J. Chem., 55, 425 (1977); and (f) ref 7.
(11) In the case of N-chlorosuccinimide, arguments for both structures have been put forward; see ref 10d and E. Vilsmaier and W. Sprügel, Justus Liebigs Ann. Chem., 747, 151 (1971).
(12) On the other hand, the structure of the relatively stable 1:1 adduct of THT and bromine has been studied by NMR spectroscopy and X-ray diffraction: G. Allegra, G. E. Wilson, Jr., C. Pedone, E. Benedeth, and R. Albert, J. Am. Chem. Soc., 92, 4002 (1970).
(13) When a similar experiment was done with THF and sulfuryl chloride, no change in the spectrum was observed. The enhanced reactivity of THT toward sulfuryl chloride is also apparent from Table I, where THF is used as a solvent for the chlorination of THT.
(14) Yields were not improved by the addition of 2 equiv of sodium iodide or by reaction at 50 °C.
(15) For a discussion of the mechanism of the reaction of 2-Cl-THF with alcohols, see ref 3d.
(16) Some data for 1-hexanol: in acetonitrile the product contains 35% of dimer 3, and the yield of THT ether is 35%; in benzene these values are 5 and 75%, respectively; and in carbon tetrachloride no dimer is detectable with GC and NMR spectroscopy.
(17) A discussion of the relative reaction rates of tertiary and primary alcohols with 2-Cl-THF can be found in ref 3d.
(18) Thiacarbenium ion 4 is also an intermediate in the chlorination of THT (ref 7). In apolar solvents it reacts immediately with chloride ion, but in polar solvents this reaction is reversible and the formation of 2,3-dihydrothiophene, which reacts with chloride to form 2,3-dichloro-THT, is favored.
(19) The introduction of THP groups with 2,3-dihydropyran, which is a standard technique, requires considerably less subtile conditions; see, for instance, ref 2, p 105.
(20) Chloromethyl methyl ether has been used for the introduction of MM groups, but a new reagent is desirable because (i) it is a powerful carcinogen and (ii) for a convenient reaction, alcoholate anions are needed. The use of dimethoxymethane as a reagent is restricted to phenols: J. P. Yardley and H. Fletcher, Synthesis, 244 (1976).
(21) R. A. Holton and R. G. Davies, Tetrahedron Lett., 533 (1977); see also T. L. Ho and C. M. Wong, J. Chem. Soc., Chem. Commun., 244 (1973), for the synthesis of MTM esters by reaction with chlorodimethyl sulfide and triethylamine in refluxing acetonitrile.
(22) L.G. Wade, J. M. Gerdes, and R. P. Wirth, Tetrahedron Lett., 732 (1978).
(23) (a) When hexanol MTM ether was refluxed in carbon tetrachloride containing 5% p-toluenesulfonic acid, a 90% conversion into 10 and 11a occurred within 120 min. (b) Using the conditions from ref 23a, hexanol MM ether was transformed in 50% conversion into 10 and 11b within 100 min.
(24) W. E. Truce, G. H. Girum, and E. T. McBee, J. Am. Chem. Soc., 74, 3594 (1952).
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Reaction of Isocyanides with Divalent Sulfur-Containing Heterocycles[1]

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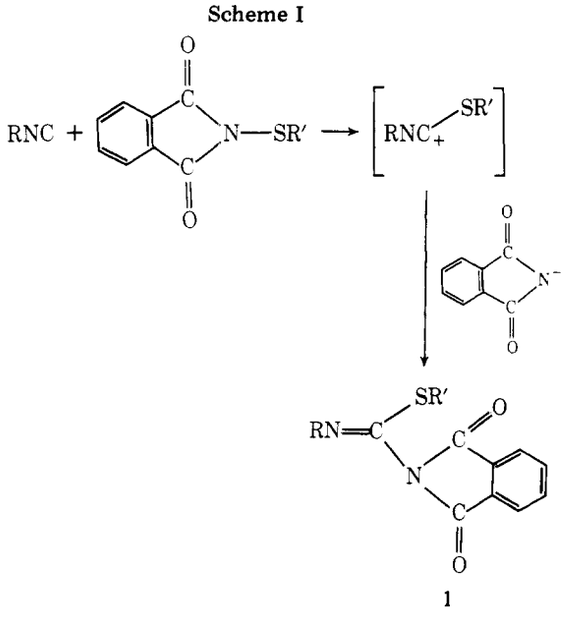
Reaction of *N*-(substituted thio)phthalimides with organic isocyanides results in sulfur–nitrogen bond cleavage and formation of new α adducts **1**. In addition to **1**, 2-alkylthio-5-aminooxazoles (**2**) were prepared for the first time by this method from 2-isocyanoacetamides. Likewise, when sulfur transfer reagents such as 2-alkyldithiobenzimidazoles and benzothiazoles are reacted with isocyanides, sulfur–sulfur fission results in the formation of α adducts possessing attachment of the heterocycle through nitrogen (**4, 6**) or sulfur (**5**) to the isocyanide carbon. Product structure, isomer distribution, and reaction scope are discussed. Reactions of the parent heterocycles with isocyanides are also found to give α adducts **7, 8, 9,** and **10** formed by nitrogen–hydrogen heterolysis.

Reaction of sulfenamides with organic isocyanides (Scheme I) has been found to give α adducts **1** (Table I). The reaction is visualized as proceeding through a polar intermediate, much in keeping with the generally accepted mechanism encountered with a number of other well-known α additions to isocyanides,[2] including certain sulfur compounds.[3–5]

Moreover, sulfenamides have been shown to serve as effective sulfur transfer agents,[6–8] with the products therefrom indicative of sulfur transfer via a positive sulfenium intermediate.

