved in DMF (3 mL) and stirred with powdered 4A molecular sieves. Tetrahydroisoquinoline (0.040 mL, 43 mg, 0.32 mmol) was added, followed by diisopropylethylamine (0.060 mL, 45 mg, 0.34 mmol). After 1 min, water (6 mL) was added and the precipitate that formed was filtered off, washed with water, and dried. The crude product was dissolved in $CHCl_3$, the sieves were filtered off, and the filtrate was crystallized from MeCN/$CHCl_3$ to yield **23** (130 mg, 2 crops, 76%): mp 116–125 °C; $[\alpha]_D$ −5° (*c* 1.05, $CHCl_3$); NMR δ 7.17 (4 H, br s, arom), 5.37 (1 H, br s, H-6), 4.23 (2 H, br s, H-1), 3.32 (t) and 2.92 (t) (H-3′ and H-4′); MS 533 (M^+) 402. Anal. Calcd for $C_{36}H_{55}NS$: C, 80.99; H, 10.38; N, 2.62; S, 6.01. Found: C, 80.74; H, 10.22; N, 2.40; S, 6.21. Compound **23** decomposed giving a mixture of compounds on attempted chromatography (silica TLC).

Reaction of 4c with Morpholine To Give 11. Morpholine (0.200 mL, excess) was added to a solution of the sulfenylating agent **4c** (255 mg, 0.277 mmol) in CH_2Cl_2. The product was isolated by preparative T.L.C. to afford **11** (68 mg, 37%) (some decomposition took place on the plate). A sample of **11** crystallized from $CHCl_3$/CH_3CN had: mp 99–103 °C; $[\alpha]_D$ −18 (*c* 1.3%, $CHCl_3$); NMR δ 5.37 (1 H, s, H-6), 3.63 (4 H, m), 3.0 (4 H, m). Anal. Calcd for $C_{31}H_{33}NOS$: C, 76.32; H, 10.95; N, 2.87; S, 6.57. Found: C, 76.09, H, 10.97; N, 2.71; S, 6.57.

Reaction of 4a with Propranolol To Give 22b: Propranolol (**22a**; 33 mg, 320 μmol) was added to a solution of the sulfenylating agent **4a** (200 mg) dissolved in DMF (1.5 mL) and the mixture stirred until solution was complete. Diisopropylethylamine (56 μL, 41 mg, 320 μmol) was added and the solvent removed in vacuo. The residue was dissolved in toluene and the solvent removed in vacuo. This was repeated several times. Chromatography afforded pure **22b** (160 mg, 76%) as an oil: NMR δ (7 H, aromatic), 5.3 (1 H, br s, H-6). Anal. Calcd for $C_{43}H_{65}NO_2S$: C, 78.24; H, 9.93; S, 4.86. Found: C, 78.10; H, 9.74; S, 4.95.

Notes

A "One-Pot" Synthesis of Sulfenamides[1]

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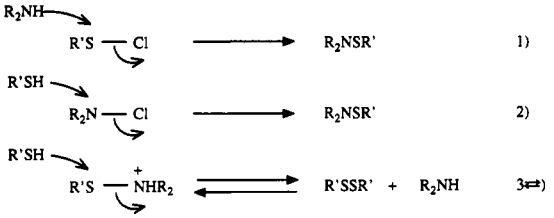
While sulfenamides are stable and reactive sulfenylating agents,[2] they are not commonly employed for this purpose, due largely to the fact that they are typically prepared through reaction of another sulfenylating agent (e.g. sulfenyl chloride) with an amine[2] (eq 1). Although sulfenyl chlorides are generally useful reagents, their application is limited by their very reactivity. For example, the double bond in cholestenethiol (**3a**) would be incompatible with a sulfenyl chloride functionality in the same molecule.

In principle, sulfenamides can be formed through an umpolung of eq 1, i.e., reaction of a thiol with a halamide (eq 2) (Scheme I). This method serves for the synthesis of certain heterocyclic sulfenamides (e.g., **1** and **2**), used as vulcanization accelerators in the rubber industry,[4] typically using aqueous or two-phase conditions. However, this reaction is by no means general, and in fact aliphatic and simple aromatic thiols are reported to lead exclusively to disulfides[5] rather than sulfenamides.

Scheme I



The difference in behavior between the aforementioned heterocyclic thiols (which yield sulfenamides) and ordinary thiols (which yield disulfides) can be rationalized using the following mechanistic scheme.

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(1) Taken in part from the Ph.D. Thesis of A. C. O'Sullivan, University of London, 1981.

(2) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai S., Ed.; Wiley: Chichester, UK, 1990; pp 403–516. Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689. We have found that sulfenamides are particularly useful for the synthesis of unsymmetrical disulfides, when treated with a thiol in the presence of acetic acid.[3]

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(5) Sisler, H. H.; Kotia, N. K.; Highsmith, R. E. *J. Org. Chem.* **1970**, *35*, 1742.

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