Synthesis and Reactions of Lactam Sulfonium Salts with a Sulfonio Bridgehead. II. 1,1a,4,5,6-Pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorates

Tadashi KATAOKA,*[a] Yoshihide NAKAMURA,[a] Harutoshi MATSUMOTO,[a] Tetsuo IWAMA,[a] Hiroshi SHIMIZU,[a] Osamu MURAOKA,[b] and Genzoh TANABE[b]

Gifu Pharmaceutical University,[a] 6–1, Mitahora-higashi 5-chome, Gifu 502, Japan and Kinki University, Faculty of Pharmaceutical Sciences,[b] 3–4–1, Kowakae, Higashi-osaka, Osaka 577, Japan.

Received August 30, 1996; accepted October 11, 1996

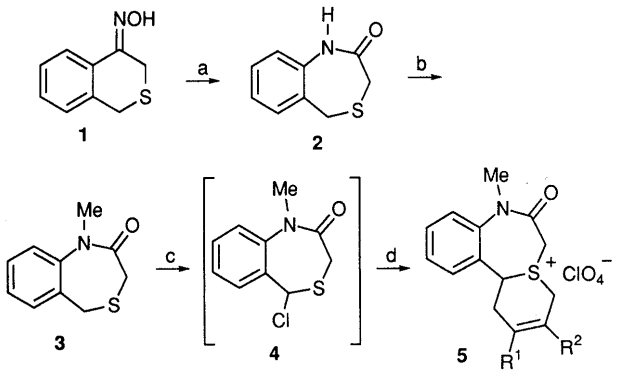
Tricyclic benzothiazepinium salts (5) were prepared by [2⁺ + 4] polar cycloaddition of thionium intermediates (4A), generated from corresponding α-chloro sulfides (4) and dienes in the presence of silver perchlorate. X-Ray analysis of 5a revealed that the configuration of the thiazepinone skeleton and the dihydrothiopyran ring is *cis*-fused. Reactions of benzothiazepinium salts (5) with $NaBH_4$ or NaH afforded 3,6-epithiobenzazocinone derivatives (9) in high yields by [2,3]-sigmatropic rearrangement of an ylide intermediate (11). The stereochemistry of epithiobenzazocinone (9a) was determined by the nuclear Overhauser enhancement (NOE) technique and finally by X-ray analysis of the sulfoxide (10) derived from epithiobenzazocinone (9a) by *m*-chloroperbenzoic acid (MCPBA) oxidation. Alkylation of epithiobenzazocinone (9a) afforded 3-alkyl-3,6-epithiobenzazocinones (12) with retention of the configuration at C-3. Dihydrothiopyran derivatives (13) were obtained in good yields by SmI_2 reduction of benzothiazepinium salts (5).

Key words tricyclic benzothiazepinium salt; 3,6-epithiobenzazocinone; [2,3]-sigmatropic rearrangement; X-ray analysis; samarium diiodide reduction

We previously synthesized medium-sized lactam sulfides by reduction of bicyclic lactam sulfonium salts with a sulfonio bridgehead by the cleavage of the cross-piece C–S bond.[1] It has recently been reported that bicyclic sulfonium salts were generated by the reactions of α-chloro sulfides or thionium ions with 1,3-dienes and that treatment of the salts with a base furnished vinylcyclopropanes.[2,3] We applied this method to the synthesis of tricyclic benzothiazinium salts fused with a 2*H*-5,6-dihydrothiopyran skeleton and prepared new lactam sulfides with unusual skeletons by the ring transformation of the salts with a reducing agent or a base,[4] because some benzothiazinone derivatives such as semotiadil, a Ca^{2+} antagonist[5] and SPR-210, an aldose reductase inhibitor,[6] are pharmacologically active. Since various benzothiazepinone derivatives, represented by diltiazem[7] and tiazesim,[8] possess potent pharmacological activity,[9] we recently reported the preparation of tricyclic benzothiazepinium salts and their transformation into new lactam sulfides with both a benzothiazepinone skeleton and a tetrahydrobenzazocine framework.[10] It is known that some tetrahydrobenzazocine derivatives possess potent pharmacological activity.[11] In this paper we describe our study on the transformation of benzothiazepinium salts with a sulfonio bridgehead and on the C-3 modification of 3,6-epithiobenzazocinone.

Synthesis of Lactam Sulfonium Salts by [2⁺ + 4] Polar Cycloaddition A benzothiazepinone **3** was synthesized by a modification of Hill's procedure.[12] We attempted the Beckmann rearrangement of isothiochromanone oxime (**1**) with *p*-tosyl chloride in pyridine, and obtained 3,5-dihydro-4,1-benzothiazepin-2(1*H*)-one (**2**) in low yield. Thus, we examined the Beckmann rearrangement under nearly neutral conditions. The rearrangement of **1** took place smoothly on treatment with PPSE (polyphosphoric acid trimethylsilyl ester)[13] in 1,2-dichloroethane under reflux and the resultant crude benzothiazepinone **2** was methylated with MeI to furnish **3** in 40% overall yield. The benzothiazepinone **3** was treated with *N*-chlorosuccinimide (NCS) and the resultant crude α-chloro sulfides **4** reacted with 1,3-dienes such as 1,3-butadiene, isoprene and 2,3-dimethyl-1,3-butadiene in the presence of silver perchlorate to give benzothiazepinium salts **5** in moderate to good yield (Chart 1).

Chlorination of **3** would occur at the 3-position rather than at the 5-position because the 3-position is situated between the sulfur atom and the carbonyl group, and sulfonium salts **5′** would be formed (Chart 2). Since an intermediate α-chloro sulfide, **4** or **4′**, could not be isolated because of its instability, we examined whether the adduct was **5** or **5′** on the basis of the ^{1}H-NMR spectrum. If the product obtained from the chloro sulfide and 2,3-dimethyl-1,3-butadiene is the sulfonium salt **5a′**, the doublets at δ



a : $R^1 = R^2 = Me$ (50%)
b : $R^1 = R^2 = H$ (57%)
c : $R^1 = Me$, $R^2 = H$ (61%)

a. PPSE, $ClCH_2CH_2Cl$, reflux, 1h. b. NaH, DMF then MeI, 40% from **1**. c. NCS, CH_2Cl_2, 0°C then r.t. 5 h. d. diene, $AgClO_4$, CH_3CN, 0°C then r.t. 30 min.

Chart 1

* To whom correspondence should be addressed.