Scheme I



1

The reaction appears fairly general, although with certain isocyanides possessing an active methylene group, an alternative reaction is also possible (Scheme II). Although the corresponding α adduct can be isolated, significant amounts of the novel 2-alkylthio-5-aminooxazoles **2** are also formed. Since oxazole formation has been postulated in certain instances to proceed through a nitrile ylid,[9] especially during the Cornforth rearrangement, its intermediacy is suggested here. Curiously, present evidence indicates that the α adduct in Scheme II cannot be transformed to the substituted oxazole, but rather the two products are formed simultaneously and apparently independently regardless of whether the reaction is carried out at room temperature or in refluxing acetonitrile.

To further define the reaction scope, other types of divalent sulfur compounds were reacted with organic isocyanides, with the results diagrammed in Scheme III.

From the examples given in Schemes I–III it becomes apparent that the α additions depicted require facile cleavage of the sulfenamides or mixed disulfides to give relatively stable sulfenium cation and mercaptide or amine anions. A case in point is disulfides derived from benzothiazoline-2-thione which behave analogously to *N*-alkylthiophthalimides, except that while the sulfenamides derived from imides and amines cleave to give a nitrogen anion and sulfenium cation, the mixed disulfides give the latter ion and resonance stabilized mercaptide anion as addends.

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Table I. Products[a] From Reaction of Isocyanides with Sulfenamides and Disulfides

Material	registry no.	R	R′	R″	% yield	mp, °C	pertinent spectral data[b-d]
1a	66858-78-4	2,6-$(CH_3)_2C_6H_3$	$CH(CH_3)_2$		75	109–110	IR 5.6, 5.8–5.9 (C=O), 6.25 μm (C=N); NMR δ 1.35 (d, 6, $CH(CH_3)_2$), 2.28 (s, 6, $ArCH_3$), 3.42 (m, 1, $CH(CH_3)_2$)
b	66858-79-5	$(CH_3)_3C$	$CH(CH_3)_2$		54	140–142	IR 5.65, 5.8 (C=O), 6.08–6.2 μm (C=N); NMR δ 1.20 (s, 9, $C(CH_3)_3$), 1.30 (d, 6, $CH(CH_3)_2$), 3.6 (m, 1, $SCH(CH_3)_2$)
c	66858-80-8	$C_6H_5CH(CH_3)$	$CH(CH_3)_2$		77	105–106	IR 5.60, 5.8 (C=O), 6.18 μm (C=N); NMR δ 1.1–1.3 (multiple doublets, unequal intensity, syn/anti and chiral $CH(CH_3)_2$), 3.2 and 3.9 (minor and major heptet, syn/anti $CH(CH_3)_2$), 4.6 and 5.05 (major and minor quartet, syn/anti $CH(CH_3)_2$), 7.2 (m, 5, ArH)
d	66858-81-9	$C_6H_5CH_2CH(C_6H_5)$	$CH(CH_3)_2$		50	98–100	IR 5.6, 5.8 (C=O), 6.2 μm (C=N); NMR δ 1.1 (d, fractional $(CH(CH_3)_2)$, 1.4 (2d, fractional chiral $CH(CH_3)_2$), total at 1.1 and 1.4 (6 protons), 3.15 (m, 2, chiral CH_2CH), 3.85 (heptet, 1, $CH(CH_3)_2$), 4.6 and 5.1 (unequal triplet, syn/anti $ArCHCH_2$), 7 (m, 10, ArH)
e		$C_2H_5OC(O)CH_2$	$CH(CH_3)_2$		51	89–91	IR 5.65, 5.8 (C=O), 6.2 μm (C=N); NMR δ 1.20 (t, 3, CH_3CH_2), 1.35 (d, 6, $(CH_3)_2C$), 4.07 (heptet, 1, SCH), 4.12 (s, ca. 1.6, NCH_2), 4.13 (quartet, 2, CH_2CH_3), 4.30 (s, ca. 0.5, NCH_2, remaining syn/anti isomer)
f[e]		$C_6H_5N(i\text{-}Pr)C(O)CH_2$	$CH(CH_3)_2$		<10	140–145	IR 5.65, 5.8 (C=O), 6.05 (C=O), 6.2–6.3 μm (C=N); NMR δ 1–1.16 (multiple doublets, 12, syn/anti $CH(CH_3)_2$), 3.8 and 3.97 (2s, 2, syn/anti CH_2N), 4.95 (heptet, 1, $NCH(CH_3)_2$)
g	66858-82-0	2,6-$(CH_3)_2C_6H_3$	n-C_3H_7		71	130–132	IR 5.7, 5.8–5.9 (C=O), 6.2–6.3 μm (C=N); NMR δ 0.82 (t, 3, CH_2CH_3), 1.5 (m, 2, CH_2CH_3), 2.20 (s, 6, $ArCH_3$), 2.8 (t, 3, SCH_2)
h	66858-83-1	2,6-$(CH_3)_2C_6H_3$	C_6H_5		62	169–171	IR 5.65, 5.8 (C=O), 6.2 μm (C=N); NMR δ 2.4 (s, 6, $ArCH_3$), 6.9–7.5 (m, 5, ArH)
i	66858-84-2	2,6-$(CH_3)_2C_6H_3$	$C(CH_3)_3$		43	160–162	IR 5.68, 5.85 (C=O), 6.2 μm (C=N); NMR δ 1.6 (s, 9, $C(CH_3)_3$) 2.22 (s, 6, $ArCH_3$)
2a	66858-85-3	$(CH_3)_2CH$	$(CH_3)_2CH$	C_6H_5	31	oil	IR 6.2, 6.3 μm (oxazole and phenyl ring); NMR δ 1.23 (d, 6, $CH(CH_3)_2$), 1.43 (d, 6, $CH(CH_3)_2$), 3.82 (heptet, 1, $CH(CH_3)_2$), 4.20 (heptet, 1, $CH(CH_3)_2$), 6.75 (s, 1,4-oxazole H)
2b	66858-86-4	cyclohexyl	$(CH_3)_2CH$	C_6H_5	63	oil	IR 6.18, 6.3 μm (oxazole and phenyl ring); NMR δ 1.2 [d, 6, $(CH_3)_2C$], 1–2.3 (m, 10, cyclohexyl H), 3.6 (m, 1, CHS), 4.1 (heptet, 1, NCH), 6.42 (s, 1, 4-oxazole H)

