a colorless oil which is easily decomposed by light, yield 50%. Anal. Calcd for $C_{18}H_{15}NS_3$: C, 63.3; H, 4.43; N, 4.10; S, 28.17. Found: C, 63.38; H, 4.53; N, 4.02; S, 27.89. Mass spectrum: *m/e* (rel intensity) 341 (56) M^+, 309 (34), 276 (15), 232 (91), 199 (100).

Anal. Calcd for $C_{18}H_{15}NS_3$·HCl (mp 150 °C): C, 57.19; H, 4.27; N, 3.71; S, 25.45; Cl, 9.38. Found: C, 57.19; H, 4.22; N, 3.82; S, 25.25; Cl, 9.45.

Reaction of 1,2,3-Benzothiadiazole (1) with Thiophenol and AIBN. A solution of 1,2,3-benzothiadiazole (1,[7] 1.36 g, 1×10^{-2} mol), thiophenol (1.10 g, 1×10^{-2} mol), and AIBN (1.6 g) in ethyl acetate was refluxed for 1 h. Column chromatography of the reaction mixture on silica gel with light petroleum (bp 40–70 °C) as eluent gave diphenyl disulfide (**5**,[15] 1.37 g 6.3×10^{-3} mol), thianthrene (**3**, 0.19 g, 0.9×10^{-3} mol), dibenzo[*c,e*]-*o*-dithiin (**2**,[16] 0.06 g, 0.3×10^{-3} mol), and 2-(phenylthio)diphenyl disulfide (**4**, 0.33 g, 1×10^{-3} mol).

Reaction of 1,2,3-Benzothiadiazole (1) with Diphenyl Disulfide. A solution of 1,2,3-benzothiadiazole (**1**,[7] 2.04 g, 1.5×10^{-2} mol) and diphenyl disulfide[15] (1.64 g, 0.75×10^{-2} mol) in methyl benzoate (28 ml) was warmed at 165 °C for 20 h. The solvent was distilled under vacuum (17 mmHg) and the residue was chromatographed on silica gel with light petroleum as eluent. The following products were separated: diphenyl disulfide (**5**,[15] 0.9 g, 4.13×10^{-3} mol), dibenzothiophene (0.05 g, 0.27×10^{-3} mol), thianthrene (**3**, 0.35 g, 1.62×10^{-3} mol), dibenzo[*c,e*]-*o*-dithiin (**2**,[16] 0.45 g, 2.08×10^{-3} mol), 2-(phenylthio)diphenyl disulfide (**4**, 0.45 g, 1.38×10^{-3} mol), and 2,2'-bis(phenylthio)diphenyl disulfide (0.20 g, 0.46×10^{-3} mol), identified by mixture melting point with an authentic specimen obtained from 2-mercaptodiphenyl sulfide[11] by oxidation with bromine in chloroform, mp 124–125 °C. Mass spectrum: *m/e* (rel intensity) 434 (38) M^+, 217 (100), 184 (49). GLC analysis of a solution of **1** (0.136 g, 1×10^{-3} mol) in methyl benzoate, heated at 165 °C for 20 h, showed unchanged **1** (94%). Thianthrene (**3**) and dibenzo[*c,e*]-*o*-dithiin (**2**) were not present.

Reaction of 1,2,3-Benzothiadiazole (1) with *p*-Methylthiophenol and AIBN. A solution of 1,2,3-benzothiadiazole (1.77 g, 1.3×10^{-2} mol), *p*-methylthiophenol (1.62 g, 1.3×10^{-2} mol), and AIBN (2.40 g) in ethyl acetate (23 ml) was refluxed for 1 h. The solvent was evaporated and the residue was chromatographed on silica gel with light petroleum as eluent. The following products were eluted in the order cited: a mixture of diphenyl and *p,p'*-ditolyl disulfide[17] (0.63 g), thianthrene (**3**, 0.31 g, 1.43×10^{-3} mol), and 2-methyldibenzo[*c,e*]-*o*-dithiin (**9**, 0.08 g, 0.34×10^{-3} mol), mp 95 °C. Anal. Calcd for $C_{13}H_{10}S_2$: C, 67.75; H, 4.4; S, 27.85. Found: C, 67.7; H, 4.65; S, 27.45. **9**, by desulfuration with Raney nickel in boiling ethanol, gave 3-methylbiphenyl.

