Alkylation and Sulfenylation of Amino Thioethers. Tetrahydro-1,3-thiazine and Related Compounds

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Received August 16, 1988

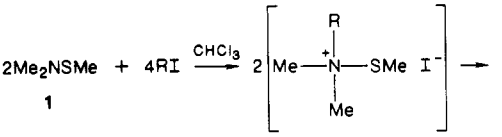
Reactions of electrophiles with several amino thioethers of varying chain length and ring structure are described. The reactants include *N,N*-dimethylmethanesulfenamide, [[(*N,N*-dimethylamino)methyl]thio]methane, 1-(*N,N*-dimethylamino)-2-(methylthio)ethane, tetrahydro-1,3-thiazine, tetrahydro-2-methyl-1,3-thiazine, and the corresponding *N*-methyl and *N*-acetyl derivatives. Electrophiles include methyl iodide, ethyl iodide, 3-chloro- and 3-bromopropene, trimethyloxonium fluoroborate, methanesulfenyl chloride, and dimethyl(methylthio)sulfonium fluoroborate. The objective was to assess the influence of one heteroatom on the other in competition for an electrophile. The conditions of S–N, S–C, and N–C cleavage, and attack at sulfur as opposed to nitrogen, are described.

Introduction

The initial purpose of the work described in this paper was to investigate the behavior of sulfenamides with electrophiles. The project developed into a more general study of the methylation and methylthiolation of bifunctional compounds containing both sulfide and amine functions. The tetrahydro-1,3-thiazine system was studied in some detail, as were the linear analogues **1–3**, $CH_3S(CH_2)_nN(CH_3)_2$, where n = 0, 1, or 2. The questions of interest are whether electrophilic attack occurs preferentially at sulfur or nitrogen and how the proximity of one heteroatom influences the other. The results show a degree of complexity that was unanticipated but which is nonetheless interesting. The behavior of the linear compounds **1–3** is described first, and the synthesis and reactions of 1,3-tetrahydrothiazines are described second.

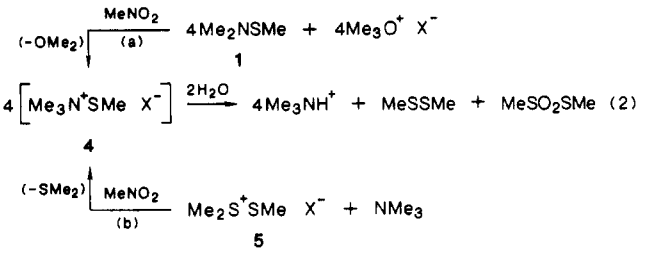
Results and Discussion

Sulfenamides. Although sulfenamides are not stable in acid solution,[1] it is generally assumed that they protonate at nitrogen rather than sulfur for the reason that alkylamines are more basic than sulfides.[2] However, with respect to *alkylation*, the generally poor correlation between basicity and nucleophilicity makes it difficult to prescribe the preferred site.[3] Alkylation at either nitrogen or sulfur appears feasible based on isolated reports of thioammonium salts (RSN^+R_3)[4,5] and more abundant examples of azasulfonium salts ($R_2S^+NR_2$).[6] However, in general, amines appear to be somewhat stronger nucleophiles than sulfides,[3] and the observation that neutral trimethylamine demethylates methylsulfonium salts suggests that methylation of **1** should occur at nitrogen to produce the ammonium compound **4**. However, all attempts to alkylate **1** led consistently to products of S–N cleavage. The products observed varied with the nature of the electrophile and the solvent, but in each case it is reasonably certain that **4** is formed initially, only to dissociate rapidly to other products. Methyl disulfide and ammonium salts were invariably formed. Thus, alkyl iodides in chloroform produced iodine and tetraalkylammonium salts according to the stoichiometry of eq 1 (R = Me or Et).



$$2Me_2NSMe\ (\mathbf{1}) + 4RI \xrightarrow{CHCl_3} 2[Me{-}\overset{R}{\underset{Me}{\overset{|}{\overset{+}{N}}}}{-}SMe\ I^-]\ (\mathbf{4}) \rightarrow MeSSMe + I_2 + 2Me_2R_2N^+\ I^- \quad (1)$$

Methyloxonium salts in nitromethane gave hydrolysis products (eq 2 path a, X = BF_4^-) unless extreme care was taken in drying the solvent. The same products were obtained by methylthiolation of trimethylamine with **5** in nitromethane, which further implicates **4** as the first-formed intermediate (eq 2 path b).[7] The products of eq



$$\xrightarrow[(-OMe_2)]{MeNO_2,\ (a)} 4Me_2NSMe\ (\mathbf{1}) + 4Me_3O^+\ X^-$$

$$4[Me_3N^+SMe\ X^-]\ (\mathbf{4}) \xrightarrow{2H_2O} 4Me_3NH^+ + MeSSMe + MeSO_2SMe \quad (2)$$

$$\xrightarrow[(-SMe_2)]{MeNO_2,\ (b)} Me_2S^+SMe\ X^-\ (\mathbf{5}) + NMe_3$$

2 illustrate the extreme sensitivity of thioammonium intermediates to water. Methylation of **1** with methyloxonium salts in scrupulously dry chloroform, or dichloromethane, minimized hydrolysis but gave a complex mixture of products (MeSSMe, MeSSSMe, Me_3NH^+, and Me_4N^+). Attempts to prepare **4** under high vacuum conditions in order to exclude moisture, air, and solvent were no less complicated. Distillation of dry trimethylamine directly onto solid dimethyl(methylthio)sulfonium fluoroborate (**5**) at low temperatures followed by warming the mixture to room temperature gave MeSSMe and Me_2S as volatile products and Me_4N^+ and Me_3NH^+ as residual fluoroborate salts—*but no thiammonium salt* **4**. A related reaction with dimethylamine gave similar results.

Allylation of **1** in nitromethane with allyl bromide gave *N,N*-diallyl-*N,N*-dimethylammonium bromide (eq 3, path a), and **1** with allyl chloride and $AgBF_4$ gave *N*-allyl-*N,N*-

(1) Noth, H.; Mikulaschek, G. *Ber. Dtsch. Chem. Ges.* **1961**, *94*, 634–641.
(2) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley: New York, 1985; Chapter 8.
(3) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 369.
(4) Kim, J. K.; Kline, M. L.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 6243.
(5) Wevers, H. H.; Kloosterziel, H. *J. Chem. Soc., Chem. Commun.* **1975**, 413–414.
(6) See, for example: (a) Oae, S.; Furukawa, N. *Sulfilmines and Related Derivatives*; ACS Monograph 179, 1983. (b) Haake, M.; Benack, H. *Synthesis* **1976**, 308–309. (c) Tamura, Y.; Matsushima, J.; Minamikawa, J.; Ikeda, M. *Tetrahedron* **1975**, *31*, 3035–3040. (d) Richards, J. L.; Tarbell, D. S. *J. Org. Chem.* **1970**, *35*, 2079–2080.
(7) We reported previously that thioammonium intermediates generated by methylation of **1** can be trapped by π-nucleophiles such as cycloalkenes to give 1,2-addition products. See: Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231.