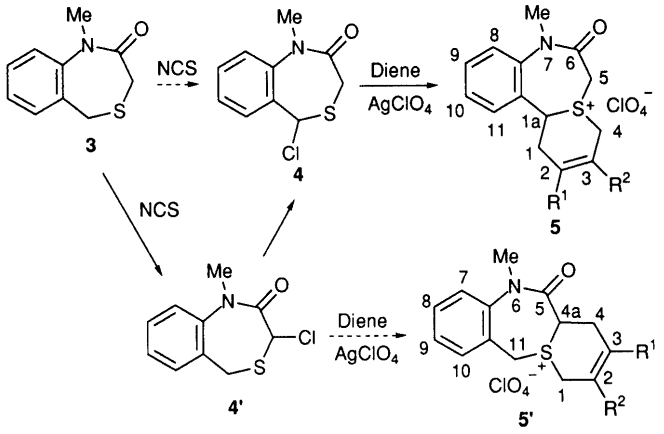


Chart 2

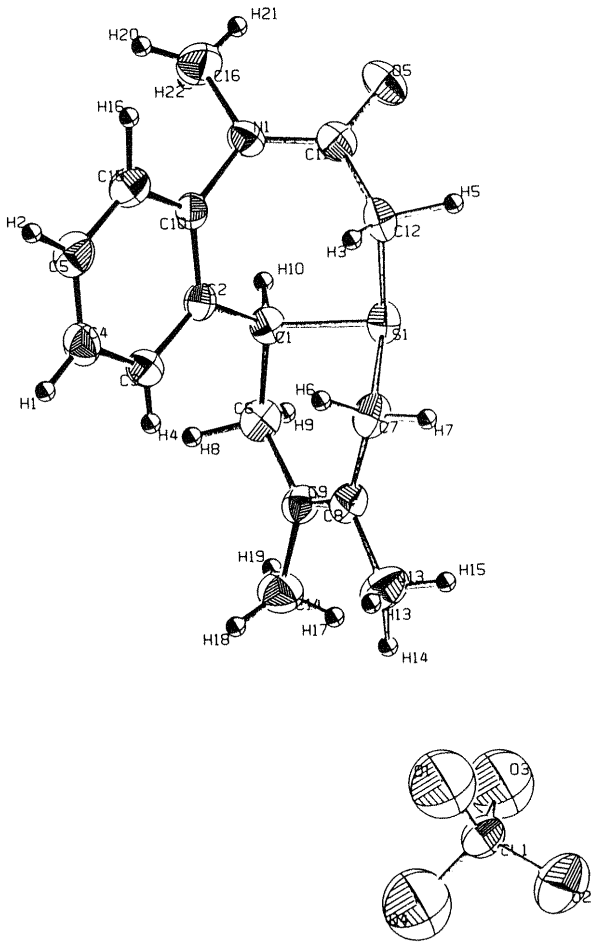


Fig. 1. ORTEP Drawing of the Benzothiazepinium Salt **5a**

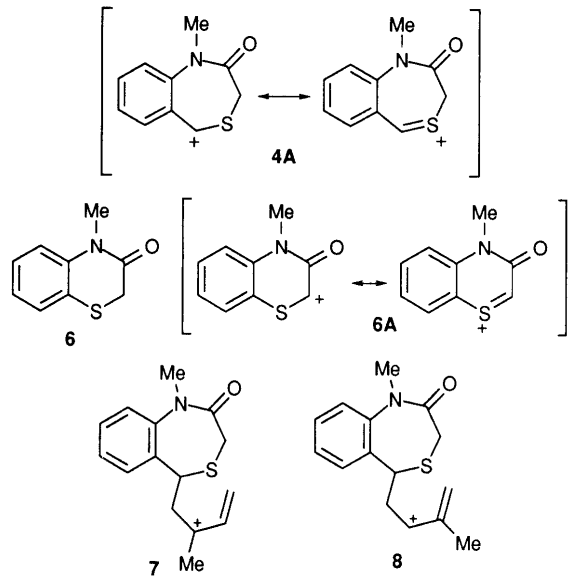


Fig. 2

3.53 and 4.01 ($J=12$ Hz) in the ^{1}H-NMR can be assigned to the 11-CH_2 group. However, α-CH_2 signals of sulfonium salts usually appear at lower field than those of the corresponding sulfides. Therefore, the 11-CH_2 signals of **5a'** should be observed at lower field than the δ 3.42 and 4.09 signals due to the benzyl protons of the sulfide **3**. This can be resolved by assignment of the doublets to the 5-CH_2 signals of the other sulfonium salt **5a**, whose chemical shifts are lower than those of the 3-CH_2 group of **3** at δ 2.89 and 3.14. The structure and the stereochemistry of the salt **5a** were finally determined by X-ray crystallographic analysis (Fig. 1). The X-ray structure analysis revealed that the thiazepinone ring and the dihydrothiopyran one are *cis*-fused. The *cis*-configuration of **5a** was stable under reflux in acetone or acetonitrile and no pyramidal inversion to the *trans* isomer was observed.

The reaction of **3** with NCS was followed by ^{1}H-NMR spectroscopy to determine the pathway from **3** to **4**. The ^{1}H-NMR spectrum initially showed peaks due to **4'** [δ 3.49 (s, N-Me), 3.63, 4.42 (d, $J=13$ Hz, 5-H), 5.65 (s, 3-H)] at -30 °C and gradually changed to the spectrum of **4** [δ 3.15, 3.39 (d, $J=13$ Hz, 3-H), 3.41 (s, N-Me) and 6.26 (s, 5-H)] with increase of the temperature to 30 °C. This spectral evidence indicates that the 3-chloro compound **4'** is formed first and then transformed into the thermodynamically more stable 5-chloro derivative **4**.

The isoprene adduct **5c** was obtained as a single isomer from the benzothiazepinone **3**. We previously reported that the benzothiazinone **6** afforded a 2:1 mixture of regioisomeric isoprene adducts.[4] This difference may be explained as follows (Fig. 2): the α-thiocarbocation **4A**, generated from **4**, is relatively stable because the thionium ion of **4A** resonates with the aromatic ring. Instability of **6A** lowers the regioselectivity in the reaction of **6A** with isoprene, whereas the reaction of the more stable thiocarbocation **4A** selectively proceeds *via* the carbocation intermediate **7**, which is stabilized by the methyl group of isoprene, but not *via* intermediate **8**. However, the precise reason for the stereoselectivity is not clear at present.

Ring Transformation of Benzothiazepinium Salts We planned to prepare new compounds bearing both thiazepinone and azocinone skeletons by [2,3]-sigmatropic rearrangement of benzothiazepinium ylides generated from the corresponding benzothiazepinium salts **5** with a base,[10] since some tetrahydrobenzazocines possess potent pharmacological activity.[11] Treatment of the benzothiazepinium salts **5a**—**c** with NaH in dimethylformamide (DMF) at 0 °C provided 4-vinyltetrahydro-3,6-epithiobenzazocinone derivatives **9a**—**c** in high yield (Chart 3, Table 1, entries 1,3 and 5). These compounds (**9**) were also afforded by the reactions of the salts **5** with $NaBH_4$ in EtOH in good yield (entries 2,4 and 6).