Table I (*continued*)

Material	registry no.	R	R′	R″	% yield	mp, °C	pertinent spectral data[b-d]
3	66858-87-5				59	oil	IR 6.2–6.35 μm (C=N); NMR δ 1.1 (d, 6, $OCHCH_3$), 0.8–1.8 (m, 10, cyclohexyl **H**), 1.95 (s, 6, $ArCH_3$), 2.3–2.7 (m, 4, NCH_3), 3.3–4.2 (m, 3, OCH and SCH)
4	66858-88-6	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	H		136–138	NMR δ 1.0–1.9 (m, 10, cyclohexyl **H**), 2.40 (s, 6, $ArCH_3$), 3.05 (m, 1, SCH), 7.0 (m, 3, ArH), 7.4 (m, 4, heterocyclic **H**); ^{13}C=N 152.5, ^{13}C=S 188.6
5a	66858-89-7	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	H		50–60	NMR δ 1.1–1.9 (m, 10, cyclohexyl **H**), 2.2 (s, 6, ArH), 3.8 (m, 1, CHS), 7.2–8.2 (m, 4, heterocyclic **H**); ^{13}C=N 152.6, 155.6
b	66858-90-0	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	Cl	76	140–141	IR 6.3 (C=N), 6.4 μm (hetero ring); NMR δ 1.05–1.9 (m, 10, cyclohexyl **H**), 2.20 (s, 6, $ArCH_3$), 3.8 (m, 1, SCH), 8.07 (d, J = 2 Hz, 1,4-heterocyclic **H**); ^{13}C=N 153.2, 155.1; single-crystal X-ray
6a	66858-91-1	2,6-$(CH_3)_2C_6H_3$	cyclohexyl		64	160–162	IR 6.2 (C=N), 6.35 μm (heteroaromatic); NMR δ 0.9–1.9 (m, 20, cyclohexyl **H**), 2.40 (s, 12, $ArCH_3$), 3.05 (m, 2, SCH), 7.3 (AB quartet, 4, hetero **H**), ^{13}C=N 151.7, ^{13}C=S 169.1
b	66858-92-2	2,6-$(CH_3)_2C_6H_3$	n-C_3H_7		65	201–203	IR 6.2 (C=N), 6.35 μm (heteroaromatic); NMR δ 0.88 (t, 6, $CH_2CH_2CH_3$), 1.55 (m, 4, $CH_2CH_2CH_3$), 2.48 (s, 12, $ArCH_3$), 2.80 (t, 4, $SCH_2CH_3CH_3$), 7.04 (m, 6, ArH), 7.4 (AB quartet, 4, hetero **H**); ^{13}C=S 168.0

[a] Elemental analyses [C, H(S), N] consistent with structure. [b] IR ($CHCl_3$), NMR ($CDCl_3$). [c] All materials possessing 2,6-xylyl and/or phthaloyl moieties display respectively ca. δ 2.2–2.4 (s, $ArCH_3$), ca. 7.0 (s, 3, ArH), and ca. 7.8 (A_2B_2 quartet, 4, ArH). [d] ^{13}C NMR resonances in ppm from Me_4Si. [e] Per general formula **1**, Scheme I.

Addition products with attachment at nitrogen (**4**) or sulfur (**5**) have been isolated. In one instance these pure isomers were separately shown to be convertible in refluxing acetonitrile to an equilibrium mixture of ca. 42% **4** and 58% **5a**. This observation is in accord with previous studies of S vs. N attachments of benzothiazole-2-thione derivatives,[10] although in the present case the S derivative is predominate. In fact, **5b** was isolated without evidence for nitrogen attachment and further completely resisted isomerization to **4** in refluxing acetonitrile, suggesting a steric influence on equilibrium.

In Scheme III reaction occurs only at both heteronitrogens, leading to bisadduct **6**. Attachment of the isocyanide carbon to heteronitrogens rather than mercapto exo-sulfur does not, however, necessarily preclude initial attack of isocyanide at this latter atom, followed by rearrangement. The propensity for final nitrogen rather than sulfur alkylation and acylation in these heterocyclic ring systems has previously been studied by Halasa.[11]

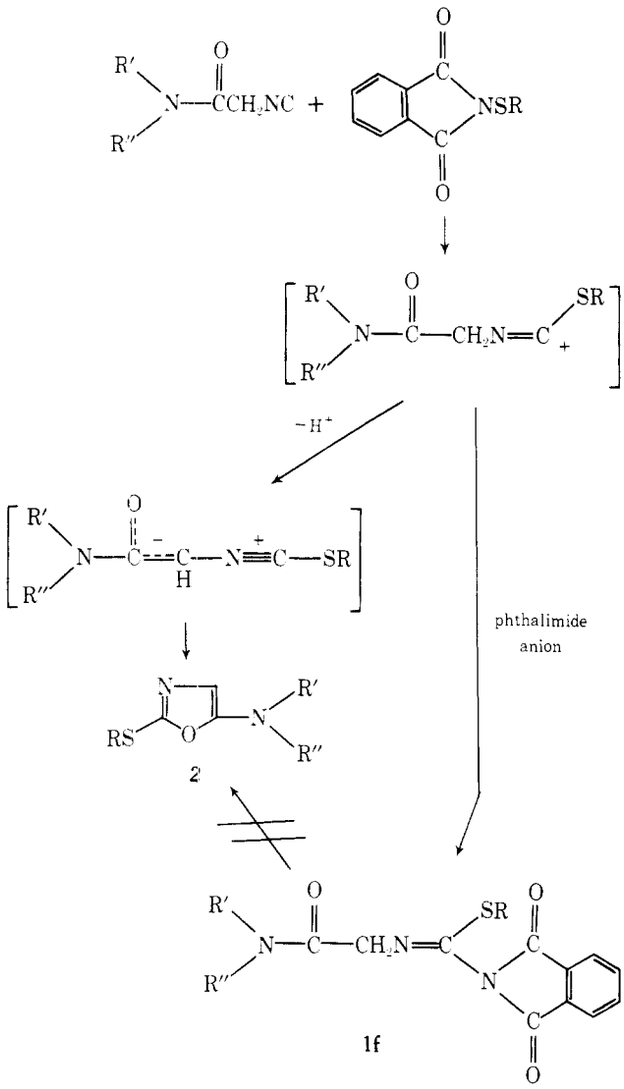
Nitrogen attachment is exclusively found with simple uncatalyzed α addition of isocyanides to benzothiazole-2-thione and other heterocyclic thiones (Scheme IV). The preparation of such adducts appears new[12] and a limited scope expansion is presented in Table II. Although benzothiazoline-2-thione and certain of its nuclear substituted derivatives react with isocyanide in a few hours or less in refluxing toluene, other ring systems require more stringent conditions. Refluxing dimethylformamide was found to effect reaction between sluggish benzimidazoline-2-thione rings and isocyanide. Certain closely related ring systems underwent addition to give materials **7, 8** and **9.**