A mixture of 2-(*p*-tolylthio)phenyl-*p*-tolyl disulfide (**10**) and 2-(phenylthio)phenyl-*p*-tolyl disulfide (**11**, 0.4 g) was also separated. The ratio of **10** to **11**, determined by NMR spectra, was 65:35.

Aprotic Diazotization of 2-(*o*-Aminophenylthio)diphenyl Disulfide (8). A. To a solution of **8** in boiling ethyl acetate an equimolecular amount of *n*-pentyl nitrite was added carefully. After nitrogen evolution was finished (~5 min) the solvent was evaporated and the residue chromatographed on silica gel. Thianthrene (**3**) and diphenyl disulfide (**5**) was separated in 90% yields.

B. The diazotization of **8** in methyl benzoate at 165 °C yields **3**, **5**, and thianthrene *S*-oxide,[18] mp 143–144 °C.

Acknowledgment. We thank Consiglio Nazionale delle Ricerche (Rome) for financial support.

Registry No.—**1**, 273-77-8; **4**, 58074-42-3; **8**, 58074-43-4; **8** HCl, 58074-44-5; **9**, 58074-45-6; 2-mercaptodiphenyl sulfide, 53691-60-4; benzenesulfonyl chloride, 931-59-9; 2-amino-2'-mercaptodiphenyl sulfide, 58074-46-7; thiophenol, 108-98-5; diphenyl disulfide, 882-33-7; 2,2'-bis(phenylthio)diphenyl disulfide, 58074-47-8; *p*-methylthiophenol, 1073-72-9.

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Chemistry of the Sulfur–Nitrogen Bond. XI. Synthesis and Thermal Decomposition of *N,N'*-Thiodiamines

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The synthesis and thermal decomposition of *N,N'*-thiodiamines (**1**) and *N,N'*-thioareneaminopiperidines (**5**) were investigated. Series **1** was prepared by addition of piperidine-1-sulfenyl chloride to the aryl amine at −20 °C. An intermediate in the formation of **1** is **5** which is obtained in good yield when the addition of the sulfenyl chloride to the aryl amine is carried out at −78 °C. Azobenzene (**6**), aryl amine, and sulfur are the principal products in the thermal decomposition of **1**. A mechanism involving the initial formation of thionitrosobenzene (ArN=S) was proposed. The thermal decomposition of **5** yields aryl amine and lower amounts of azobenzene. Homolytic cleavage of the S–N bond in **5** followed by recombination of the intermediate radicals yields **1** which is believed to account for the formation of **6**. Oxidation of **1** under anhydrous conditions yields *N*-sulfinylaniline.

N,N'-Thiodianilines (**1**) are a class of important sulfur–nitrogen compounds that have received relatively little attention. Their importance stems from the fact that they are at present the only known source of thionitrosobenzene (**2**).[2,3] The existence of **2** was demonstrated in the thermal decomposition of **1** by trapping with 2,3-dimethyl-1,3-butadiene to yield the 1,2-thiazine **3**.[2] An unstable *N*-thionitrosoamine (R_2N–N=S) has been reported.[4] Attempts to pre-