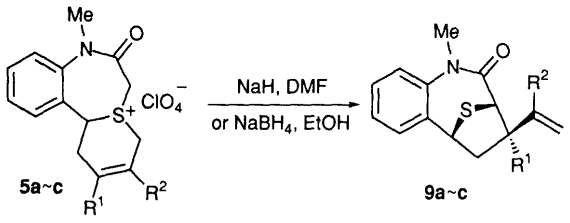


Chart 3

Table 1. Ring Transformation of Benzothiazepinium Salts **5**

Entry	Sulfonium salt	Reagent	Time (h)	Product (% yield)
1	**5a**	NaH	0.5	**9a** (86)
2	**5a**	$NaBH_4$	12	**9a** (61)
3	**5b**	NaH	0.5	**9b** (82)
4	**5b**	$NaBH_4$	20	**9b** (58)
5	**5c**	NaH	0.5	**9c** (83)
6	**5c**	$NaBH_4$	18	**9c** (64)

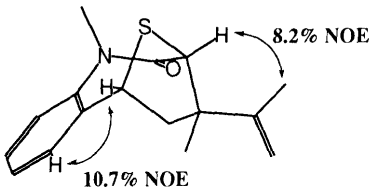


Fig. 3. Stereoscopic View of the Epithiobenzazocinone **9a**

The structure of **9a** was determined by analysis of the ^{1}H- and ^{13}C-NMR spectra. ^{1}H-NMR signals were assigned by the H–H decoupling technique. A singlet at δ 4.10 was assigned to a methine proton α to a carbonyl group. A benzylic methine proton was observed at δ 4.42 as a double doublet ($J=3$, 9 Hz), which was coupled with a pair of double doublets (δ 1.91, $J=3$, 14 Hz and δ 2.95, $J=9$, 14 Hz) assignable to methylene protons. The ^{13}C-NMR spectrum exhibited two methine carbons at δ 51.1 and 60.4, a methylene carbon at δ 43.8 and a terminal methylene carbon at δ 112.2. The stereochemistry of the vinyl group and the bridging sulfur of **9a** was determined by nuclear Overhauser enhancement (NOE) measurement. NOE was observed between 3-H and the methyl protons on the vinyl group and between 6-H and 7-H (8.2%, 10.7%, respectively; Fig. 3). The relative configuration of the epithiobenzazocinone skeleton was finally determined by the X-ray crystallographic analysis of the sulfoxide **10** derived from **9a** by *m*-chloroperbenzoic acid (MCPBA) oxidation (Fig. 4). The stereochemistry of **9a** was consistent with the structure proposed on the basis of [2,3]-sigmatropic rearrangement of a sulfonium ylide intermediate (Chart 4). The carbanion of an ylide **11**, generated by abstraction of a methylene proton α to the carbonyl group of **5a**, underwent [2,3]-sigmatropic rearrangement by back side attack at olefinic carbon to give the epithiobenzazocinone **9a** with the configuration shown in Chart 4.

We examined modification at the C-3 position of tetrahydro-3,6-epithiobenzazocinone derivative **9a**. Deprotonation at C-3 with *n*-BuLi in tetrahydrofuran (THF) at $-78\,^\circ$C gave the carbanion, which was treated with

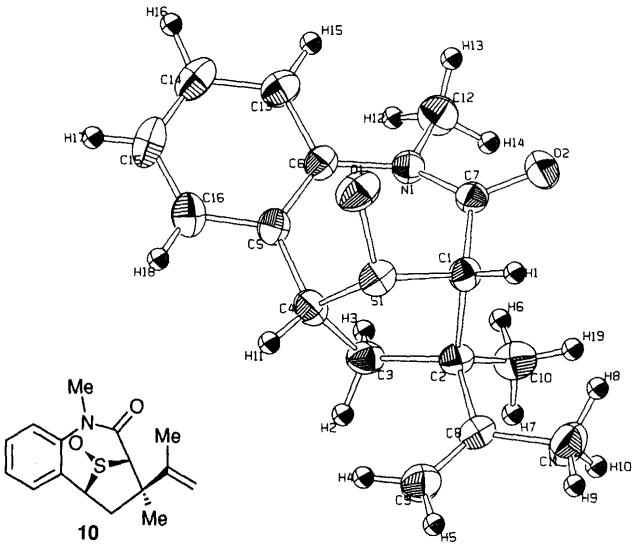


Fig. 4. ORTEP Drawing of the Sulfoxide **10**

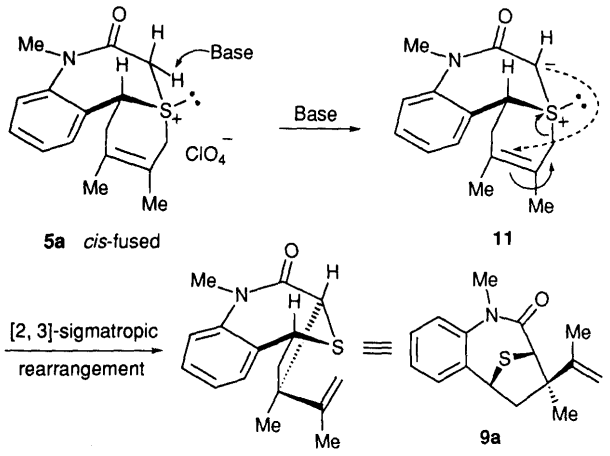
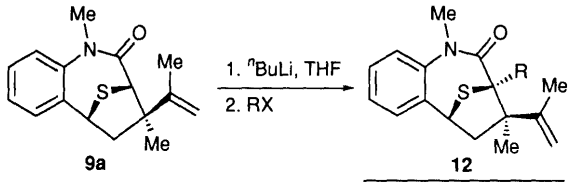


Chart 4



RX	Product(%)
MeI	**12a**(78)
EtBr	**12b**(63)

Chart 5

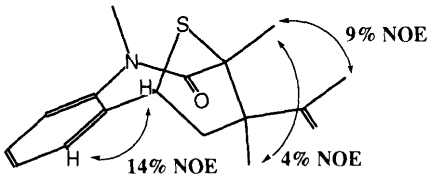


Fig. 5. Stereoscopic View of the 3-Methylepithiobenzazocinone **12a**

iodomethane to give 3-methyl-3,6-epithiobenzazocinone **12a** in 78% yield (Chart 5). Methylation took place with retention of the relative configuration due to the rigid 3,6-epithiobenzazocinone framework. The stereochemistry of **12a** was confirmed by NOE measurement (Fig. 5).

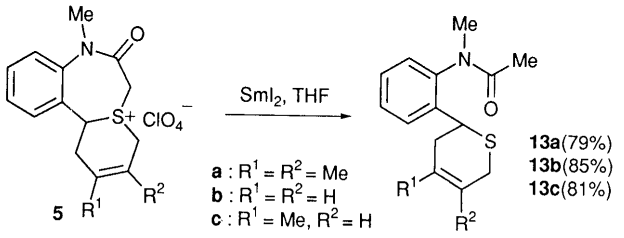


Chart 6

NOE of 9% was observed between the C-3 and the vinylic methyl groups and relatively weak NOE (4%) was detected between the C-3 and C-4 methyl groups. The 3-ethyl derivative **12b** was obtained in 63% yield by treatment with bromoethane instead of iodomethane. Further modification at C-3 is under investigation.