The formations of **7–10,** like **5** and **6,** are sensitive to steric influences. Benzothiazoline-2-thione reacted a good deal faster than the more acidic 5-chloro isomer with 2,6-xylyl isocyanide. 5-Methylbenzimidazole-2-thione, unlike the unsubstituted homologue, when permitted to react with 2 mol of 2,6-xylyl isocyanide produced only the monoadduct, and from the downfield shift of the 7-proton multiplet (coupled to the adjacent 6 proton), reaction occurred only at the 1-nitrogen to give **7h,** with no formation of 2:1 adduct.

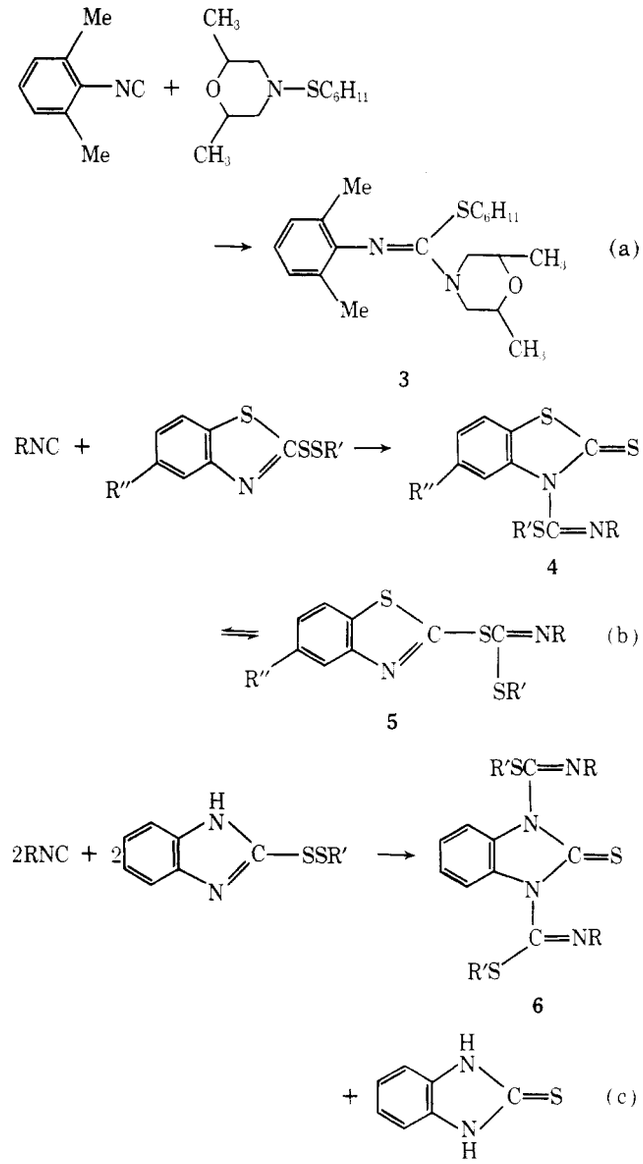
Structure proofs for the new products arising from organic isocyanides and divalent sulfur compounds as listed in Tables I and II are based on methods of preparation, elemental analyses, and spectral interpretations with pertinent absorptions listed in the tables.

Thus materials **1** and **3–10** are characterized by strong imino IR bands at 6.2–6.3 μm. Compounds **1e** and **1f** are the only materials that seemingly display syn/anti forms as indicated by multiple absorptions for the $N–CH_2$ and $CH(CH_3)_2$.

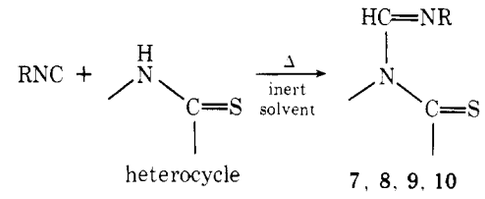
Scheme II



Scheme III[a]



Scheme IV



Spectra of the oxazoles **2** are quite consistent with those found for such ring systems.[13] Additionally, simple acid hydrolysis of **2a** furnishes the expected degradation product, namely 2-(isopropylthiocarbamoyl)-*N*-isopropylacetanilide.

Compounds **6** possess one sharp xylyl methyl peak (12 protons) (^{1}H NMR) and by ^{13}C display the predicted maximum decoupled absorptions for the requisite different carbon atoms. If **6** were unsymmetrical, with one imino moiety linked through sulfur, the ^{1}H and ^{13}C spectra would entail more complexities. Similarly, only one kind of aromatic methyl and formyl proton respectively could be observed for the symmetrical adduct **10.**

^{13}C NMR analysis is especially valuable in verifying the presence of a thiocarbonyl moiety in materials **4** and **6–10.** The ^{13}C=S absorption, particularly those derived from thiazole or oxazole ring systems (**4, 7a–f**), is prominent with its downfield position between 178 and 200 ppm, in keeping with this resonance as found in the parent heterocycles such as benzothiazole-2-thione.[14] The absence of such thiocarbonyl absorptions immediately suggests derivatization through sulfur as in **5** rather than nitrogen (single-crystal X-ray crystallography of **5b** confirms this assignment, see Experimental Section).