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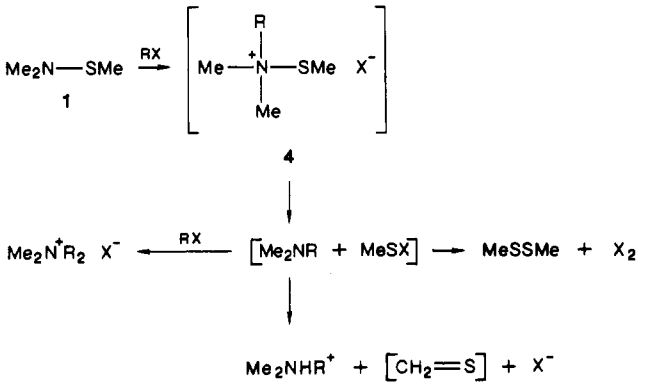
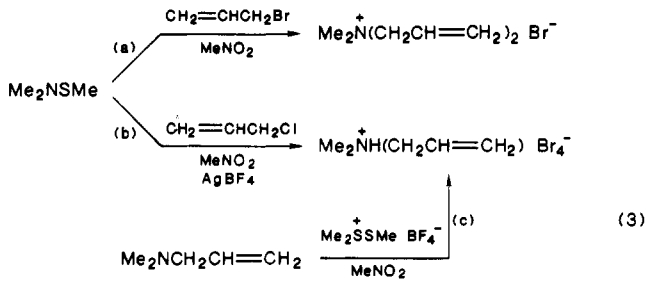
Scheme I



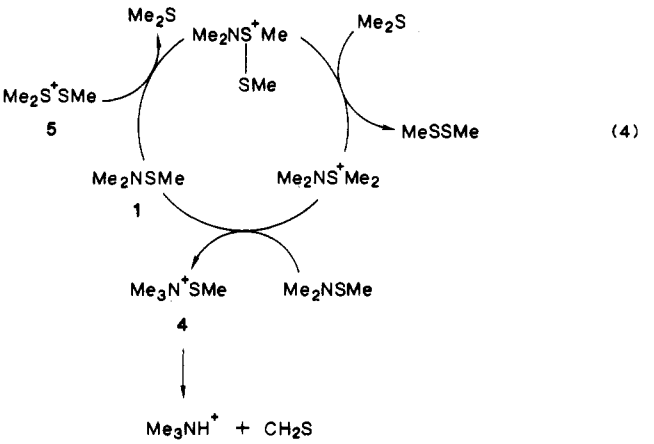
dimethylammonium fluoroborate (path b), which was also formed from *N*-allyl-*N*,*N*-dimethylamine and **5** (path c).



(3)

Each of the observed products in the reactions of eq 1–3 can be accounted for by the sequence shown in Scheme I, the key feature of which is S–N$^+$ cleavage of the presumed thiammonium intermediate. Ammonium salts result from further alkylation of the free amine. Methyl disulfide and protonated amine salts arise from the redox decomposition of methylsulfenyl compounds MeSX, which is well precedented, including E2-type elimination to CH_2=S.[8,9] Even so, we were unable to detect thioformaldehyde or its products, and the fate of this elusive compound remains unresolved.

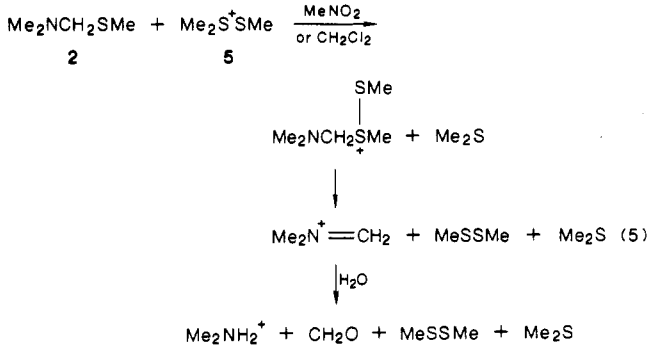
Methylthiolation of sulfenamide **1** is also of interest and was conveniently followed by NMR by using the thiosulfonium salt **5** in dry CD_3NO_2 as the sulfenyl (thiolating) agent. Release of methyl sulfide is essentially instantaneous and quantitative (judging from the immediate appearance of a sharp singlet around 2.16 ppm), which indicates that the methylthio group of **5** is transferred to the sulfenamide. However, the NMR spectrum changed with time, and the methyl sulfide signal shifted downfield as the methyl disulfide signal grew in intensity. After 9 days, identifiable products were Me_2S and MeSSMe in a 1:2 ratio and methylammonium salts. It appears that a number of thiosulfonium species are in mobile equilibrium, but, overlaid thereon is a slower irreversible conversion to ammonium species. A possible sequence is shown in eq 4 and is presaged on the equilibrium behavior of thiosulfonium ions in the presence of sulfur nucleophiles.[10] Thioformaldehyde is proposed as a product, and, although unverified, an unidentified singlet at 3.08 ppm in the spectrum of the reaction mixture in nitromethane could be due to $(CH_2S)_n$.[11]



(4)

The main point of interest in the methylthiolation of **1** is the inference that electrophilic attack occurs at *sulfur*. If methylthiolation occurs at nitrogen to give $Me_2N^+(SMe)_2$, this species must rearrange to the sulfonium species $Me_2NS^+Me(SMe)$ to account for the observed products. This contrasts with the results of alkylation, which indicate that attack occurs at nitrogen only.

[[(*N*,*N*-Dimethylamino)methyl]thio]methane (2), prepared from chloromethyl methyl sulfide and dimethylamine, was initially selected to represent an amino thioether in which the heteroatoms were separated by a one-carbon chain. However, only a cursory examination of its reactions with alkylating and sulfenylating agents was made. Cleavage of both the C–N and C–S bonds was noted, and identification of products was difficult. Equation 5 illustrates behavior typical of **2** on methylthiolation with **5**. The reaction amounts to hydrolysis, possibly of iminium ions Me_2N^+=CH_2. Further infor-



(5)

mation on the reactivity of the N–C–S functionality and supporting evidence for the reactions in eq 5 were obtained from a study of tetrahydro-1,3-thiazines and are discussed later in the paper.

1-(*N*,*N*-Dimethylamino)-2-(methylthio)ethane (3). In comparison with **1** and **2**, the behavior of **3** with electrophiles was straightforward and informative. Not surprisingly, separation of the heteroatoms by two carbons substantially reduces but does not eliminate their interaction.

Treatment of the free amine **3** in dichloromethane with hydrogen chloride gas gave the expected ammonium salt **6a** (Scheme II). The corresponding fluoroborate salt **6b** was prepared from **6a** by metathesis with $AgBF_4$ and by direct addition of HBF_4 to **3**. The proton chemical shifts observed for these and related salts are recorded in Table I.