We recently reported that single electron transfer reduction of sulfonium salts with Mg, Grignard reagents[14] or SmI_2[15] gave sulfides and that medium-sized lactam sulfides were obtained by reduction of bicyclic lactam sulfonium salts with a sulfonio bridgehead.[1,4] Therefore, we applied SmI_2 reduction to benzothiazepinium salts **5** (Chart 6). Treatment of **5a** with 3.0 eq of SmI_2 in THF at room temperature under a nitrogen atmosphere provided the (2*H*)-5,6-dihydrothiopyran derivative **13a** in 79% yield as a mixture of two geometrical isomers (1 : 1) caused by restricted rotation of the N–C=O moiety, instead of an 11-membered lactam sulfide. Other benzothiazepinium salts **5** also gave exclusively dihydrothiopyrans in high yields.

In summary, benzothiazepinium salts bearing a dihydrothiopyran skeleton with a sulfonio bridgehead were synthesized from α-chloro sulfides with dienes in the presence of silver perchlorate by [2⁺+4] polar cycloaddition. 4-Vinyltetrahydro-3,6-epithiobenzazocinone derivatives with both a thiazepinone framework and an azocinone skeleton were obtained by ring transformation of benzothiazepinium salts with NaH or $NaBH_4$. Alkylation of 3,6-epithiobenzazocinone derivatives gave 3-alkyl-3,6-epithiobenzazocinones with retention of the configuration. Dihydrothiopyran derivatives were generated by SmI_2 reduction of the salts.

Experimental

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra of solids (KBr) and liquids (NaCl) were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL GX-270 (270 MHz) or a JEOL EX-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra and NOE were obtained on a JEOL EX-400 spectrometer. The *J* values are given in Hz. Mass spectra were recorded on a JEOL JMS-D 300 spectrometer with a direct-insertion probe at 70 eV. Elemental analyses of new compounds were performed by a Yanaco CHN Corder MT-5. All chromatographic isolations were accomplished with either Kieselgel 60 (70—230 mesh) for column chromatography or Kieselgel 60 PF_{254} containing gypsum for preparative TLC.

Synthesis of 1-Methyl-3,5-dihydro-4,1-benzothiazepin-2(1*H*)-one (3) PPSE[13] was prepared from P_2O_5 (10 g, 70 mmol) and hexamethyldisiloxane (21 ml, 100 mmol) in 60 ml of 1,2-dichloroethane under reflux for 2 h under a nitrogen atmosphere. Isothiochromanone oxime (**1**)[12] (3.58 g, 20 mmol) was added at once to the stirred solution of PPSE at room temperature. The mixture was refluxed for 1 h under a nitrogen atmosphere. The cooled reaction mixture was poured into 80 ml of water and extracted with chloroform. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude amide **2**. The amide **2** was dissolved in 60 ml of DMF and NaH (839 mg, 21 mmol) was added to this solution at 0 °C. The mixture was stirred for 1 h at room temperature, then methyl iodide (3.123 g, 22 mmol) was added at 0 °C and the whole was stirred for 3 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate : hexane (1 : 10) to give 1.55 g (40%) of **3** as colorless prisms. mp: 135—137 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (1H, br s, 3-H), 3.15 (1H, br s, 3-H), 3.35 (3H, s, NMe), 3.40 (1H, br s, 5-H), 4.10 (1H, br s, 5-H), 7.20—7.41 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 30.5 (t), 31.1 (t), 35.4 (q), 123.7 (d), 127.9 (d), 128.9 (d), 129.5 (d), 131.7 (s), 142.9 (s), 168.5 (s). IR (KBr) cm^{-1}: 1650 (C=O). MS *m/z* (rel. int. %): 193 (M^+, 66), 121 (100). *Anal.* Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.72; N, 7.36.

Synthesis of 7-Methyl-1,1a,4,5,6-pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorates (5) General Procedure: A stirred solution of benzothiazepinone **3** (5 mmol) in dry CH_3CN (25 ml) was treated with NCS (668 mg, 5 mmol) at 0 °C. After 30 min at room temperature, a diene (10 mmol) and $AgClO_4$ (90% purity, 1.150 g, 5 mmol) were added successively to the reaction mixture at 0 °C. The whole was stirred for 30 min at room temperature, then the precipitate of AgCl was filtered off and washed with CH_3CN. The filtrate and washing were evaporated and the resultant benzothiazepinium salt **5** was purified by recrystallization from CH_3CN–ether.

2,3,7-Trimethyl-1,1a,4,5,6-pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorate (**5a**): Yield 50%. Colorless prisms (CH_3CN–ether). mp: 219—221 °C (dec.). ^{1}H-NMR (CD_3CN) δ: 1.90, 2.23 (each 3H, s, Me×2), 2.87 (1H, br d, *J*=20 Hz, 1-H), 3.08 (1H, br d, *J*=17 Hz, 4-H) 3.14 (1H, br d, *J*=20 Hz, 1-H), 3.35 (3H, s, NMe), 3.36 (1H, d, *J*=12 Hz, 5-H), 3.81 (1H, d, *J*=17 Hz, 4-H), 3.88 (1H, d, *J*=12 Hz, 5-H), 5.30 (1H, br d, *J*=5 Hz, 1a-H), 7.30 (1H, d, *J*=8 Hz, ArH), 7.45—7.51 (2H, m, ArH), 7.66 (1H, t, *J*=8 Hz, ArH). ^{13}C-NMR (CD_3CN) δ: 18.8 (q), 19.4 (q), 31.4 (t), 35.9 (q), 36.7 (t), 40.1 (t), 43.6 (d), 118.3 (s), 125.5 (d), 126.2 (s), 128.4 (d), 128.5 (d), 129.7 (s), 131.6 (d), 142.7 (s), 159.9 (s). IR (KBr) cm^{-1}: 1660 (C=O), 1100 (ClO_4^-). *Anal.* Calcd for $C_{16}H_{20}ClNO_5S$: C, 51.40; H, 5.39; N, 3.75. Found: C, 51.88; H, 5.30; N, 3.80.

7-Methyl-1,1a,4,5,6-pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorate (**5b**): Yield 57%. Colorless prisms (CH_3CN–ether). mp: 213—214 °C (dec.). ^{1}H-NMR (CD_3CN) δ: 3.10—3.30 (3H, br m, 4-H (1H), 1-H (2H)), 3.46 (3H, s, NMe), 3.52 (1H, d, *J*=12 Hz, 5-H), 3.99 (1H, d, *J*=12 Hz, 5-H), 4.15 (1H, dd, *J*=7, 15 Hz, 4-H), 5.46 (1H, br d, *J*=4 Hz, 1a-H), 6.08 (1H, br dd, *J*=7, 11 Hz, 2-H), 6.43 (1H, br dd, *J*=8, 11 Hz, 3-H), 7.53—7.75 (3H, m, ArH), 7.80 (1H, t, *J*=8 Hz, ArH). ^{13}C-NMR (CD_3CN) δ: 26.0 (t), 33.0 (t), 36.2 (q), 40.4 (t), 44.2 (d), 117.7 (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 (C=O), 1100 (ClO_4^-). *Anal.* Calcd for $C_{14}H_{16}ClNO_5S$: C, 48.63; H, 4.66; N, 4.05. Found: C, 48.72; H, 4.54; N, 4.11.