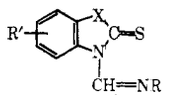
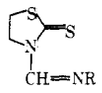
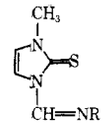
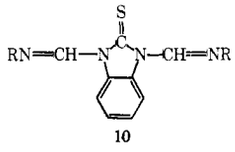
The iminoformyl groups (HC=N) in materials **7–10** are also confirmed by ^{13}C off-resonance experiments, where the single proton coupling serves to locate this resonance among the other sp^2 carbon–heteroatom absorptions. In these cases where measurements were made (see Table II), this absorption was located at ca. 145 ppm, upfield only from the thiocarbonyl resonance.

Experimental Section

Representative procedures for the preparation of the materials listed in Tables I and II are as follows:

1,3-Dioxo-*N*-(2,6-xylyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1a). Technical *N*-(isopropylthio)phthalimide[15] (4.4 g, 0.02 mol) was placed in 100 mL of acetonitrile with 2.6 g of 2,6-xylyl isocyanide. The mixture was heated to reflux after an initial IR at room temperature indicated partial reaction (C=N band emerging at 6.2–6.3 μm). After 30 min at reflux, the reaction was substantially complete, although 0.6 g of additional sulfenamide was added, as it became clear that this reagent contained significant amounts of phthalimide. The cooled mixture was filtered to remove phthalimide and solvent evaporated from the filtrate to give a mushy solid that

Table II. α Adducts[a] From Isocyanides and Heterocyclic Thioamides

material[b]	registry no.	R	R′	X	% yield	mp, °C	pertinent spectral data[c-e]
 7							
a	66858-93-3	2,6-$(CH_3)_2C_6H_3$		S	64	150–151	NMR δ 7.1–7.5 (m, 3, Ar**H**), 9.00 (m, 1, 4-BT), 9.29 (s, 1, C**H**=N); ^{13}CH=N 148.2, ^{13}C=S 193.6
b	66858-94-4	2,6-$(CH_3)_2C_6H_3$	5-Cl	S	67	175–180	IR 6.05 μm (C=N); NMR δ 7.4 (m, 2, Ar**H**), 9.17 (m, 1, 4-BT), 9.27 (s, 1, C**H**=N); ^{13}CH=N 147.9, ^{13}C=S 193.6
c	66858-95-5	2,6-$(CH_3)_2C_6H_3$	6-NO_2	S	36	>290	NMR δ 8.3 (m, 2, Ar**H**), 9.33 (d, J = 8 Hz, 4-BT), 9.35 (s, 1, C**H**=N)
d	66858-96-6	2,6-$(CH_3)_2C_6H_3$	6-C_2H_5O	S	69	155–156	NMR δ 1.4 (t, 3, $CH_2C\mathbf{H}_3$), 4.03 (q, 2, $C\mathbf{H}_2CH_3$), 6.8–7.2 (m, 5, ArH), 8.97 (d, J = 8 Hz, 4-BT), 9.30 (s, 1, CH=N)
e	66858-97-7	2,6-$(CH_3)_2C_6H_3$		O	50	167–168	NMR δ 7.2–7.4 (m, 3, Ar**H**), 8.4 (m, 1, 4-BO), 8.96 (s, 1, C**H**=N); ^{13}CH=N 146.8, ^{13}C=S 181.0
f	66858-98-8	cyclohexyl		S	34	131–132	NMR δ 1.1–2.2 (m, 10, cyclohexyl), 3.40 (m, 1, C**H**N=C), 7.2–7.5 (m, 3, Ar**H**), 8.83 (m, 1,4-BT), 9.32 (s, 1, C**H**=N); ^{13}CH=N 145.4, ^{13}C=S 192.6
g	66922-24-5	2,6-$(CH_3)_2C_6H_3$		NH		245–247	NMR (Me_2SO), 7.0–7.4 (m, 6, Ar**H**), 8.58 (m, 1, 7-BI), 9.23 (s, 1, C**H**=N)
h	66858-99-9	2,6-$(CH_3)_2C_6H_3$	5-CH_3	NH	40	231–234	NMR δ 2.42 (s, 3, 5-$C\mathbf{H}_3$), 7.0 (m, 5, Ar**H**), 8.40 (m, 1, 7-BI), 9.17 (s, 1, C**H**=N); ^{13}CH=N 147.0, ^{13}C=S 170.6
 8	66859-00-5				47	125	NMR δ 3.42 (t, 2, $C\mathbf{H}_2$S), 4.60 (t, 2, $C\mathbf{H}_2$N), 8.70 (C**H**=N); ^{13}CH=N 147.0, ^{13}C=S 200.7
 9	66859-01-6				15	113–115	NMR δ 3.62 (d, J = 1 Hz, 3, $NC\mathbf{H}_3$), 6.75 and 7.6 (2 m, J = 1 Hz, NC**H**=C**H**N), 8.88 (s, 1, CH=N)
 10	66858-63-7					268–270	IR 6.05 μm (C=N); NMR δ 7.35–7.6 (m, 2, 5, 6-BI), 8.70–9.02 (m, 2, 4, 7-BI), 9.30 (s, 2, CH=N)

[a] Elemental analyses (C, H, N) consistent with structure. [b] In **8**, **9**, **10**, R = 2,6-$(CH_3)_2C_6H_3$. [c] IR ($CHCl_3$), NMR ($CDCl_3$), ^{13}C in ppm from Me_4Si. [d] All materials possessing 2,6-xylyl displayed NMR δ ca. 2.2 (s, $ArCH_3$) and ca. 7.0 (ArH). [e] BT-benzothiazole, BI-benzimidazole, BO-benzoxazole.

crystallized hard after several hours. Recrystallization from hot methylcyclohexane (after filtering off more phthalimide) afforded 2.9 g of **1a** as a first crop, mp 109–111 °C, and 0.8 g additional compound from the mother liquors.