Methylation of **6b** with trimethyloxonium fluoroborate gave the double salt **7**, possessing both ammonium and

(8) (a) Field, L. In *Organic Chemistry of Sulfur*, Oae, S., Ed.; Plenum Press: New York, 1977; Chapter 7. (b) Capozzi, G.; Modena, G. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; John Wiley: New York, 1974; Chapter 17.

(9) Armitage, D. A.; Clark, M. J. *J. Chem. Soc., Chem. Commun.* **1970**, 104; *J. Chem. Soc. C* **1971**, 2840–2842.

(10) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826.

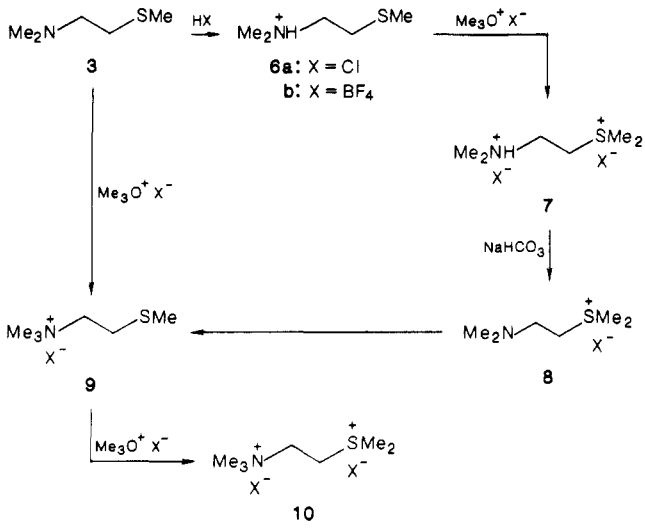
(11) The proton chemical shift of 1,3-5-trithiane is 3.00 ppm.

Table I. Proton Chemical Shifts of Ammonium and Sulfonium Salts of $Me_2NCH_2CH_2SCH_3$

structure[a]	δ,[b] ppm (mult, J, Hz)				
	MeN^+	MeN	MeS^+	MeS	NCH_2CH_2S
$Me_2NCH_2CH_2SMe$ (3)		2.20 (s)		2.10 (s)	2.55 (m)
$Me_2NH^+CH_2CH_2SMe$ Cl^- (6a)	2.83 (d, J = 7)			2.20 (s)	3.0–3.7 (m)
$Me_2NH^+CH_2CH_2SMe$ X^- (6b)	3.06 (d, J = 5.5)			2.20 (s)	3.5 (q), 3.0 (q)
$Me_2NH^+CH_2CH_2S^+Me_2$ (7)	3.18 (d, J = 4)		3.14 (s)		3.84 (m)
$Me_2NCH_2CH_2S^+Me_2$ (8)		2.33 (s)	2.96 (s)		2.96 (q), 3.55 (q) (J = 5.5)
$Me_3N^+CH_2CH_2SMe$ (9)	3.25 (s)			2.20 (s)	2.8–3.75 (m)
$Me_3N^+CH_2CH_2S^+Me_2$ (10)	3.35 (s)		3.16 (s)		3.96
$Me_2N^+(CH_2CH_2)_2Me_2$ (11)	3.42 (s)				3.98 (s)

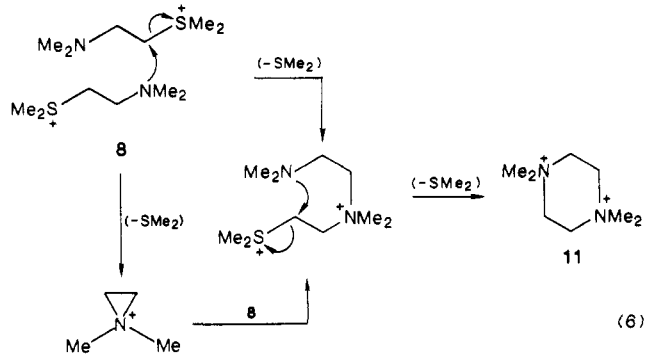
[a] Counterion X^- is BF_4^-. [b] Spectra were recorded at 60 MHz in CD_3NO_2 solution. The methylene protons were imcompletely resolved in some cases.

Scheme II



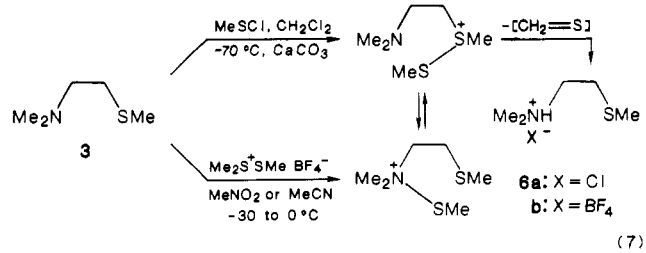
sulfonium functions (mp 173.5–174.5 °C). Deprotonation of 7 with sodium bicarbonate produced the sulfonium salt 8. However, isolation of 8 as a pure salt did not prove possible as it rearranged at ambient temperature to the corresponding ammonium salt 9. This rearrangement was clearly evident from the NMR spectrum of the sulfonium salt 8. Soon after the formation of 8, additional resonances appeared that intensified over a period of days and which were identified as due to the ammonium salt 9. After 10 days, the ratio of 8:9 was 1:1.5. The identity of 9 was verified by direct methylation of the neutral amino thioether 3. One equivalent of methylating agent gave the single salt 9 and a second equivalent gave the double salt 10 (mp 224–226 °C). The sequence of reactions is summarized in Scheme II. Although direct methylation at the amine nitrogen of 3 and the rearrangement of 8 to 9 point to a preference for methylation at nitrogen over sulfur, we have not demonstrated that 9 rearranges to 8, hence the ratio 8:9 at equilibrium is unconfirmed.

Salt 8 also displayed interesting chemistry when heated. At 100 °C, solutions of 8 in nitromethane or acetonitrile rapidly generated methyl sulfide and precipitated a white crystalline solid of mp 320–321 °C. The solid was identified as *N,N,N,N*-tetramethylpiperazinium fluoroborate (11) from its NMR spectrum, high melting point, and similarity with the previously reported iodide and related piperazinium salts.[12] Formation of 11 from the sulfonium salt is a further illustration of alkyl transfer from sulfur to nitrogen which, in this case, is an intermolecular event leading to cyclic products (eq 6). There was no evidence of intramolecular alkylation leading to an aziridium salt,[13] but it could be an intermediate, as indicated in eq 6.



(6)

The results of methylthiolation of 3 with both methanesulfenyl chloride and thiosulfonium salt 5 are noteworthy from the standpoint that, unlike 1 and 2, cleavage of bonds to the heteroatoms was *not* observed. Every precaution was taken to exclude moisture and acid impurities yet the only product identified, besides ubiquitous Me_2S and MeSSMe, was an ammonium salt 6a or 6b (eq 7). It is quite likely that methylthiolation of 3 results in the transfer of a methylthio group reversibly between sulfur and nitrogen, but the process is interrupted by an intramolecular elimination induced by the amine nitrogen (eq 7).