2,7-Dimethyl-1,1a,4,5,6-pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorate (**5c**): Yield 61%. Colorless prisms (CH_3CN). mp: 196—210 °C (dec). ^{1}H-NMR (CD_3CN) δ: 1.97 (3H, s, Me), 2.87 (1H, br d, *J*=19 Hz, 1-H), 3.07—3.12 (2H, m, 1-H, 4-H), 3.35 (3H, s, NMe), 3.37 (1H, d, *J*=12 Hz, 5-H), 3.87 (1H, d, *J*=12 Hz, 5-H), 4.01 (1H, dd, *J*=7, 15 Hz, 4-H), 5.35 (1H, br d, *J*=6 Hz, 1a-H), 5.71 (1H, d, *J*=7 Hz, 3-H), 7.32 (1H, d, *J*=8 Hz, ArH), 7.45—7.52 (2H, m, ArH), 7.67 (1H, t, *J*=8 Hz, ArH). ^{13}C-NMR (CD_3CN) δ: 23.5 (q), 30.5 (t), 33.5 (t), 36.3 (q), 40.2 (t), 44.6 (d), 112.3 (d), 126.0 (d), 126.5 (s), 128.6 (d), 128.9 (d), 132.4 (d), 139.1 (s), 143.1 (s), 160.3 (s). IR (KBr) cm^{-1}: 1660 (C=O), 1090 (ClO_4^-). *Anal.* Calcd for $C_{15}H_{18}ClNO_5S$: C, 50.07; H, 5.04; N, 3.89. Found: C, 50.06; H, 5.01; N, 3.90.

Reactions of Benzothiazepinium Salts 5 with Sodium Hydride General Procedure: A suspension of NaH (60% in paraffin oil, 44 mg, 1.1 mmol) in dry DMF (2 ml) was stirred, and a benzothiazepinium salt **5** (1 mmol) was added to it at 0 °C. After 30 min at room temperature, water was added to the reaction mixture and the whole was extracted with ethyl acetate. The extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate : hexane (1 : 5). The reaction conditions and the results are summarized in Table 1.

4-Isopropenyl-1,4-dimethyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one (**9a**): Colorless prisms (AcOEt–hexane). mp: 121—122 °C.

^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, s, 4-Me), 1.85 (3H, d, J=1 Hz, vinylic Me), 1.91 (1H, dd, J=3, 14 Hz, 5-H), 2.95 (1H, dd, J=9, 14 Hz, 5-H), 3.49 (3H, s, NMe), 4.10 (1H, s, 3-H), 4.42 (1H, dd, J=3, 9 Hz, 6-H), 4.90 (1H, s, C=CH_2), 5.00 (1H, q, J=1 Hz, C=CH_2), 6.98—7.07 (2H, m, ArH), 7.12—7.26 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.7 (q), 23.9 (q), 40.9 (q), 43.8 (t), 51.1 (d), 59.6 (s), 60.4 (d), 112.2 (t), 122.0 (d), 123.8 (d), 127.0 (d), 127.1 (d), 139.3 (s), 139.9 (s), 148.4 (s), 171.3 (s). MS m/z (rel. int. %): 273 (M^+, 25), 113 (100). IR (KBr) cm^{-1}: 1630 (C=O). *Anal.* Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12. Found: C, 70.25; H, 7.12; N, 5.19.

1-Methyl-4-vinyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one (**9b**): Colorless prisms (AcOEt–hexane). mp: 112—113 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (1H, ddd, J=5, 9, 13 Hz, 5-H), 2.34 (1H, ddd, J=1, 7, 13 Hz, 5-H), 2.85—2.95 (1H, br m, 4-H), 3.46 (3H, s, NMe), 4.11 (1H, d, J=3 Hz, 3-H), 4.60 (1H, dd, J=1, 5 Hz, 6-H), 5.02 (1H, dd, J=1, 10 Hz, CH=CH_2), 5.05 (1H, dd, J=1, 17 Hz, CH=CH_2), 5.83 (1H, ddd, J=8, 10, 17 Hz, CH=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 (rel. int. %): 245 (M^+, 36), 150 (100). IR (KBr) cm^{-1}: 1640 (C=O). *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.

1,4-Dimethyl-4-vinyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one (**9c**): Colorless prisms (AcOEt–hexane). mp: 116—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, s, 4-Me), 1.96 (1H, dd, J=2, 14 Hz, 5-H), 2.69 (1H, dd, J=9, 14 Hz, 5-H), 3.47 (3H, s, NMe), 3.88 (1H, s, 3-H), 4.46 (1H, dd, J=2, 9 Hz, 6-H), 5.10 (1H, d, J=17 Hz, CH=CH_2), 5.12 (1H, d, J=11 Hz, CH=CH_2), 6.03 (1H, dd, J=11, 17 Hz, CH=CH$_2$), 6.97—7.06 (2H, m, ArH), 7.18—7.27 (2H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 23.4 (q), 40.7 (q), 45.5 (t), 51.7 (d), 56.1 (s), 63.2 (d), 112.5 (t), 121.8 (d), 123.7 (d), 127.1 (d), 127.2 (d), 138.9 (s), 139.6 (s), 145.6 (d), 170.8 (s). MS m/z (rel. int. %): 261 (M^+, 65), 150 (100). IR (KBr) cm^{-1}: 1640 (C=O). *Anal.* Calcd for $C_{15}H_{17}NOS$: C, 69.46; H, 6.61; N, 5.40. Found: C, 69.60; H, 6.50; N, 5.51.

Reduction of Benzothiazepinium Salts 5 with Sodium Borohydride General Procedure: A suspension of a benzothiazepinium salt **5** (1 mmol) in EtOH (5 ml) was treated with $NaBH_4$ (38—42 mg, 1.0—1.1 mmol) at 0 °C. The mixture was stirred at room temperature for several hours, then water was added and the whole was extracted with CH_2Cl_2. The extracts were washed with water and saturated aqueous NaCl successively, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate : hexane (1 : 10). The reaction conditions and the results are summarized in Table 1.

MCPBA Oxidation of 9a to Give the Sulfoxide 10 A stirred solution of **9a** (408 mg, 1.5 mmol) in AcOEt (10 ml) was treated with MCPBA (303 mg, 85% purity, 1.5 mmol) in several portions at 0 °C. After 30 min, saturated aqueous $NaHCO_3$ was added to the reaction mixture. The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate : hexane (1 : 2) to give 4-isopropenyl-1,4-dimethyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one *S*-oxide (**10**) in 321 mg (74%) yield together with its diastereomer **10′** at the sulfoxide in 95 mg (22%) yield.

