NEW TRANSFORMATION OF LACTAM SULFIDES TO TETRAHYDRO-3,6-EPITHIOBENZAZOCINES *VIA* BICYCLIC SULFONIUM SALTS WITH A SULFONIO BRIDGEHEAD

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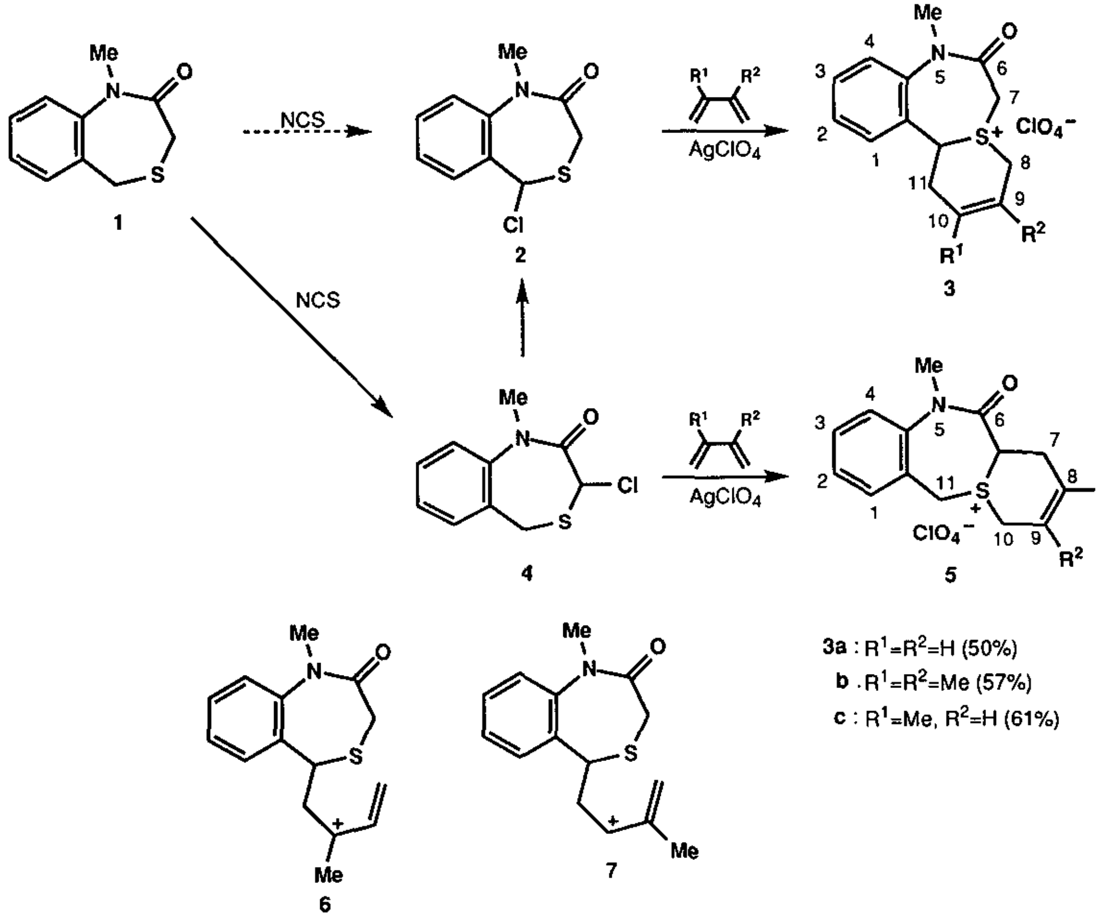
Abstract - Benzothiazinone (**1**) was chlorinated with *N*-chlorosuccinimide and subsequently submitted to $[2^{+}+4]$ cycloaddition with 1,3-dienes in the presence of silver perchlorate to afford cyclic sulfonium salts (**3**). Reactions of **3** with sodium borohydride or sodium hydride provided 4-vinyltetrahydro-3,6-epithiobenzazocine derivatives (**9**) in good yields.