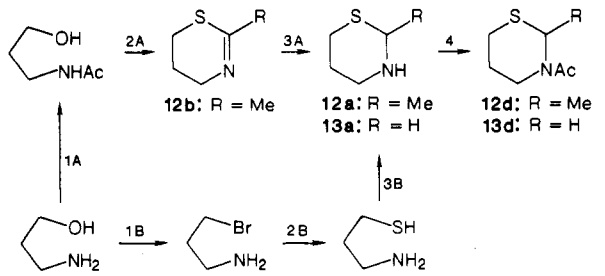
(7)

Tetrahydro-1,3-thiazine Derivatives. To obtain a more complete picture of alkylation and sulfenylation of amino thioethers comparable to 2, the related chemistry of tetrahydro-1,3-thiazines was studied. This proved more

(12) Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1965**, *30*, 821; *Tetrahedron* **1969**, *25*, 1651.

(13) Piperazinium salts 11 can be distinguished from aziridium salts from the chemical shifts of the methylene protons, which are reported to be 3.92 for 11 and 3.08 ppm for the aziridium analogue (ref 12). See also: Bottini, A. T.; Sousa, L. R.; Dowden, B. F. *J. Org. Chem.* **1974**, *39*, 355.

Scheme III[a]

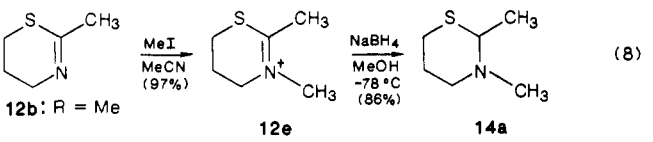


[a] (1A) AcOMe (99%); (2A) P_2S_5, 145 °C (50%); (3A) Al–Hg, THF (41%); (1B) PBr_3; (2B) NaSH; (3B) RCHO, EtOH (86%); (4) AcCl, Et_3N, C_6H_6, 5 °C.

of an undertaking than was at first realized, but the results are informative.

Synthesis. Tetrahydro-1,3-thiazines have been prepared previously by cyclization routes involving carbonyl addition.[14] We were able to prepare the parent compound **13a** by route B in Scheme III and the 2-methyl derivative **12a**[15] by either of the routes A and B shown in Scheme III (see the Experimental Section).

Each of these compounds, **12a** and **13a**, was acetylated to give the respective *N*-acetyl derivative, **12d** and **13d**. The *N*-methyl analogue **14a** was obtained by methylation of the imine derivative **12b** followed by borohydride reduction of the iminium salt **12e**, as shown in eq 8.[16] A different route was necessary for the preparation of *N*-methyltetrahydro-1,3-thiazine (**15a**)[17] and is summarized in the reactions of eq 9.



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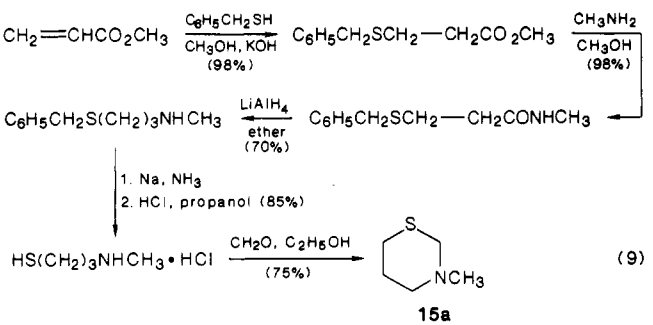
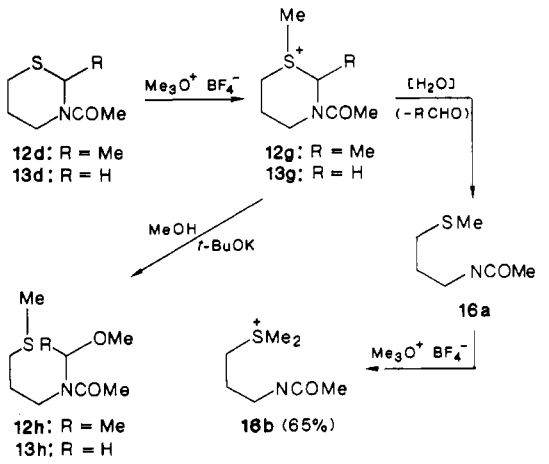
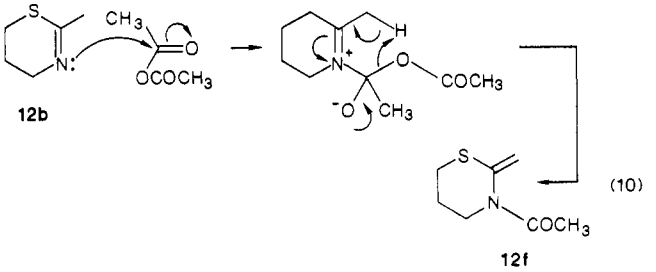


(9)

The reduction step **12b** to **12a** in Scheme III presented unexpected difficulties. Catalytic hydrogenation of the imine **12b** over platinum oxide in acetic anhydride did not produce the desired reduction product **12a** but gave instead the acetylated derivative **12f**, which defied reduction. (It was subsequently determined that the imine **12b** could be converted quantitatively to **12f** by simply adding acetic anhydride, probably by the pathway in eq 10.) Attempts to hydrogenate **12b** in ethanol solvent also failed as hydrolysis to 3-aminopropane-1-thiol occurred. Of the reduction methods tried, only the aluminum amalgam route[18] in Scheme III resulted in the reduction of **12b** to **12a**.

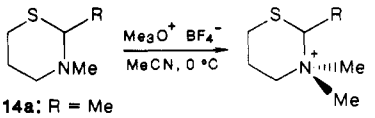
Scheme IV





(10)

Methylation Reactions. The *N*-methyltetrahydrothiazines **14a** and **15a** reacted with trimethyloxonium fluoroborate to give the corresponding *N,N*-dimethylammonium salts **14e** and **15e**, respectively, leaving no doubt that the amine nitrogen is the preferred site of attack by a carbon electrophile. Even the imine nitrogen of **12e** was methylated (by MeI) in preference to the ring sulfur (see eq 8).



To direct methylation to the ring sulfur it was necessary to protect the amine nitrogen of **12a** and **13a** by acetylation with acetyl chloride. The *N*-acyl product **12d** from **12a** was a 3:2 mixture of conformational isomers associated with restricted rotation about the N–C bond of the amide function; product **13d** from **13a** was a 1:1 mixture of isomers. Structural assignments were made by ^{13}C NMR analysis by analogy with substituted acetamides[19] and are presented as supplementary material.