Compound **10**: Colorless prisms (CH_2Cl_2–hexane). mp: 218—221 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s, 4-Me), 1.86 (3H, s, vinylic Me), 2.41 (1H, dd, J=4, 15 Hz, 5-H), 3.00 (1H, dd, J=9, 15 Hz, 5-H), 3.52 (3H, s, NMe), 4.54 (1H, s, 3-H), 4.71 (1H, dd, J=4, 9 Hz, 6-H), 4.98, 5.01 (each 1H, s, C=CH_2), 7.08 (1H, d, J=7 Hz, ArH), 7.15 (1H, d, J=7 Hz, ArH), 7.33 (1H, d, J=7 Hz, ArH), 7.37 (1H, d, J=7 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 18.6 (q), 25.6 (q), 38.1 (t), 40.9 (q), 48.2 (s), 61.7 (d), 72.1 (d), 112.3 (t), 121.9 (d), 124.7 (d), 125.0 (s), 129.1 (d), 132.0 (d), 142.0 (s), 146.4 (s), 166.7 (s). MS m/z (rel. int. %): 289 (M^+, 100). IR (KBr) cm^{-1}: 1620 (C=O), 1060 (S-O). *Anal.* Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84. Found: C, 66.29; H, 6.68; N, 4.82.

Compound **10′**: Colorless prisms (CH_2Cl_2–hexane). mp: 184—188 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, s, 4-Me), 1.86 (3H, d, J=1.5 Hz, vinylic Me), 2.28 (1H, d, J=13 Hz, 5-H), 3.55 (3H, s, NMe), 3.72 (1H, dd, J=6, 13 Hz, 5-H), 4.66 (1H, s, 3-H), 4.67 (1H, br d, J=6 Hz, 6-H), 4.88 (1H, q, J=1.5 Hz, C=CH_2), 5.00 (1H, s, C=CH_2), 7.19 (1H, d, J=8 Hz, ArH), 7.18—7.37 (3H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 20.6 (q), 26.3 (q), 39.2 (q), 47.0 (t), 53.2 (s), 71.6 (d), 79.6 (d), 110.4 (t), 121.7 (d), 125.6 (d), 126.4 (s), 129.3 (d), 131.1 (d), 139.9 (s), 150.9 (s), 167.0 (s). MS m/z (rel. int. %): 289 (M^+, 83), 241 (100). IR (KBr) cm^{-1}: 1635 (C=O), 1045 (S-O). *Anal.* Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84. Found: C, 66.16; H, 6.68; N, 4.76

Alkylation of the 3,6-Epithiobenzazocinone Derivative 9a General Procedure: A stirred solution of **9a** (136 mg, 0.5 mmol) in THF (3 ml) was treated with *n*-BuLi (1.6 M in *n*-hexane, 0.5 ml, 0.8 mmol) at −78 °C under a nitrogen atmosphere. After 15 min at −78 °C, an alkyl halide (1.5 mmol) was added to the solution and the whole was stirred for 1—3 h. Saturated aqueous NH_4Cl was added to the reaction mixture and the organic layer was separated. The water layer was extracted with ethyl acetate. The organic layer and the extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate : hexane (1 : 10). The results are summarized in Chart 5.

4-Isopropenyl-1,3,4-trimethyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one (**12a**): Colorless prisms (AcOEt–hexane). mp: 120—123 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s, 4-Me), 1.42 (3H, s, 3-Me), 1.92 (3H, d, J=1 Hz, vinylic Me), 2.24 (1H, dd, J=3.5, 14 Hz, 5-H), 2.91 (1H, dd, J=10, 14 Hz, 5-H), 3.46 (3H, s, NMe), 4.23 (1H, dd, J=3.5, 10 Hz, 6-H), 4.85, 5.14 (each 1H, s, C=CH_2), 6.96—7.19 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.6 (q), 22.4 (q), 23.4 (q), 42.0 (q), 48.4 (t), 48.7 (d), 60.2 (s), 66.2 (s), 115.8 (t), 121.8 (d), 123.3 (d), 125.6 (d), 126.5 (d), 140.5 (s), 141.1 (s), 147.3 (s), 172.7 (s). MS m/z (rel. int. %): 287 (M^+, 32), 177 (100). IR (KBr) cm^{-1}: 1610 (C=O). *Anal.* Calcd for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36; N, 4.87. Found: C, 71.06; H, 7.37; N, 4.90.

3-Ethyl-4-isopropenyl-1,4-dimethyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one (**12b**): Colorless prisms (AcOEt–hexane). mp: 162—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz, CH_2CH_3), 1.17 (3H, s, 4-Me), 1.30 (1H, dq, J=14, 7 Hz, CH_2CH_3), 1.90 (3H, s, vinylic Me), 2.23 (1H, dd, J=3.5, 14 Hz, 5-H), 2.45 (1H, dq, J=14, 7 Hz, CH_2CH_3), 2.91 (1H, dd, J=10, 14 Hz, 5-H), 3.51 (3H, s, NMe), 4.21 (1H, dd, J=3.5, 10 Hz, 6-H), 4.84 (1H, s, C=CH_2), 5.15 (1H, s, C=CH_2), 6.98—7.19 (4H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 13.6 (q), 22.9 (q), 23.7 (q), 27.6 (t), 42.3 (q), 48.1 (d), 48.9 (t), 61.1 (s), 73.7 (s), 116.0 (t), 122.5 (d), 123.5 (d), 125.6 (d), 126.5 (d), 141.2 (s), 141.4 (s), 147.8 (s), 171.1 (s). MS m/z (rel. int. %): 301 (M^+, 35), 188 (100). IR (KBr) cm^{-1}: 1620 (C=O). *Anal.* Calcd for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69; N, 4.65. Found: C, 71.91; H, 7.80; N, 4.64.

Reduction of Benzothiazepinium Salts 5 with Samarium Diiodide General Procedure: A suspension of a benzothiazepinium salt **5** (1 mmol) in THF (5 ml) containing 0.6 ml of MeOH was treated with 0.1 M SmI_2 solution in THF[16] (30 ml, 3 mmol) at 0 °C under a nitrogen atmosphere. After 2 h at room temperature, concenrated HCl was added to the reaction mixture and the whole was extracted with ether. The extracts were washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and water successively, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by preparative TLC with ethyl acetate : hexane (1 : 10). The results are summarized in Chart 6.