Table I. Properties of *N,N'*-Thiodiamines

Compd	Yield, %	Mp, °C	Ir, cm^{-1} (NH)	NMR ($CDCl_3$), δ
1a	55	102–103[a]	3310	3.8 (s, 6 H, OMe), 6.2–3 (broad, 2 H, NH), 7.0 (m, 8 H)
b	75 (90, oil)[b]	73–74[c]	*b*	5.9–6.2 (broad, 2 H, NH), 7.5–6.7 (m, 10 H)
c	67 (55)[b]	106–108	*b*	5.8–6.1 (broad, 2 H, NH), 6.8–7.4 (m, 8 H)
d	70 (53)[b]	102–103	*b*	5.8–6.1 (broad, 2 H, NH), 6.8–7.3 (m, 8 H)
e	64	190–195	3350	5.8–6.4 (broad, 2 H, NH), 7.0–7.6 (m, 8 H)
5a	42	Oil	3330	1.2–1.8 (m, 6 H), 3.0 (m, 4 H), 3 (s, 3 H, OMe), 5.8 (broad, 1 H, NH), 6.9–7.5 (q, 4 H)
b	46	Oil	3320	1.2–1.9 (m, 6 H), 2.9–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 7.0–7.5 (s, 5 H)
c	60	81–82[a]	3455	1.0–1.9 (m, 6 H), 3.0–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 6.9–7.5 (q, 4 H)
d	70	53–54[a]	3220	1.0–1.9 (m, 6 H), 2.9–3.3 (m, 4 H), 5.9 (broad, 1 H, NH), 7.0–7.5 (q, 4 H)
e	65	125–126[a]	3360	1.3–1.7 (m, 6 H), 2.8 (m, 4 H), 5.8 (broad, 1 H, NH), 7.0–7.5 (m, 4 H)

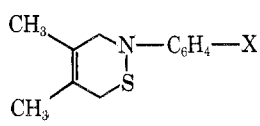
[a] A satisfactory elemental analysis was obtained. [b] See ref 2. [c] This compound was reported as an oil.

pare **2** (X = 4-NMe_2) by treatment of the nitrosobenzene with phosphorus pentasulfide gave an *N*-thiosulfinylaniline (ArN=S=S).[5]

$$(X\text{—}C_6H_4NH)_2S \longrightarrow X\text{—}C_6H_4\text{—}N{=}S + X\text{—}C_6H_4\text{—}NH_2$$

1 **2** **4**

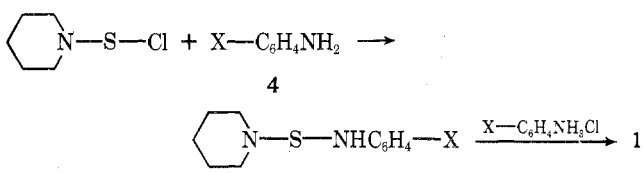
X = **a**, 4-OMe
b, H
c, 4-Br
d, 4-Cl
e, 3-NO_2



3

Our interest in the chemistry of the sulfur–nitrogen bond[6] and the thionitroso group prompted a study of the synthesis and thermal decomposition of *N,N'*-thiodiamines and we report here the results of that investigation.

Synthesis. Compounds **1a–d** were prepared by addition of piperidine-1-sulfenyl chloride to a twofold excess of the appropriate aryl amine at −20 °C. When the addition of the sulfenyl chloride to **4** was carried out at −78 °C *N,N'*-thioareneaminopiperidines (**5**) were obtained in good yield.



4

5

An NMR spectrum of the crude reaction mixture indicated the presence of both **1** and **5**. These results suggest that **5** is an intermediate in the formation of **1**. This is supported by the isolation of **1b** in greater than 80% yield when **5b** was treated with aniline hydrochloride. All attempts to prepare unsymmetrical thiodianilines by allowing aniline hydrochloride to react with **5e** gave only the symmetrical thiodianiline, **1e**. Compound **1e** was prepared by dropwise addition of sulfur dichloride to 3-nitroaniline and triethylamine. Thiodiamines **1** and **5** are moderately stable compounds that can be stored for short periods of time without noticeable decomposition. Electron-attracting groups appear to increase the stability of both **1** and **5** since **1e** and **5e** were stable for more than 2 years.

Structural proof for **1** and **5** is supported by their elemental analyses, where stability of the compound permitted, ir, and NMR (Table I).

Thermal Decomposition of 1 and 5. When **1a–e** were heated in benzene at 50 °C for 72 h in the absence of trapping agent, azobenzene (**6**), aryl amine, **4**, and sulfur were obtained (eq 1).

$$1 \longrightarrow X\text{—}C_6H_4N{=}NC_6H_4\text{—}X + X\text{—}C_6H_4NH_2 + S \quad (1)$$