Methylation of the *N*-acetyl mixture **13d** was relatively straightforward and gave the *S*-methyl-*N*-acetyl salt **13g** as a 6:1 mixture of conformational diastereomers (Scheme

(14) (a) Cook, M. J.; Jones, R. A. Y.; Katritsky, A. R.; Marcas, M. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 326. (b) Hamer, Rathbone, Pfizer Corp Netherland, Appl. 661002204, Jan 30; *Chem. Abstr.* **1967**, *68*, 39631*k*.

(15) Fernandez, J. P.; Robbe, Y.; Chapat, J. P.; Grenger, R. *Farmaco Ed. Sci.* **1981**, *36*, 740.

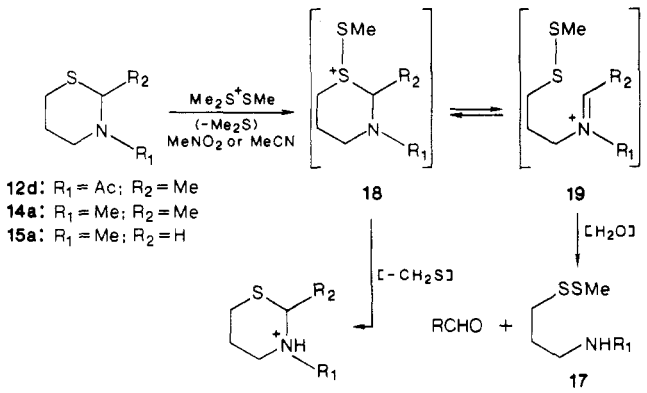
(16) Ito, Y.; Ammo, Y.; Naksuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586.

(17) Angiolini, L.; Katritsky, A. R.; Read, D. M. *Gazz. Chim. Ital.* **1976**, *106*, 111.

(18) Tarbell, D. S.; Buckley, D. A.; Brownlee, P. P.; Thomas, R.; Todd, J. S. *J. Org. Chem.* **1964**, *29*, 3314.

(19) Levy, G. C.; Nelson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 4897.

Scheme V



IV). Methylation of **12d**, on the other hand, was not straightforward and gave an impure product. About 15% of the product was a diastereomeric mixture of sulfonium salts **12g** arising from chirality associated with the S^+ and C2 positions *and* conformations associated with the amide function. The *major* product was the acyclic sulfonium salt **16b** corresponding to hydrolytic ring opening of **12g** followed by S-methylation (Scheme IV). Acetaldehyde was also released in the methylation of **12g** (as detected by NMR), which indicates that **12g** is extremely moisture-sensitive. This was confirmed by the addition of moist chloroform to the salt mixture containing **12g** with the result that hydrolysis to *N*-[3-(methylthio)propyl]acetamide (**16a**) was immediate at room temperature. Also, when **12g** was dissolved in methanol containing a small amount of potassium *tert*-butoxide, the amino ether product **12h** was produced along with **16a**. It appears that potassium *tert*-butoxide prevents further methanolysis and release of dimethyl acetal. The analogous hydrolytic reactions were observed with **13g** but at significantly slower rates.

Methylthiolation Reactions. Reaction of the thiosulfonium salt **5** with **12d** or **13d** instantly released methyl sulfide as the volatile product. Acetaldehyde was also detected from **12d**, but the residual product was a complex mixture of salts that were not identified. By analogy with their methylation reactions just described, it seems very likely that **12d** and **13d** methylthiolate at sulfur to form thiosulfonium salt intermediates (**18** in Scheme V) that rapidly cleave to acetaldehyde, probably by way of **19**, in the presence of any moisture.

Methylthiolation of tetrahydrothiazines **14a** and **15a** with **5** led to similar results, as determined from the following observations:

1. By following the reactions by proton NMR, it is clear that methyl sulfide is formed along with varying amounts of methyl disulfide; the ring is cleaved—as evidenced by the disappearance of signals due to the C-2 substituents (CH_2 from **15a** and CH_3CH from **14a**).

2. No salts were recovered that could be ascribed to methylation of starting material to give either ammonium or sulfonium products.

3. Treatment of the reaction mixture with aqueous potassium carbonate led to the isolation of a small amount of starting material (5–25%) and a compound identified as the disulfide **17**. The latter compound was obtained from both **14a** and **15a**.

4. ^{13}C NMR spectra of reaction mixtures reveal the formation of iminium ion intermediates based on chemical shift assignments reported for ions of this type (see the supplementary material).[20] The iminium ion from **14a** was a 3:2 mixture of *E* and *Z* isomers.

These observations and those from related reactions imply that sulfenylation of **14a** and **15a** occurs at *sulfur*. The thiosulfonium intermediates are not stable under the conditions of reaction, and cleave either to hydrolysis products (aldehyde and **17**) by way of an iminium ion intermediate **19** or to protonated starting material (see Scheme V).

Conclusions

Methylation of compounds with the bifunctional structure $RS(CH_2)_nNR_2$ results in dissociation products for $n = 0$ and 1 but in stable ammonium salts for $n = 2$. In every case, the products can be explained by attack of the methylating agent at nitrogen. This is an obvious result in structures where the sulfur and nitrogen atoms are independent because the amine function is recognized to be generally more nucleophilic than the sulfide function. However, the result is noteworthy for sulfenamides wherein sulfur–nitrogen interaction is at a maximum. In this case, it might be anticipated that delocalization of the type S–N $\leftrightarrow$ $S^-{=}N^+$ would reduce the nucleophilicity of nitrogen below that of sulfur toward a carbon electrophile, yet nitrogen was methylated exclusively.

In comparison, methylthiolation gives products that arise from attack at sulfur rather than nitrogen. Reversible attack at nitrogen cannot be excluded, but attack at sulfur leads to the formation of thiosulfonium ions $MeSS^+R_2$, which react with great rapidity in the presence of an amine function. Ammonium salts are products, with coproducts methyl sulfide (from **5**) and methyl disulfide, but the stoichiometry or material balance is not clear in all cases. These results are well accommodated by Pearson's HSAB principle[21] in which a soft acid (RS^+) reacts with a soft base (R_2S) in preference to a hard base (R_3N). Likewise the hard acid (CH_3^+) reacts with the hard base (R_3N) in preference to the soft base (R_2S).