Previously we reported that bicyclic lactam sulfonium salts with a sulfonio bridgehead underwent the cleavage of the cross-piece C-S bond to give the medium-sized lactam sulfides.[1] Recently it has been reported that α-chlorosulfides or thionium ions reacted with 1,3-dienes to form the bicyclic sulfonium salts, which underwent rearrangement by base treatment.[2,3] These papers suggested us the possibility for preparing new lactam sulfides with the unusual skeletons starting from benzothiazepinones. Since some tetrahydrobenzazocines possess the potent pharmacological activity,[4] we planed to prepare new compounds bearing both thiazepinone and azocinone skeletons. This paper describes a synthesis of sulfur-bridged tetrahydrobenzazocinones. Sulfonium salts with a sulfonio bridgehead were prepared as shown in Scheme 1. 1-Methyl-3,5-dihydro-4,1-benzothiazin-2(1*H*)-one (**1**)[5] was chlorinated with *N*-chlorosuccinimide (NCS) to give 5-chloro derivative (**2**). The α-chlorosulfide (**2**) was treated with dienes in the presence of silver perchlorate to afford sulfonium salts (**3**). The structure of the benzothiazepinone sulfonium salt (**3a**) was determined by ^{1}H-nmr spectral data.[6] Chlorination of **1** would be expected to occur at 3-position rather than at 5-position because the 3-position is α to both the sulfur atom and the carbonyl group, and sulfonium salts (**5**) would be formed. If a product obtained from **4** and 1,3-butadiene was the sulfonium salt (**5a**), a pair of doublets at δ 3.53 and 4.01 (J=12 Hz) are assigned to the 11-CH_2 signals in ^{1}H-nmr spectrum. When sulfides are led to sulfonium salts, α-CH_2 signals

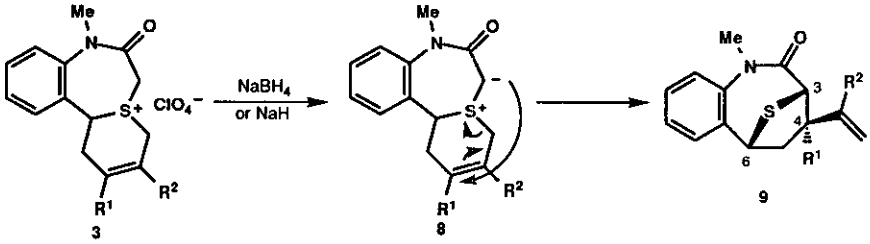


Scheme 1

of the sulfonium salts usually shift to the down-field. Therefore, the 11-CH_2 signals of **5a** should be observed in the lower field than the benzyl protons of the sulfide (**1**) at δ 3.42 and 4.09. This conflict could be solved by assignment of the doublets to the 7-CH_2 signals of the other sulfonium salt (**3a**), whose chemical shifts are lower than those of the 3-CH_2 group of **1** at δ 2.89 and 3.14.

Chlorination of **1** with NCS was followed by measuring the ^{1}H-nmr spectrum from -30°C to 30°C to determine whether the chloride (**2**) was directly formed or the chloride (**4**) was first formed and then isomerized to the more stable chloride (**2**). The ^{1}H-nmr spectrum initially showed peaks of **4** [δ 3.49 (s, N-Me), 3.63 and 4.42 (d, J=13 Hz, 5-H), 5.65(s, 3-H)] and gradually changed to the spectrum of **2** [δ 3.15 and 3.39 (d, J=13 Hz, 3-H), 3.41(s, N-Me) and 6.26 (s, 5-H)]. This spectral evidence indicates that the 3-chloro compound (**4**) is formed and then transformed into a thermodynamically more stable 5-chloro derivative (**2**).

Isoprene adduct (**3c**) is the single regio-isomer. Regio-selectivity of the reaction of **2** with isoprene can be explained by the stability of the carbocation intermediate (**6** is more stable than **7**).