6 **4**

Table II. Thermal Decomposition of *N,N'*-Thiodiamines at 50 °C for 72 h

Compd	Solvent	Products (% yield)[a]
1a	Benzene	**6a** (99), **4a** (91), S (47)
b	Benzene	**6b** (83), **4b** (66), S (60)
	Benzene, 2,3-dimethyl-1,3-butadiene	**4b** (82), **9** (56)
c	Benzene	**6c** (90), **4c** (92), S (89)
d	Benzene	**6d** (89), **4d** (93), S (92)
e	Benzene	No reaction
e[b,c]	Bromobenzene	**6e** (83), **4e** (74), S (10)
5a	Benzene	**6a** (21), **4a** (75)
b	Benzene	**6b** (11), **4b** (78)
	Benzene, 2,3-dimethyl-1,3-butadiene	**4b** (60), **9** (10)
c	Benzene	**4c** (84)
d	Benzene	**6d** (25), **4d** (75)

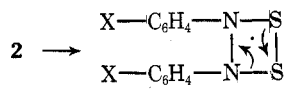
[a] Yields calculated assuming that **1** and **5** yield 1 mol of **4** and 0.5 mol of **6**. [b] Heated at 120 °C for 96 h. [c] Isolated by chromatography on Florisil.

The composition of the reaction mixture was determined by comparison of GLC analysis with authentic samples. These results are summarized in Table II.

At least two mechanisms may be considered for the formation of **4** and **6** in the thermal decomposition of **1**. The first mechanism involved a sulfur extrusion from **1** to yield a hydrazobenzene which disproportionates to **4** and **6**. The thermal instability of the S–N bond in sulfenamides is well known.[6] Arenesulfenanilides when heated at 150–190 °C give among other products azobenzene and aniline.[7] A mechanism involving homolytic cleavage of the S–N bond and formation of hydrazobenzene was proposed.

The formation of hydrazobenzene in the decomposition of **1**, however, can be eliminated as a major mechanistic pathway for the formation of azobenzene since under the reaction conditions hydrazobenzene was converted to less than 4% azobenzene. Furthermore, when the reaction of **1b** was monitored by NMR, absorption due to the NH protons of hydrazobenzene was not detected.

A second and more likely mechanism for the formation of **4** and **6** from **1** involves the formation of **2**. Dimerization of two thionitroso units may give **7** which disproportionates to azobenzene and sulfur (eq 2). The formation of alkenes



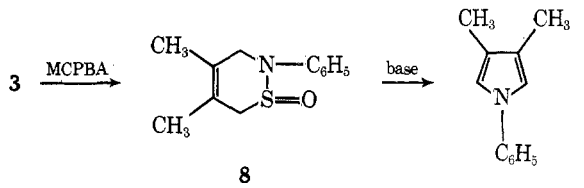
$$\longrightarrow S + 6 \quad (2)$$

7

from thiocarbonyl compounds under the influence of heat,[8] the isolation of benzophenone anil from thiobenzophenone and nitrosobenzene,[9] and the formation of mixed thioketones and imines in the photolytic decomposition of thio-

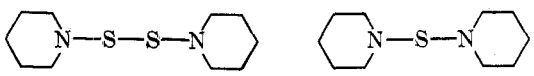
benzophenone and imines[10] have been suggested to involve intermediates similar to 7.

The trapping of 2 with 2,3-dimethyl-1,3-butadiene under our reaction conditions to give **3b** further supports the proposed mechanism. Since 3 is unstable toward analysis by GLC it was necessary to devise an alternate procedure for its analysis. The procedure developed for the GLC analysis of 3 involved the oxidation of 3 with *m*-chloroperbenzoic acid (MCPBA) to give the 1,2-thiazine 1-oxide (8) followed by alkaline hydrolysis to yield the pyrrole[11] which could be analyzed by GLC techniques. In a separate experiment oxidation of **3b** followed by alkaline hydrolysis gave an 82% yield of **9**.