Experimental Section

***N,N*-Dimethylmethanesulfenamide (1).** Freshly prepared methanesulfenyl chloride (82.5 g, 1 mol) in 250 mL of dry ether at −65 °C was added slowly to a stirred, cooled solution of dimethylamine (200 mL, 3 mol) in 500 mL of ether. After being warmed to room temperature (overnight), the mixture was filtered. The filtrate was dried (magnesium sulfate), evaporated, and distilled at reduced pressure to give 64–70 g (70–77%) of a colorless lachrymatory liquid [bp 31–32 °C (75 mmHg); lit.[1] bp 32–34 °C (75 mmHg)]. ^1H NMR[9] ($CDCl_3$): δ 2.20 (s, 3 H), 2.68 (s, 6 H). Distillation at atmospheric pressure gave a mixture of 1, methyl disulfide, methyl trisulfide, and an unidentified compound.[9]

Alkylation of *N,N*-Dimethylmethanesulfenamide. To an ice-cooled solution of alkyl iodide (0.105 mol) in 10 mL of $CHCl_3$ was added 1 (4.55 g, 0.05 mol) in 5 mL of $CHCl_3$. The mixture was stirred at room temperature overnight (4 days with EtI). The volatile product methyl disulfide (2.2–2.3 g, 92–96%) was removed by distillation at reduced pressure. The residue was treated with sodium dithionite solution to remove iodine. Starting with methyl iodide, the colorless salt that remained was identified as $Me_4N^+I^-$ (9.2–9.6 g, 92–96%, mp 300 °C). ^1H NMR (DMSO-d_6): δ (ppm) 3.10 (s). The salt from ethyl iodide was identified as $Me_2N^+Et_2I^-$ (10–11.2 g, 88–96%; mp 288–294 °C dec; lit.[9] mp 298–299 °C dec). NMR (DMSO-d_6): δ (ppm) 1.42 (three triplets, CH_3CH_2, J_{NH} = 2 Hz),[22] 3.30 (s, CH_3), 3.68 (q, CH_2N).

1-(*N,N*-Dimethylamino)-2-(methylthio)ethane (3), bp 51 °C (17 mmHg), was prepared from 1-(*N,N*-dimethylamino)-2-chloroethane and 2 equiv of freshly prepared sodium methane-

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thiolate in methanol. A general method of azasulfenylation of alkenes is also suitable for the synthesis of **3**.[7,24]

[[(*N*,*N*-Dimethylamino)methyl]thio]methane (2), bp 44–45 °C (38 mmHg), was prepared from chloromethyl methyl sulfide and 2 equiv of dimethylamine in ether at 0 °C.

Methylation of **3** with trimethyloxonium fluoroborate in nitromethane-d_3 (or in some cases acetonitrile-d_3) was followed by proton NMR (chemical shift data is given in Table I). Addition of 2 equiv led to the isolation of the double salt **10**, mp 224–226 °C. Anal. Calcd for $C_7H_{19}B_2F_8NS$: C, 26.04; H, 5.93. Found: C, 25.21; H, 5.58. Methylation of salt **6b** gave **7**, mp 173.5–174.5 °C. Anal. Calcd for $C_6H_{17}B_2F_8NS$: C, 23.33; H, 5.55; N, 4.53. Found: C, 23.33; H, 5.22; N, 4.55.

Tetrahydro-2-methyl-1,3-thiazine (12a). Route A, Scheme III. 3-(*N*-Acetylamino)-1-propanol was prepared in 99% yield by the reaction of 3-amino-1-propanol with methyl acetate by refluxing a mixture (without solvent) for 12 h. The product, after removal of methanol and distillation, had bp 138 °C (0.1 mmHg). ^{1}H NMR ($CD_3NO)_2$: δ (ppm) 1.91 (s, CH_3CO), 3.53 (t, CH_2OH), 3.25 (t, CH_2NH), 1.66 (dt, CH_2).

5,6-Dihydro-4*H*-2-methyl-1,3-thiazine (12b) was prepared in 50% yield by heating 3-(*N*-acetylamino)-1-propanol (65.5 g, 0.56 mol) at 145 °C with phosphorus pentasulfide (26 g, 0.117 mol), which was added in small portions. Reaction is exothermic, and on completion of the addition the temperature reached 220 °C. Distillation gave 33g of **12b**, bp 52–53 °C (10 mmHg) [lit.[14b] 63 °C (13 mmHg)]. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.78 (m, CH_2), 2.09 (t, CH_3), 3.00 (t, CH_2S), 3.61 (t, CH_2N).

Reduction of 12b by Aluminum Amalgam.[18,22] Aluminum amalgam, prepared from 10.8 g of aluminum turnings and 4.25 g of mercuric chloride, was covered with a mixture of 9.2 g of **12b** (80 mmol), 150 mL of THF, and 20 mL of methyl acetate. Water was added slowly, and vigorous evolution of gas resulted. Thereafter, the solution was refluxed for 3 h, filtered, and washed with methyl acetate, and the combined filtrate was condensed to one-third volume at reduced pressure. The organic layer was separated after saturating the aqueous phase with NaCl and gave, on distillation, 3.8 g (14%) of tetrahydro-2-methyl-1,3-thiazine (**12a**) as a clear liquid of bp 68–70 °C (13 mmHg). CI-MS showed a peak of highest mass at m/z 118 (MW 117). ^{1}H NMR ($CDCl_3$): δ (ppm) 1.36 (d, CH_3), 1.6 (m, CH_2), 2.80 (m, CH_2S), 3.08 (m, CH_2N), 4.17 (q, CH), 1.1 (s, broad, N*H*).

Tetrahydro-2-methyl-1,3-thiazine (12a). Route B. The cyclization step 3B in Scheme III was accomplished by the procedures of Grenger and associates.[15] To a stirred solution of 3-mercapto-1-propylamine hydrochloride (30 g, 0.234 mol) in 250 mL of 95% ethanol was added freshly distilled acetaldehyde (10.3 g, 0.234 mol) in 15 mL of ethanol. After 4 h at room temperature, the mixture was refrigerated overnight and the solid product was separated by filtration. Addition of 200 mL of ether to the filtrate gave additional solid product, the combined yield of which was 34.1 g (95%), mp 198–201 °C (lit.[15] mp 198 °C). ^{1}H NMR (D_2O): δ (ppm) 1.54 (d, CH_3), 1.95–2.30 (m, CH_2), 2.5–3.7 (m, CH_2S and CH_2N), 4.46 (q, CH), 4.70 (s, N^+H_2). Neutralization of the amine salt with dilute NaOEt/EtOH and distillation gave **12a** in 86% yield.

Tetrahydro-1,3-thiazine (13a). To a solution of 3-mercapto-1-propylamine hydrochloride (19.2 g, 150 mmol) in 200 mL of anhydrous ethanol was added 12.6 mL of 36% formaldehyde solution (150 mmol). The solution was stirred at room temperature overnight and then evaporated, and the residue was recrystallized from absolute ethanol, giving 20.8 g (99%) of white powder of mp 229–231 °C (lit.[15] mp 216–221 °C). ^{1}H NMR (D_2O): δ 2.15 (p, CH_2), 2.86 (t, CH_2S, J = 5.5 Hz), 3.34 (t, CH_2N, J = 5.8 Hz), 4.27 (s, SCH_2N), 4.70 (s, broad, N^+H_3). Neutralization of the amine salt with 1.05 equiv of NaOEt/EtOH and distillation gave **13a** as a clear colorless liquid (11.5 g, 77%), bp 56–58 °C (8 mmHg) [lit.[15] bp 80 °C (15 mmHg)].