1,3-Dioxo-*N*-(*tert*-butyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1b). *tert*-Butyl isocyanide (1.66 g, 0.02 mol) was dissolved in 50 mL of dry acetonitrile containing 4.86 g (0.022 mol) of *N*-(isopropylthio)phthalimide. After standing 24 h at room temperature, the isocyanide (IR) had vanished to be replaced by a strong C=N band at 6.2 μm. After solvent removal, the residue was dissolved in hot hexane and filtered and product allowed to crystallize on cooling, thereby yielding 3.3 g of white crystals. An analytical sample was obtained by a second recrystallization from hexane.

1,3-Dioxo-*N*-(ethoxycarbonylmethyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1e). Ethyl 2-isocyanoacetate[16] (0.02 mol, 2.26 g) was mixed with 4.5 g (0.02 mol) of technical *N*-(isopropylthio)phthalimide and allowed to stand at room temperature for 2 days. After this time there was still a trace of isocyanide present as determined by IR. The mixture was filtered to remove small amounts of phthalimide and the filtrate treated on a vacuum rotary evaporator to remove solvent. The residual 3.4 g of oil proved to be nearly pure *1e* (NMR and IR). Scratching induced crystallization and the material was recrystallized from methylcyclohexane to give 2.2 g of solid, while a final recrystallization from hexane furnished the analytical sample.

1,3-Dioxo-*N*-(*N*-isopropylcarbaniloylmethyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1f), and 5-(*N*-Isopropylanilino)-2-(isopropylthio)oxazole (2a). 2-Isocyano-*N*-isopropylacetanilide[17] (0.02 mol, 4.04 g) and an equimolar amount of *N*-(isopropylthio)phthalimide (4.5 g) were dissolved in 100 mL of acetonitrile and the mixture heated at reflux for 2 h, then permitted to stand overnight. At the same time an identical charge was placed in acetonitrile and without heating the solution was allowed to stand overnight at room temperature. Infrared spectra of both solutions after standing were identical. They were both separately worked up in an identical manner as follows to give essentially the same distribution of products **1f** and **2a**: Acetonitrile was removed under vacuum then the residue taken up in ether and washed with 2.5% caustic to

remove phthalimide. During this process 1.1 g of solid, neutral **1f** was filtered off. The ether filtrate after drying over magnesium sulfate was vacuum treated to remove solvent and the residue triturated with ca. 50 mL of pentane. An additional 1.0 g of **1f** was thereby obtained. The clear pentane solution was evaporated to give 2.5 g of oil as crude **2a.** Although a sample of this material did not survive injection into a GLC column at 200 °C, it was purified by elution with pentane through neutral (Wöhme) alumina, to give after filtering through clay 1.4 g of clear, near-colorless oil which exhibited an NMR spectra indicative of high assay **2a.**

The combined solids obtained as described above were dissolved in chloroform and eluted through a silicic acid column with 98% $CHCl_3$/2% EtOH, to give a viscous white oil, which was characterized by only one spot on TLC. The material was triturated with pentane to give 0.3 g of white powdery solid, which by NMR was shown to consist of both syn and anti α adduct **1f.**

Material **2a,** 0.4 g, was shaken at room temperature with ca. 20 mL of 12% HCl. The oil appeared to nearly dissolve in this medium when crystals appeared. After standing 0.5 h, the acidic mixture was diluted with 25 mL of water and filtered. The washed and then dried crystals were recrystallized from isopropyl alcohol to give 0.24 g of 2-(isopropylthiocarbamoyl)-*N*-isopropylacetanilide: mp 138–139 °C; IR 5.95–6.15 μm (C=O); ^{1}H NMR ($CDCl_3$) δ 1.04 and 1.08 (2 d, 12, J = 7 Hz, 2 $(CH_3)_2CH$), 3.54 (heptet, 1, J = 7 Hz, SCH), 3.60 (d, 2, J = 6 Hz, $HNCH_2$), 4.98 (heptet, 1, J = 7 Hz, NCH), 6.48 (m, broad, 1, NH), 7–7.6 (multiplets, 5, ArH); MS revealed parent molecular ion at 294 and fragmentation pattern consistent with structure.

Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7 53; N, 9.51. Found: C, 61.19; H, 7.55; N, 9.48.

2-Cyclohexylthio-5-(*N*-isopropylanilino)oxazole (2b). Equimolar amounts (0.01 mol) of 2-isocyano-*N*-isopropylacetanilide and 4-cyclohexylthio-2,6-dimethylmorpholine[18] were heated at reflux in acetonitrile until the isocyanide band had essentially vanished. Upon cooling, the solvent was removed and the residual oil was eluted through neutral alumina with pentane to give, on solvent removal, 2.0 g of **2b.**

2,6-Dimethyl-4-morpholine-*N*-(2,6-xylyl)carboximidothioic Acid, Cyclohexyl Ester (3). 2,6-Xylyl isocyanide (0.05 mol) was mixed in 100 mL of acetonitrile with an equimolar amount of 4-cyclohexylthio-2,6-dimethylmorpholine.[18] The mixture was refluxed for several hours, until the isocyanide band (IR) had essentially disappeared. On evaporation of solvent an oil was obtained which was filtered through clay as product.

***N*-(2,6-Xylyl)benzothiazoline-2-thione-3-carbonimidothioic Acid, Cyclohexyl Ester (4).** 2,6-Xylyl isocyanide (0.01 mol, 1.3 g) and 2-cyclohexyldithiobenzothiazole[18] (0.01 mol, 2.8 g) were mixed together in 50 mL of acetonitrile and the temperature was raised to reflux. After 12 h at this temperature, the mixture was cooled and solvent evaporated to give a viscous syrup. Column chromatography through silica gel (elution with cyclohexane/ethyl acetate v/v 4:1) gave the first elutant collected as **4,** recrystallized hexane, mp 136–138 °C, yield 0.4 g.