8 9

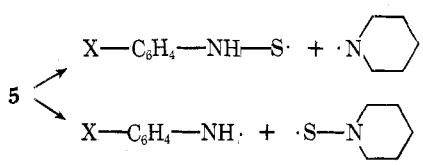
A quite different product distribution is observed in the thermal decomposition of **5a–d** (Table II). Only low yields of azobenzene 6 were found with the major product being the amine 4. Monitoring the decomposition of **5a–d** by NMR indicated a slow decrease in the NH absorption due to 5 with buildup and slow decrease of a new NH absorption. This new absorption in the NMR, which was not hydrazobenzene, was established to be the symmetrical *N,N'*-thiodiamine 1 by addition of authentic samples of 1 to the reaction mixture. When **5b** was heated in the presence of 2,3-dimethyl-1,3-butadiene followed by oxidation and alkaline hydrolysis, a 10% yield of 9 (1,2-thiazine 3) was obtained. A TLC of the dark reaction residue indicated the presence of *N,N'*-piperidinyl disulfide (**10**)[12a] and *N,N'*-piperidinyl sulfide (**11**).[12b]



10 11

The formation of 4 and 6 and the detection of 1, 10, and 11 in the thermal decomposition of 5 is best accounted for in terms of a mechanism which involves homolytic cleavage of the S–N bond in 5 (Scheme I).

Scheme I



Recombination of the radical intermediates (Scheme I) would lead to 1, 10, and 11. Abstraction of a hydrogen atom by the aryl amino radical yields 4. The hydrogen atom apparently is abstracted from the piperidine unit since an NMR of the polymeric-like residue shows absorption characteristic of piperdine ring protons.

The major source of azobenzene 6 appears to result from the intermediate thionitrosobenzene (eq 2) since **2b** was trapped and 1 was detected by NMR in the decomposition of 5 (eq (eq 3).

$$5 \longrightarrow \underset{1}{(X—C_5H_4NH)_2S} \longrightarrow 6 + 4 \qquad (3)$$

The possibility that some of 2 is formed directly from 5, however, cannot be excluded.

Oxidation of *N,N'*-Thiodiamines. The oxidation of *N,N'*-thiodiamine **1b** was briefly explored. When **1b** was allowed to react with 1 equiv of MCPBA in chloroform–sodium bicarbonate–water mixture an 81% yield of aniline (**4b**) was obtained. When the oxidation was carried out under anhydrous conditions followed by reaction of the dark oil with 2,3-dimethyl-1,3-butadiene a 55% yield of 9 was obtained. These results may be interpreted in terms of the intermediate formation of 12 which rapidly eliminates aniline to give *N*-sulfinylaniline (13). *N*-Sulfinylaniline is known

$$\mathbf{1b} \xrightarrow{\text{MCPBA}} \underset{12}{(C_6H_5NH)_2SO} \xrightarrow{-C_6H_5NH_2} \underset{13}{C_6H_5N{=}S{=}O}$$

to react with 2,3-dimethyl-1,3-butadiene to give 8 and to be hydrolyzed to aniline and sulfur dioxide.[13]

Experimental Section

Solvents and aromatic amines were purified by standard methods. Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrometer. Proton NMR spectra were performed on a Varian A-60A spectrometer. Elemental analyses were obtained from Chemalytics, Inc., Tempe, Ariz. Gas chromatography was performed on a Perkin-Elmer 900 gas chromatograph using a 12 ft, 15% silicone grease on 60/80 mesh Chromosorb W (regular) and on a 6 ft 3% OV-1 on 60/80 mesh Chromosorb W (regular) columns.

Preparation of *N,N'*-Thiodianilines (1). The preparation of 1 is a modified version of that reported by Tavs.[2] In a 250-ml three-necked flask equipped with nitrogen inlet, magnetic stirrer, and dropping funnel was placed 0.025 mol of the appropriate amine in 50 ml of ether. The reaction mixture was cooled to 10 °C in an ice–salt bath and 1.9 g (0.0125 mol) of piperidine-1-sulfenyl chloride[14] (*Caution:* an explosion occurred on distillation of piperidine-1-sulfenyl chloride when the flask temperature exceeded 80 °C) in 50 ml of ether was added dropwise within 5 min. The reaction mixture was allowed to stir under N_2 for 1 h at room temperature and the precipitate removed by filtration. The reaction can be tested for completeness at this point by dissolving a small amount of the precipitate in 1 N NaOH solution. If the precipitate fails to dissolve the collected precipitate and filtrate are recombined. When the reaction was complete the ether solution was washed with water (3 × 50 ml) and dried over $MgSO_4$. Removal of the solvent gave crude 1 which may be crystallized from pentane–ether.