***N*-Methyltetrahydro-1,3-thiazine (15a).** To methyl acrylate (86 g, 1 mol) in 500 mL of methanol and 10 g of KOH was added benzyl mercaptan (125 g, 1 mol) slowly with stirring and cooling to maintain the temperature below 30 °C. The mixture was then refluxed (3 h) and evaporated. Ether was added (200 mL), filtered, and dried to give 207 g (98%) of methyl 3-[(phenylmethyl)thio]propanoate. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.6 (m, CH_2CH_2), 3.65 (s, OCH_3), 3.71 (s, $PhCH_2S$), 7.25 (s, Ph). The ester was treated with methylamine (50 g, 1.6 mol) in 500 mL of methanol. After refluxing overnight, using a dry ice–2-propanol condenser, the volatile components were distilled leaving *N*-methyl 3-[(phenylmethyl)thio]propanamide (201 g, 98%). ^{1}H NMR ($CDCl_3$): δ (ppm) 2.35 (t, CH_2CO), 2.60 (t, CH_2S), 2.73 (d, NCH_3), 3.69 (s, $PhCH_2$), 7.25 (s, Ph). The amide (127 g, 0.607 mol) in 200 mL of ether was added to a suspension of LAH (32 g, 0.83 mol) in 1500 mL of dry ether at a rate to maintain reflux. After refluxing overnight, excess hydride was destroyed with sequential addition of water (32 mL), 10% NaOH (32 mL), and water (96 mL). On filtration, the filtrate was distilled, giving 83 g (70%) of *N*-[3-[(phenylmethyl)thio]propyl]-*N*-methylamine, bp 146–148 °C (3 mmHg). ^{1}H NMR ($CDCl_3$): δ (ppm) 1.20 (s, N*H*), 1.74 (p, $CH_2CH_2CH_2$), 2.38 (s, $NHCH_3$), 2.46 (t, SCH_2), 2.60 (t, CH_2N), 3.67 (s, $PhCH_2$), 7.25 (m, Ph). The amine (39 g, 0.2 mol) in 300 mL of liquid ammonia was treated with sodium metal (about 6.9 g, 0.3 mol) until the blue color persisted for 50 min. Thereafter the mixture turned dark orange. The color disappeared on addition of ammonium chloride (17 g, 0.31 mol). After the ammonia evaporated overnight, propanol (100 mL) was added, and the mixture heated to 80 °C for 30 min to expel residual ammonia. On cooling, excess hydrogen chloride gas was bubbled in. The white precipitate that formed was filtered off. A second crop was recovered from the filtrate on addition of ether. The combined yield of amine hydrochloride as a hygroscopic solid was 23.7 g (85%). ^{1}H NMR (D_2O): δ 1.40 (p, $CH_2CH_2CH_2$), 2.57 (CH_2S), 2.68 (s, NCH_3), 3.1 (t, CH_2N). To the hydrochloride salt (15.5 g, 114 mmol) in 150 mL of absolute ethanol was added formaldehyde solution (13 mL, 37% in water). The mixture was stirred overnight and then evaporated to give 15.4 g (91%) of *N*-methyltetrahydro-1,3-thiazine as the hydrochloride salt mp 211–212 °C. The free base **15a** was generated by neutralization with aqueous sodium carbonate to give 8.8 g (75%) of colorless liquid, bp 39 °C (0.25 mmHg) [lit.[17] bp 74–75 °C (25 mmHg)]. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.75 (m, CH_2), 2.50 (s, CH_3), 2.71 (t, SCH_2), 2.80 (t, CH_2N), 3.85 (s, SCH_2N).

***N*,2-Dimethyltetrahydro-1,3-thiazine (14a).** A solution of **12b** (5.75 g, 50 mmol) in 50 mL of dry acetonitrile was treated with methyl iodide (12 g, 85 mmol, 1.7 equiv). After briefly being heated (10 min), the mixture was cooled, and the volatile components were removed at reduced pressure to give **12e** as a slightly yellow salt (12.5 g, 97%), mp 142–145 °C. ^{1}H NMR (CD_3NO_2): δ (ppm) 2.62 (s, CH_3), 2.41 (m, CH_2), 3.33 (dd, CH_2S), 3.94 (dd, CH_2N), 3.63 (s, N^+CH_3). The salt **12e** (12.85 g, 50 mol) was dissolved in 60 mL of anhydrous methanol and cooled to −78 °C. Sodium borohydride (0.95 g, 25 mmol) was added in one portion with stirring. After a further 5 min of stirring, the mixture was quenched with aqueous potassium carbonate and extracted with ether. Distillation of the extracts gave 5.6 g (86%) of a colorless fishy-smelling liquid, bp 66–67 °C (9 mmHg). ^{1}H NMR ($CDCl_3$): δ (ppm) 1.35 (d, CH_3), 1.28–1.95 (m, CH_2), 2.45 (s, CH_3N), 2.65–3.12 (m, CH_2S, CH_2N), 4.44 (q, CH); CI-MS base peak 132 (MW 131).

***N*-Acetyltetrahydro-1,3-thiazine (13d).** To an ice-cold solution of **13a** (3.09 g, 30 mmol) and triethylamine (4.3 g, 42 mmol) in 100 mL of dry benzene was slowly added acetyl chloride (2.58 g, 32.8 mmol) in 10 mL of benzene. After being stirred for 30 min the mixture was filtered, and the filtrate was concentrated under vacuum. The residue on distillation gave 3.9 g (91%) of **13d** as a colorless liquid, bp 75–76 °C (0.12 mmHg), which solidified, mp 41–42 °C. ^{1}H NMR ($CDCl_3$) showed the presence of two conformers in a 1:1 ratio: δ (ppm) 1.8–2.0 (m, CH_2), 2.85–2.95 (m, CH_2S), 2.12 (s, CH_3CO), 2.16 (s, CH_3CO), 3.66 (t, CH_2N), 3.58 (t, CH_2N), 4.64 (s, SCH_2N), 4.53 (s, SCH_2N). CI-MS: highest mass 146 (MW 145). (For ^{13}C NMR data, see supplementary material).

***N*-Acetyl-2-methyltetrahydro-1,3-thiazine (12d)** was prepared similarly from **12a** (4.68 g, 40 mmol), giving 5.86 g (93%) of a colorless liquid of bp 122–124 °C (2.0 mmHg). ^{1}H NMR ($CDCl_3$) as two conformers in a 3:2 ratio: δ (ppm) 1.58 (d, CH_3), 1.73 (d, CH_3), 1.70–2.0 (m, CH_2), 2.35–4.8 (m, CH_2S and CH_2N), 2.08 (s, CH_3CO), 2.15 (s, CH_3CO). CI-MS: highest mass 160 (MW 159). For ^{13}C NMR data, see supplementary material.