***N*-(2,6-Xylyl)-*S*-(2-benzothiazolyl)carbonimidodithioic Acid, *S'*-Cyclohexyl Ester (5a).** The second fraction collected from **4** was rechromatographed with cyclohexane/ethyl acetate (LC) to give upon solvent evaporation 0.6 g of solid, recrystallized from pentane.

Isomerization of 4 and 5a. Solutions of pure **4** and **5a** were separately boiled in CD_3CN for ca. 24 h. During this time (after ca. 12 h) it was established by examining the ^{1}H NMR of the solutions that each had established an equilibrium of ca. 42% **4** and 58% **5a.** Upon evaporation of the NMR solvent, both pure **4** and **5a** were isolated from the reaction mixtures by recrystallization from hexane (**4**) and chromatography (**5a**).

***N*-(2,6-Xylyl)-*S*-(5-chloro-2-benzothiazolyl)carbonimidodithioic Acid, *S'*-Cyclohexyl Ester (5b).** 2,6-Xylyl isocyanide (0.015 mol, 1.96 g) and 5-chloro-2-cyclohexyldithiobenzothiazole[18] (0.015 mol) were mixed together in acetonitrile and the temperature raised to reflux. A clear solution was thereby achieved. Reflux was continued overnight, but on cooling an oil layer was observed. IR of the solvent phase showed almost no isocyanide remaining. The lower layer was separated and scratching induced crystallization of the lower oil layer with 5.1 g filtered from the mixture. An analytical sample was recrystallized from isopropyl alcohol. Material **5b** was examined by single crystal X-ray and found to be monoclinic, space group $P2/a$, with a = 11.515 (3) Å, b = 16.585 (5) Å, c = 11.681 (4) Å, β = 95.66 (2)°, with unit cell volume = 2219.9 Å^3 for Z = 4. Preliminary structural refinement has resulted in R_1 = 0.09. Details of the complete structure refinement will be published elsewhere.[19]

Bis[*N,N'*-(2,6-xylyl)]benzimidazole-1,3-dicarboximidothioic Acid, Dicyclohexyl Ester (6a). 2-Cyclohexyldithiobenzimidazole[20] (0.022 mol, 5.8 g) was mixed in 100 mL of dry acetonitrile with 0.02 mol (2.62 g) of 2,6-xylyl isocyanide and the mixture refluxed overnight. After this time, the IR indicated no remaining isocyanide. Small amounts of solid were filtered off the cooled reaction mixture and the solution treated under vacuum to remove acetonitrile. The residue was taken up in ether and washed with 2.5% caustic, then water. After drying over magnesium sulfate, the material was vacuum treated to remove solvent and the residue permitted to stand under hexane for 2 days. Crystals (4.1 g) were deposited, which were once again recrystallized from isopropyl alcohol. An analytical sample was obtained by a further recrystallization from heptane.

5-Chloro-3-[*N*-(2,6-xylyl)formidoyl]benzothiazoline-2-thione (7b). 5-Chlorobenzothiazoline-2-thione (4.0 g, 0.02 mol) was placed in 100 mL of toluene and heated at reflux with an equimolar amount of 2,6-xylyl isocyanide. After 4 h the isocyanide absorption (IR 4.7 μm) had vanished, and on cooling the product separated. The solid material was removed by filtration, taken up in methylene chloride, and washed with 5% sodium hydroxide (to remove starting thiazole). The dried organic phase was then vacuum treated and the residual solid was recrystallized from ethyl alcohol.

3-[*N*-(2,6-Xylyl)formimidoyl]benzoxazoline-2-thione (7e). Equimolar (0.02 mol) charges of benzoxazoline-2-thione and 2,6-xylyl isocyanide were placed in toluene and heated at reflux until only traces of isocyanide remained as monitored by IR. This reflux period was longer than that required for the sulfur analogues (i.e., **6a**). After cooling and separating the solid by filtration, the product was dissolved in methylene chloride and washed with 5% sodium hydroxide. After drying, the material was vacuum treated and the residue recrystallized from isopropyl alcohol.

1-[*N*-(2,6-Xylyl)formimidoyl]benzimidazolinethione (7g) and 1,3-Bis[*N*-(2,6-xylyl)formimidoyl]-2-benzimidazolinethione (10). Benzimidazoline-2-thione (3.8 g, 0.02 mol) was mixed with an equimolar amount of 2,6-xylyl isocyanide in 100 mL of DMF and refluxed for 12 h. Upon cooling overnight **10** crystallized and was separated and purified by recrystallization from pyridine. The DMF filtrate was poured into 500 mL of water and the solid formed was filtered off, dried, and recrystallized from acetonitrile to give a base soluble 1:1 adduct (**7g**).

5-Methyl-1-[*N*-(2,6-xylyl)formimidoyl]-2-benzimidazolinethione (7h). 5-Methylbenzimidazoline-2-thione (4.1 g, 0.025 mol) was mixed with 6.5 g (0.05 mol) of 2,6-xylyl isocyanide in 150 mL of DMF and the material refluxed for 24 h. On cooling, no solid separated, so the clear DMF solution was poured into water to give solid, which after air drying was recrystallized from acetonitrile to give 2.9 g of a 1:1 adduct (**7h**). There was no evidence for the 2:1 adduct.

3-[*N*-(2,6-Xylyl)formidoyl]thiazolidine-2-thione (8). Thiazolidine-2-thione (2.4 g, 0.02 mol) was placed in diglyme with an equimolar amount of 2,6-xylyl isocyanide. The mixture was refluxed for 6 h, solvent removed, and the residue placed on a porous plate. The material was recrystallized from acetonitrile to give 7.4 g.

Acknowledgment. We are indebted to Mr. Ralph Fuhrhop for preparing some of the intermediates and Mrs. Claudette Deatherage for performing and interpreting several of the ^{13}C NMR spectra.