***N,N'*-Thiobis-3-nitroaniline (1e).** In a 250-ml three-necked flask equipped with dropping funnel, condenser, nitrogen inlet, and magnetic stirrer was placed 7.3 g (0.053 mol) of 3-nitroaniline in 100 ml of ether. The reaction mixture was cooled in an ice bath and 1.5 g (0.014 mol) of sulfur dichloride in 50 ml of ether added dropwise. After refluxing for 0.5 h the precipitate was removed by filtration and the solution was washed with water and dried over $MgSO_4$. Removal of solvent gave a yellow powder which was dissolved in dimethylacetamide and water to give **1e.**

***N,N'*-Thioarylaminopiperidine (5).** Compound 5 was prepared as described above for the synthesis of 1 except that the reaction was carried out at −78 °C using a dry ice–acetone bath and the reaction mixture filtered while still cold. Alternatively 5 can be prepared by addition of 1 equiv of the sulfenyl chloride to 1 equiv of the appropriate amine in ether containing triethylamine.

Thermal Decomposition of 1 and 5. Compound 1 or 5 (usually 0.007 mol) was dissolved in 25 ml of dry benzene and placed in a sealed tube. The reaction mixture was heated in an oil bath at 50 °C for 72 h at which time the solution was filtered to remove the precipitated sulfur. The solvent was removed and redissolved in CH_2Cl_2 and a known amount of undecane was added. The reaction mixture was analyzed by GLC by comparison of peak areas with standard solutions of the reaction products. Analyses were performed at least twice and the results averaged.

Detection of Thionitrosobenzene (2) [1-Phenyl-3,4-dimethylpyrrole (9)]. Thionitrosobenzene **2b** was analyzed by GLC as 9 by the following procedure. Compound **1b** (0.5 g, 0.0023 mol) was placed in 25 ml of benzene containing 2 ml of 2,3-dimethyl-1,3-butadiene. The reaction mixture was heated in a sealed tube at 50 °C for 72 h and diluted with 50 ml of CH_2Cl_2. This solution was placed in a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer and containing 0.2 g of $NaHCO_3$ in 100 ml of water. The solution was cooled in an ice bath and 0.51 g (0.0025

mol) of 85% MCPBA in 50 ml of CH_2Cl_2 was added dropwise. Following the addition, the reaction mixture was refluxed for 15 min and dried over $MgSO_4$. The removal of the solvent gave a dark oil which was dissolved in 50 ml of alcohol containing 0.38 g of KOH. After refluxing for 1.5 h the solution was diluted with water and extracted with CH_2Cl_2. The dried CH_2Cl_2 solution was analyzed as described above by GLC.

Oxidation of 1b. In a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer and containing 0.8 g of $NaCO_3$ in 50 ml of water was placed 1.43 g (0.0066 mol) of **1b** in 50 ml of CH_2Cl_2. The reaction mixture was cooled in an ice bath and 1.43 g (0.0066 mol) of 85% MCPBA in 50 ml of CH_2Cl_2 added dropwise. The solution was stirred for 15 min, washed with water, and dried over $MgSO_4$. Removal of the solvent gave 1.0 g (81%) of an oil identified as aniline (**4b**) by comparison of its ir and NMR spectra with those of an authentic sample.

Oxidation of 1b Followed by Reaction with 2,3-Dimethyl-1,3-butadiene. In a 250-ml three-necked flask equipped with dropping funnel and magnetic stirrer was placed 3.0 g (0.0131 mol) of **1b** in 50 ml of $CHCl_3$. The solution was cooled in an ice bath and 2.8 g (0.014 mol) of 85% MCPBA in 50 ml of $CHCl_3$ was added dropwise. After stirring for 15 min the precipitate was removed and 3 ml of 2,3-dimethyl-1,3-butadiene added. After stirring for 3 days the solution was washed with 10% $NaHCO_3$ solution and dried over $MgSO_4$. Removal of the solvent gave an oil which contained **4b** and **8** by TLC (silica gel). Removal of the aniline by molecular distillation gave a solid which was crystallized from cyclohexane to give 1.5 g (52%) of white crystals, mp 78–80 °C (lit.[15] mp 79–80 °C).