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Methylation of 12d and 13d. A solution of **12d** (1.59 g, 10 mmol) in 20 mL of dry acetonitrile was added to trimethyloxonium fluoroborate (1.50 g) in 30 mL of dichloromethane and 10 mL of acetonitrile at −20 °C. After the mixture was stirred for 1 h, the solvent was evaporated, and the residue was washed with anhydrous ether. Hydrolysis to acetaldehyde was noted, and the product failed to crystallize. No simple proton or carbon NMR spectrum was obtained. A comparable procedure with **13d** (0.68 g, 5 mmol) gave crystalline material (1.14 g, 96%), assigned as **13g**, mp 87–97 °C. ^{1}H NMR (CD_3NO_2): δ (ppm) 2.1–2.4 (m, CH_2), 2.36 (s, CH_3CO), 2.90 and 2.97 (s, S^+CH_3), 3.5 and 3.8 (m, CH_2S), 3.85 and 4.12 (m, CH_2N), 5.17–5.71 (m, SCH_2N). For ^{13}C NMR data, see supplementary material.

The salt mixture obtained from the methylation of **12d** was treated with 50 mL of methanol containing 1% w/v of potassium *tert*-butoxide. After 1 h of stirring the solvent was evaporated, and the neutral products were extracted with ether (20 mL), dried, and evaporated to give a straw-colored liquid. GPLC analysis gave three peaks. Separation and analysis by NMR identified the major product as *N*-[3-(methylthio)propyl]acetamide **16a**, some starting material **12d**, and a new compound, which, by NMR and MS analysis, is assigned the structure *N*-[3-(methylthio)-propyl]-*N*-(1-methoxyethyl)acetamide (**12h**). Via the same procedure, salt **13g** (1.0 g) gave with methanol and 1% KOBu^t neutral products, one component of which is assigned the structure *N*-[3-(methylthio)propyl]-*N*-(methoxymethyl)acetamide (**13h**) (see supplementary material).

Methylthiolation of Tetrahydro-1,3-thiazines 12d, 13d, 14a, and 15a. To **12d** (0.386 g, 2.42 mmol) in dry nitromethane (5 mL) was added dimethyl(methylthio)sulfonium fluoroborate (**5**)[10] (0.477 g, 2.43 mmol) all at once. After the mixture was stirred for 3 h at room temperature, the volatile products (Me_2S and MeSSMe) and solvent were removed by evaporation at reduced pressure. Part of the residue was redissolved (CD_3NO_2) and analyzed by ^{1}H and ^{13}C NMR spectroscopy. Another part of the residue was dissolved in dilute potassium carbonate and extracted with chloroform, and the extract was examined by NMR. The same procedure was applied to **13d**. The results of the analysis are described in the Results and Discussion. In the case of **15a** and **14a**, 50 mmol of the thiazine derivative in 20 mL of dichloromethane was treated with 50 mmol of **5** (which is very slightly soluble in dichloromethane) at room temperature. After 3 h of stirring, the solvent and methyl sulfide were removed at reduced pressure, and the viscous residue was analyzed by NMR spectroscopy. The results are described in the Results and Discussion.

Registry No. **1**, 33696-21-8; **2**, 20280-45-9; **3**, 35332-10-6; **6a**, 118515-34-7; **6b**, 74500-21-3; **7**, 87094-61-9; **8**, 74484-54-1; **9**, 74484-26-7; **10**, 87094-23-3; **11**, 109857-46-7; **12a**, 73317-67-6; **12a**·HCl, 79128-35-1; **12b**, 15047-09-3; **12d**, 118515-27-8; **12e**, 118515-25-6; **12g**, 118515-33-6; **12h**, 118515-30-3; **13a**, 543-21-5; **13a**·HCl, 79128-34-0; **13d**, 118515-26-7; **13g**, 118515-29-0; **13h**, 118515-31-4; **14a**, 76888-71-6; **14j**, 118537-30-7; **15a**, 60035-84-9; **15a**·HCl, 118515-24-5; **15j**, 118515-35-8; **16a**, 54824-91-8; **16b**, 81645-14-9; **17**, 118515-36-9; $HO(CH_2)_3NHAc$, 10601-73-7; $HO(CH_2)_3NH_2$, 156-87-6; $C_6H_5CH_2SH$, 100-53-8; $C_6H_5CH_2S(CH_2)_2CO_2CH_3$, 5331-36-2; CH_3NH_2, 74-89-5; $C_6H_5CH_2S(CH_2)_2CONHCH_3$, 56788-03-5; $C_6H_5CH_2S(CH_2)_3NHCH_3$, 118515-22-3; $HS(CH_2)_3NHCH_3$·HCl, 118515-23-4; $H_2C{=}CHCO_2CH_3$, 96-33-3; $Me_4N^+I^-$, 75-58-1; $Me_2N^+Et_2I^-$, 4325-24-0; methanesulfenyl chloride, 5813-48-9; dimethylamine, 124-40-3; methyl disulfide, 624-92-0; ethyl iodide, 75-03-6; 1-(*N*,*N*-dimethylamino)-2-chloroethane, 107-99-3; sodium methanethiolate, 5188-07-8; chloromethyl methyl sulfide, 2373-51-5; 3-mercapto-1-propylamine hydrochloride, 7211-54-3; acetaldehyde, 75-07-0.

Supplementary Material Available: ^{13}C NMR chemical shifts for **12d**, **12g**, **12h**, **13d**, **13g**, **13h**, **14j**, **15j**, **16b**, and **17** (3 pages). Ordering information is given on any current masthead page.

Polyaza-Cavity Shaped Molecules. 14. Annelated 2-(2′-Pyridyl)indoles, 2,2′-Biindoles, and Related Systems

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Received July 15, 1988

The Fisher indole synthesis has been employed with a series of α-keto-2,3-cycloalkenopyridines to provide 3,3′-polymethylene bridged derivatives of 2-(2′-pyridyl)indole. The same reaction with α,α′-diketo[2,3:5,6]dicycloalkenopyridines provides bis-annelated derivatives of 2,6-di(2′-indolyl)pyridine. With 1,2-cycloalkanediones one obtains a mixture of two products resulting from one or two successful Fisher cyclizations. The cage diketone, tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione, affords a molecule with two indole rings arranged as a *syn*-orthocyclophane. UV absorption and hydrogen bonding are found to vary as a function of the planarity of the molecule while cyclopalladation occurs readily regardless of conformation.

Introduction

Over the past several years we have been interested in the study of bridged azabiaryl systems in which a polymethylene bridge may be used to control the conformation of the interior cavity of the molecule. The resulting 2,2′-bipyridines,[1] 2,2′;6′,2″-terpyridines,[2] and their related dibenzo- and dipyrido-fused analogues[3] have been investigated as ligands in forming complexes with a variety of transition metals.[4]

Our strategy in the synthesis of these materials has centered around the selection of appropriately oriented ketones or diketones. These compounds were then allowed to react with an *o*-amino aldehyde via the Friedländer condensation[5] to provide the corresponding pyridine, quinoline, or 1,8-naphthyridine system. In this work we will expand this approach, using the same carbonyl compounds to provide derivatives of 2-(2′-pyridyl)indole, 2,2′-biindole, and other related compounds.

From a conceptual point of view, 2-(2′-pyridyl)indole (1) may be considered a lower homologue of 2-(2′-pyridyl)-

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