Registry No.—RNC (R = 2,6-$(CH_3)_2C_6H_3$), 2769-71-3; RNC (R = $(CH_3)_3C$), 7188-38-7; RNC (R = $C_6H_5CH(CH_3)$), 17329-20-3; RNC (R = $C_6H_5CH_2CH(C_6H_5)$), 3128-88-9; RNC (R = C_2H_5O + C(O) + CH_2), 2999-46-4; RNC (R = $C_6H_5N(i\text{-}Pr)CO$ + CH_2), 66858-64-8; *N*-(isopropylthio)phthalimide, 17796-72-4; *N*-(propylthio)phthalimide, 17796-71-3; *N*-(phenylthio)phthalimide, 14204-27-4; *N*-(*tert*-butylthio)phthalimide, 17796-75-7; 4-cyclohexyl-2,6-dimethylmorpholine, 1774-04-5; 2-cyclohexyldithiobenzothiazole, 28084-58-4; 5-chloro-2-cyclohexyldithiobenzothiazole, 52367-82-5; 2-cyclohexyldithiobenzimidazole, 40952-49-6; 2-propyldithiobenzimidazole, 66858-65-9; benzothiazoline-2-thione, 149-30-4; 5-chlorobenzothiazoline-2-thione, 5331-91-9; 6-nitrobenzothiazoline-2-thione, 4845-58-3; 6-ethoxybenzothiazoline-2-thione, 120-53-6; benzoxazoline-2-thione, 2382-96-9; benzimidazoline-2-thione, 583-39-1; 5-methylbenzimidazoline-2-thione, 27231-36-3; thiazolidine-2-thione, 96-53-7; 1-methyl-4-imidazoline-2-thione, 60-56-0; *syn*-**1e,** 66922-22-3; *anti*-**1e,** 66922-23-4; *syn*-**1f,** 66858-66-0; *anti*-**1f,** 66858-67-1.

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Sesquiterpene Lactones of *Eupatorium recurvans*[1]

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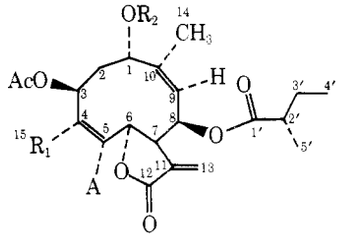
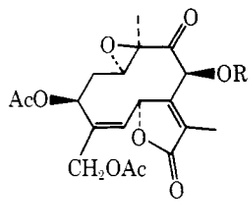
The isolation and structure determinations of three new heliangolides from *Eupatorium recurvans* Small are reported. The major lactone eurecurvin (**1a**) was a *cis*-$\Delta^{4,5}$,*cis*-$\Delta^{9,10}$-germacradienolide, as was a minor lactone constituent **1e**. The third lactone was a trans-$\Delta^{1(10)}$,cis-$\Delta^{4,5}$ isomer, **4a**. Details of the structure and stereochemistry were established by X-ray analysis of **1e** and **4a**.

In the present article we continue our reports[3-5] on constituents of *Eupatorium* species *sensu stricto* which have yielded various cytotoxic and antitumor sesquiterpene lactones and describe the isolation and structure determination of three new heliangolides **1a, 1e,** and **4a** from *Eupatorium recurvans* Small.[6] *E. capillifolium* (Lam.) Small, *E. positifolium* Walt., *E. Leptophyllum* DC., and *E. pinnatifidum* Ell. yielded no significant sesquiterpene lactone fractions.[7]



1a, $R_1 = CH_2OH$; $R_2 = H$
b, $R_1 = CH_2OAc$; $R_2 = H$
c, $R_1 = CH_2OAc$; $R_2 = Ac$
d, $R_1 = CHO$; $R_2 = H$
e, $R_1 = CH_3$; $R_2 = H$
f, $R_1 = CH_3$; $R_2 = H$



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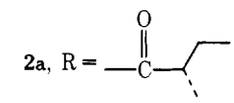
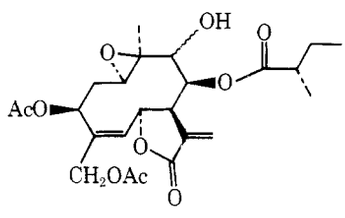


b, R = H



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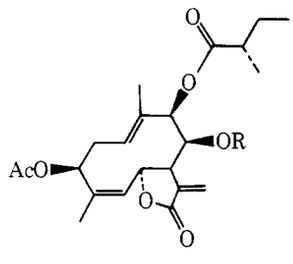
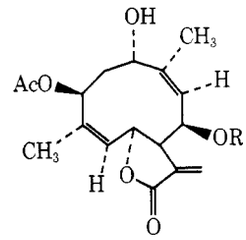


4a, R = H
b, R = Ac



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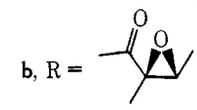
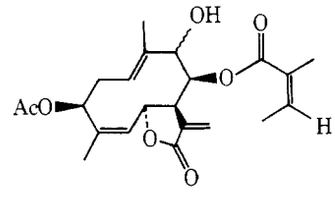


b, R =



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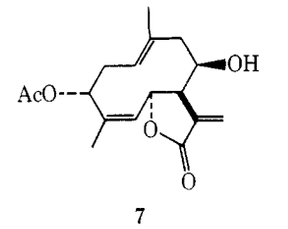

7

The major lactone component of *E. recurvans*, which we have named eurecurvin, $C_{22}H_{30}O_8$, mp 185–186 °C, was an α-methylene γ-lactone as evidenced by the usual criteria [^{1}H NMR spectral data in Table I, narrowly split doublets at 6.45 and 5.72 ppm (H_a and H_b), and appropriate signals of the ^{13}C NMR spectrum in Table II, particularly the triplet at 122.9 ppm]. That it was incorporated in partial structure A was shown by spin decoupling experiments on the lactone and its derivatives in various solvents, which will not be discussed in detail. A vinyl methyl group (broadened signal at 1.88 ppm) was found to be allylically coupled to H_f resonating at 5.44 ppm. Mass and NMR spectral analyses revealed the presence of two ester groups, an acetate and a 2-methylbutyrate.

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