6-[*o*-(*N*-Acetyl-*N*-methylamino)phenyl]-3,4-dimethyl-5,6-dihydro-2*H*-thiopyran (**13a**): Light yellow prisms as a 1 : 1 mixture of geometrical isomers (AcOEt). mp: 180—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.70, 1.79 (each 6H, s, Me×4), 1.77, 1.89 (each 3H, s, Me×2), 2.18, 2.25 (each 1H, br d, J=17 Hz, 5-H×2), 2.52—2.67 (total 2H, m, 5-H×2), 2.89 (total 2H, br d, J=17 Hz, 2-H×2), 3.19, 3.29 (each 3H, s, NMe×2), 3.41, 3.43 (each 1H, d, J=17 Hz, 2-H×2), 4.01, 4.02 (each 1H, dd, J=4, 8 Hz, 6-H×2), 7.16 (total 2H, d, J=8 Hz, ArH), 7.27—7.54 (total 6H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.3 (q), 19.4 (q), 20.3 (q×2), 22.3 (q), 22.5 (q), 33.4 (t), 33.4 (t), 36.8 (q), 37.0 (d), 37.2 (q), 37.3 (d), 39.5 (t), 40.7 (t), 123.4 (s), 123.5 (s), 127.2 (s×2), 128.0 (d), 128.2 (d), 128.6 (d×3), 128.8 (d), 129.1 (d), 129.2 (d), 139.7 (s), 140.0 (s), 141.9 (s), 142.0 (s), 170.7 (s), 171.6 (s). MS m/z (rel. int. %): 275 (M^+, 43), 150 (100). IR (KBr) cm^{-1}: 1660 (C=O). *Anal.* Calcd for $C_{16}H_{21}NOS$: C, 69.78; H, 7.69; N, 5.09. Found: C, 69.91; H, 7.63; N, 5.12.

6-[*o*-(*N*-Acetyl-*N*-methylamino)phenyl]-5,6-dihydro-2*H*-thiopyran (**13b**): Light yellow prisms as a 1 : 1 mixture of geometrical isomers (AcOEt). mp: 170—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.78, 1.91 (each 3H, s, Me×2), 2.30—2.42 (total 2H, m, 5-H×2), 2.54—2.71 (total 2H, m, 5-H×2), 3.04 (total 2H, br d, J=17 Hz, 2-H×2), 3.19, 3.30 (each 3H, s, NMe×2), 3.56, 3.61 (each 1H, dd, J=6, 17 Hz, 2-H×2), 4.04, 4.06 (each 1H, dd, J=4, 8 Hz, 6-H×2), 5.86 (total 4H, br s, 3-H×2, 4-H×2), 7.15—7.18 (total 2H, m, ArH), 7.29-7.54 (total 6H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 22.2 (q), 22.5 (q), 27.5 (t), 28.1 (t), 32.6 (t), 33.8 (t), 36.0 (d), 36.3 (d), 36.7 (q), 37.2 (q), 123.8 (d), 123.9 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.7 (d×3), 128.9 (d), 129.0 (d), 129.1 (d), 129.2 (d), 139.6 (s), 140.0 (s), 141.9 (s×2), 170.6 (s), 171.5 (s). MS m/z (rel. int. %): 247

(M^+, 92), 204 (100). IR (KBr) cm^{-1}: 1630 (C=O). *Anal.* Calcd for $C_{14}H_{17}NOS$: C, 63.13; H, 6.93; N, 5.66. Found: C, 63.25; H, 6.86; N, 5.72.

6-[*o*-(*N*-Acetyl-*N*-methylamino)phenyl]-4-methyl-5,6-dihydro-2*H*-thiopyran (**13c**): Light yellow prisms as a 1:1 mixture of geometrical isomers (AcOEt). mp: 176—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (total 6H, s, Me×2), 1.80, 1.91 (each 3H, s, Me×2), 2.18, 2.22 (each 1H, br d, J=17 Hz, 5-H×2), 2.48—2.60 (total 2H, m, 5-H×2), 3.03 (total 2H, dd, J=4, 17 Hz, 2-H×2), 3.20, 3.30 (each 3H, s, NMe×2), 3.50—3.56 (total 2H, m, 2-H×2), 4.03, 4.06 (each 1H, dd, J=4, 6 Hz, 6-H×2), 5.69 (total 2H, br s, 3-H×2), 7.15—7.18 (total 2H, m, ArH), 7.27—7.54 (total 6H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 22.6 (q), 22.8 (q), 24.9 (q), 25.0 (q), 28.5 (t×2), 36.9 (d), 37.1 (d), 37.2 (q), 37.6 (t), 37.9 (t), 39.0 (q), 118.2 (d), 118.3 (d), 128.4 (d), 128.5 (d), 128.9 (d), 129.0 (d×3), 129.2 (d), 129.4 (d), 129.5 (d), 135.5 (s×2), 139.9 (s), 140.3 (s), 142.2 (s×2), 171.1 (s), 171.9 (s). MS *m/z* (rel. int. %): 261 (M^+, 35), 150 (100). IR (KBr) cm^{-1}: 1660 (C=O). *Anal.* Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36. Found: C, 69.01; H, 7.30; N, 5.40.

X-Ray Study of 2,3,7-Trimethyl-1,1a,4,5,6-pentahydro-6-oxo-2*H*-thiopyrano[1,6-*d*]-4,1-benzothiazepinium Perchlorate (5a)[17] Crystal Data: $C_{16}H_{20}ClNO_5S$, M=373.85, monoclinic, a=9.309(2), b=10.998(2), c=16.996(1) Å, β=91.20(1)°, V=1739.7(4) Å^3, Z=4, D_c=1.427 g cm^{-3}, space group $P2_1/n$ (#14), F_{000}=784, MoK_α radiation, λ=0.71069 Å, μ_{MoK_α}=3.57 cm^{-1}.

Data Collection: A colorless prism of $C_{16}H_{20}ClNO_5S$ having approximate dimensions of 0.300×0.300×0.300 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated MoK_α radiation and a 12 kW rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range of $39.62<2\theta<42.85°$ corresponded to a monoclinic cell with dimensions: a=9.309(2) Å, b=10.998(2) Å, c=16.996(1) Å, β=91.20(1)°, V=1739.7(4) Å^3. For Z=4 and F.W.=373.85, the calculated density is 1.427 g cm^{-3}. Based on the systematic absences of $h01$: $h+1\neq 2n$, $0k0$: $k\neq 2n$, and the successful solution and refinement of the structure, the space group was determined to be: $P2_1/n$ (#14). The data were collected at a temperature of 23±1 °C using the ω–2θ scan technique to a maximum 2θ value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29° with a take-off angle of 6.0°. Scans of $(1.31+0.30\tan\theta)°$ were made at a speed of 4.0°/min (in omega). The weak reflections ($I<10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal-to-detector distance was 40 cm.

Data Reduction: Of the 4449 reflections which were collected, 3354 were unique (R_{int}=0.021). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection, indicating good crystal and electronic stability (no decay correction was applied). The linear absorption coefficient for MoK_α is 3.6 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods.[18] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement[19] was based on 2510 observed reflections ($I>3.00\sigma(I)$) and 278 variable parameters and converged (largest parameter shift was 0.14 times its estimated) with unweighted and weighted agreement factors of: $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$=0.081, $R_w=[(\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2)]^{1/2}$=0.108. The standard deviation of an observation of unit weight[20] was 3.84. The weighting scheme was based on counting statistics and included a factor (p=0.03) to downweight the intense reflections. Plots of $\Sigma w(|F_o|-|F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 1.01 and $-0.66e^-$/Å^3, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[21] Anomalous dispersion effects were included in F_{calc}[22] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[23] All calculations were performed using the TEXSAN[24] crystallographic software package of Molecular Structure Corporation.