	A	B
9a $R^1=R^2=H$	58%	82%
b $R^1=R^2=Me$	61%	86%
c $R^1=Me$, $R^2=H$	64%	83%

A $NaBH_4$
B NaH

Scheme 2

The sulfonium salts (**3**) were treated with sodium borohydride in ethanol to give 4-vinyltetrahydro-3,6-epithiobenzazocine derivatives (**9**) in good yields. The structure of the product (**9a**) was determined by ^1H- and ^{13}C-nmr spectra.[7] ^1H-Nmr signals were assigned by the H-H decoupling technique. ^{13}C-Nmr spectrum exhibited three methine carbons at δ 45.8, 54.4 and 57.8, a methylene carbon at δ 50.6 and a terminal methylene carbon at δ 115.6. Stereochemistry of the vinyl group and the bridging sulfur of **9b** was determined by the nuclear Overhauser enhancement (NOE) measurement. The NOE was observed between 3-H and the methyl protons on the vinyl group and between 6-H and 7-H in 8.2 % and 10.7 %, respectively. The stereoscopic view of **9b** is depicted in Figure 1. Reaction of **3** with sodium hydride also provided the tetrahydro-3,6-epithiobenzazocines (**9**) in high yields. From these results, the reaction would proceed *via* deprotonation of the sulfonium salt (**3**) with sodium borohydride or sodium hydride and subsequent [2,3]-sigmatropic rearrangement of the newly formed ylides (**8**).

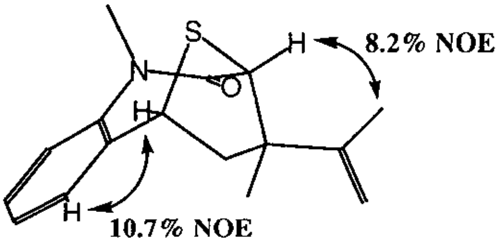


Figure 1 Stereoscopic View of Tetrahydroepithiobenzazocine (**9b**)

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6. Data for **3a** as a representative of the sulfonium salts: colorless prisms (MeCN-ether), mp 213-214°C. ^{1}H-Nmr (CD_3CN) δ: 3.07-3.34 (3H, m, 8- and 11-H), 3.46 (3H, s, 5-Me), 3.53 (1H, d, *J*=12 Hz, 7-H), 4.01 (1H, d, *J*=12 Hz, 7-H), 4.15 (1H, dd, *J*=7 and 15 Hz, 8-H), 5.46 (1H, br d, *J*=4 Hz, 11a-H), 6.08 (1H, dd,*J*=7 and 10 Hz, 9-H), 6.45 (1H, br d, *J*=10, 10-H), 7.53-7.65 (3H, m, ArH), 7.74-7.85 (1H, m, ArH). ^{13}C-Nmr (CD_3CN) δ: 26.0 (t), 33.0 (t), 36.2 (q), 40.4 (t), 44.2 (d), 117.8 (d), 126.0 (d), 126.5 (s), 128.5 (d), 128.8 (d), 130.1 (d), 132.3 (d), 143.2 (s), 160.2 (s). Ir (KBr) cm^{-1}: 1650 (CO), 1100 (ClO_4^-). Anal. Calcd for $C_{14}H_{16}NO_5ClS$: C, 48.63; H, 4.66; N, 4.05. Found: C, 48.72; H, 4.54; N, 4.11.
7. Data for **9a** as a representative of the tetrahydroepithiobenzazocines: colorless prisms (AcOEt-hexane), mp 112-113°C. ^{1}H-Nmr ($CDCl_3$) δ: 2.18 (1H, ddd, *J*=5, 9 and 12 Hz, 5-H), 2.34 (1H, dd, *J*=7 and 12 Hz, 5-H), 2.85-2.95 (1H, br m, 4-H), 3.46 (3H, s, 1-Me), 4.11 (1H, d, *J*=3 Hz, 3-H), 4.60 (1H, br d, *J*=5 Hz, 6-H), 5.02 (1H, d, *J*=10 Hz, CH_2=C), 5.05 (1H, d, *J*=17 Hz, CH_2=C), 5.83 (1H, ddd, *J*=8, 10 and 17 Hz, $C\underline{H}=CH_2$), 7.04-7.31 (4H, m, ArH). ^{13}C-Nmr ($CDCl_3$) δ: 40.4 (q), 45.8 (d), 50.6 (t), 54.4 (d), 57.8 (d), 115.6 (t), 123.0 (d), 124.1 (d), 127.6 (d), 129.7 (d), 133.4 (s), 138.9 (d), 140.6 (s), 174.8 (s). MS *m/z*: 245 (M^+), 150 (base). Ir (KBr) cm^{-1}: 1640 (CO). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.61; H, 6.06; N, 5.75.

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