Registry No.—**1a,** 58241-34-2; **1b,** 13628-09-6; **1c,** 13616-64-3; **1d,** 13616-65-4; **1e,** 19552-05-7; **4a,** 104-94-9; **4b,** 62-53-3; **4c,** 106-40-1; **4d,** 106-47-8; **4e,** 100-01-6; **5a,** 58241-35-3; **5b,** 58241-36-4; **5c,** 58241-37-5; **5d,** 58267-78-0; **5e,** 58241-38-6; sulfur dichloride, 10545-99-0; piperidine-1-sulfenyl chloride, 16005-90-6.

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Thioasparagine and Derivatives for Peptide Synthesis. A Trifluoroacetic Acid Catalyzed Anisyl Transfer to Sulfur

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Thioamidation of *N*-*p*-methoxybenzyloxycarbonyl-L-β-cyanoalanine with H_2S–NH_3 furnished *N*-*p*-methoxybenzyloxy-L-thioasparagine. Deprotection of the latter with trifluoroacetic acid or HF yielded the asparagine analogue, thioasparagine (L-aspartic acid β-thioamide). *tert*-Butyloxycarbonyl-L-thioasparagine and benzyloxycarbonyl-L-thioasparagine were prepared from the corresponding β-cyanoalanine derivatives by similar treatment, and these likewise gave thioasparagine. During the deprotection of Meoz-L-thioasparagine in TFA a major side reaction (anisyl transfer) ensued that led to the formation of aspartic *p*-methoxybenzyl β-imidothiolic ester and, from this, β-*S*-*p*-methoxybenzyl aspartic thioester. This transfer reaction has been extended to the synthesis of a thioether, *S*-*p*-methoxybenzylcysteine. Anisyl transfer can therefore be a source of decreased yield in peptide synthesis when the *N*-p-methoxybenzyloxycarbonyl group is deprotected in the presence of a preformed or newly generated thiol group. *N*-Meoz-L-alanine and *p*-methoxybenzyl carbazate in TFA under very mild conditions are convenient alternate sources of the *p*-methoxybenzyl carbonium ion. *N*-*p*-Methoxybenzyl thioacetamide was synthesized for ^1H NMR reference.

Intramolecular hydrogen bonding between the carbonyl oxygen of specific carboxamide or peptide linkages and the amide hydrogen of other peptide or amide linkages in polypeptides is considered to be one of the key features in determining and stabilizing conformation. For example, in oxytocin and vasopressin[1] the asparagine residue participates in forming the characteristic "β turn" of the ring moiety by means of hydrogen bonding. These thoughts have led us to consider the effect on biological activity of subtle structural changes that might alter chiefly the degree of intramolecular hydrogen bonding. Replacement of a carboxamide by a thiocarboxamide might be expected to introduce electronic effects suitable for such a purpose.[2] Accordingly, the desire to replace asparagine in oxytocin with thioasparagine prompted synthesis of the latter. Thioasparagine had added interest as a possible antimetabolite of asparagine since asparagine holds an important position as a nutritional requirement in the metabolism of certain neoplastic cells lacking asparagine synthetase.[3] This report deals with the synthesis and chemical properties of thioasparagine and makes available a variety of derivatives expected to be suitable for its introduction into peptides. During the deprotection of *N*-*p*-methoxybenzyloxycarbonyl-L-thioasparagine to thioasparagine with trifluoroacetic acid an unexpected alkylating side reaction was encountered that led predominantly to the formation of the *S*-anisyl ester of β-thioaspartic acid. The reaction has preparative value also for the synthesis of an *S*-anisyl thioether, *S*-anisyl-L-cysteine. Possible implication of this side reaction for peptide synthesis has been pointed out.

General methods for the synthesis of thioamides include thiolysis of nitriles, amidines, or imidic esters with H_2S and the thionation of amides with phosphorus pentasulfide.[4] The base-catalyzed addition of H_2S to the nitrile was chosen for the synthesis of thioasparagine, with the amino nitrogen group being protected by the *p*-methoxybenzyloxy-