X-Ray Study of 4-Isopropenyl-1,4-dimethyl-3,4,5,6-tetrahydro-3,6-epithiobenzazocin-2(1*H*)-one *S*-Oxide (10)[17] Crystal Data: $C_{16}H_{19}NO_2S$, M=289.39, monoclinic, a=11.539(2), b=10.160(3), c=12.441(2) Å, β=103.54(1)°, V=1418.1(5) Å^3, Z=4, D_c=1.355 g cm^{-3}, space group $P2_1/a$ (#14), F_{000}=616, MoK_α radiation, λ=0.71069 Å, μ_{MoK_α}=2.18 cm^{-1}.

Data Collection: A colorless prism of $C_{16}H_{19}NO_2S$ having approximate dimensions of 0.200×0.300×0.300 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated MoK_α radiation and a 12 kW rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 23 carefully centered reflections in the range of $48.19<2\theta<49.90°$ corresponded to a monoclinic cell with dimensions: a=11.539(2) Å, b=10.160(3) Å, c=12.441(2) Å, β=103.54(1)°, V=1418.1(5) Å^3. For Z=4 and F.W.=289.39, the calculated density is 1.355 g cm^{-3}. Based on the systematic absences of $h01$: $l\neq 2n$, $0k0$: $k\neq 2n$, and the successful solution and refinement of the structure, the space group was determined to be: $P2_1/a$ (#14). The data were collected at a temperature of 23±1 °C using the ω–2θ scan technique to a maximum 2θ value of 55.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.28° with a take-off angle of 6.0°. Scans of $(1.10+0.30\tan\theta)°$ were made at a speed of 2.0°/min (in omega). The weak reflections ($I<10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal-to-detector distance was 40 cm.

Data Reduction: Of the 3596 reflections which were collected, 3434 were unique (R_{int}=0.022). The intensities of three representative reflections, which were measured after every 150 reflections, remained constant throughout data collection, indicating good crystal and electronic stability (no decay correction was applied). The linear absorption coefficient for MoK_α is 2.2 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods.[18] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement[19] was based on 2637 observed reflections ($I>3.00\sigma(I)$) and 257 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of: $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$=0.036, $R_w=[(\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2)]^{1/2}$=0.045. The standard deviation of an observation of unit weight[20] was 1.90. The weighting scheme was based on counting statistics and included a factor (p=0.03) to downweight the intense reflections. Plots of $\Sigma w(|F_o|-|F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and $-0.37e^-$/Å^3, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[21] Anomalous dispersion effects were included in F_{calc}[22]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[23] All calculations were performed using the TEXSAN[24] crystallographic software package of Molecular Structure Corporation.

Acknowledgments This work was supported in part by a Grant from the Ministry of Education, Science, Sports and Culture.

References and Notes

1) Kataoka T., Tsutsumi K., Iwama T., Shimizu H., Hori M., *Tetrahedron Lett.*, **31**, 3027—3028 (1990); Kataoka T., Iwama T., Tsutsumi K., Nakamura Y., Matsumoto H., Shimizu H., Hori M., *J. Chem. Res. (S)*, **1992**, 393; *ibid.*, *(M)*, **1992**, 3153—3194.
2) Corey E. J., Walinsky S. W., *J. Am. Chem. Soc.*, **94**, 8932—8934 (1972); Ishibashi H., Kitano Y., Nakatani H., Okada M., Ikeda M., Okura M., Tamura Y., *Tetrahedron Lett.*, **25**, 4231—4232 (1984); Ishibashi H., Kitano Y., Nakatani H., Ikeda M., Tamura Y., *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1763—1767.
3) Shimizu H., Miyazaki S., Kataoka T., Hori M., *Tetrahedron Lett.*, **32**, 5571—5574 (1991); *idem*, *J. Chem. Soc., Chem. Commun.*, **1992**, 1586—1587; *idem*, *J. Chem. Soc. Perkin Trans. 1*, **1995**, 1583—1589.
4) Kataoka T., Nakamura Y., Matsumoto H., Iwama T., Kondo K., Shimizu H., Muraoka O., Tanabe G., *J. Chem. Soc., Perkin Trans. 1*, **1997**, in press.

5) Fujita M., Ito S., Ota A., Kato N., Yamamoto K., Kawashima Y., Yamauchi H., Iwao J., *J. Med. Chem.*, **33**, 1898—1905 (1990); Ota A., Suhara H., Kawashima Y., *Chem. Pharm. Bull.*, **40**, 833—836 (1992).
6) Aotsuka T., Hosono H., Kurihara T., Nakamura Y., Matsui T., Kobayashi F., *Chem. Pharm. Bull.*, **42**, 1264—1271 (1994).
7) Kugita H., Inoue H., Ikezaki M., Konda M., Takeo S., *Chem. Pharm. Bull.*, **19**, 595—602 (1971); Inoue H., Takeo S., Kuwazu M., Kugita H., *Yakugaku Zasshi*, **93**, 729—732 (1973); Abe K., Inoue H., Nagao T., *ibid.*, **108**, 716—732 (1988).
8) Krapcho J., Spitzmiller E. R., Turk C. F., *J. Med. Chem.*, **6**, 544—546 (1963); Krapcho J., Turk C. F., Piala J. J., *Phosphorus Sulfur*, **11**, 361—364 (1968).
9) Inoue H., Konda M., Higashiyama T., Ohtsuka H., Takahashi K., Gaino M., Date T., Abe K., Takeda M., Murata S., Narita H., Nagao T., *J. Med. Chem.*, **34**, 675—687 (1991); Slade J., Stanton J. L., Ben-David D., Mazzenga G. C., *ibid.*, **28**, 1517—1521 (1985); Ohno S., Mizukoshi K., Izumi K., Kato K., Hori M., *Chem. Pharm. Bull.*, **36**, 551—562 (1988).
10) Kataoka T., Nakamura Y., Matsumoto H., Iwama T., Shimizu H., *Heterocycles*, **38**, 1733—1736 (1994).
11) Watthey J. W. H., Gavin T., Desai M., *J. Med. Chem.*, **27**, 816—818 (1984); Watthey J. W. H., Stanton J. L., Desai M., Babiarz J. E., Finn B. M., *J. Med. Chem.*, **28**, 1511—1516 (1985).
12) Hill R. K., Cullison D. A., *J. Am. Chem. Soc.*, **95**, 2923—2927 (1973).
13) Imamoto T., Yokoyama H., Yokoyama M., *Tetrahedron Lett.*, **22**, 1803—1804 (1981).
14) Hori M., Kataoka T., Shimizu H., Tsutsumi K., *Tetrahedron Lett.*, **30**, 981—984 (1989); Kataoka T., Tsutsumi K., Kano K., Mori K., Miyake M., Yokota M., Shimizu H., Hori M., *J. Chem. Soc., Perkin Trans. 1*, **1990**, 3017—3025.
15) Kataoka T., Iwama T., Shimizu H., Hori M., *Phosphorus Sulfur*, **67**, 169—172 (1992).
16) Girard P., Namy J. L., Kagan H. B., *J. Am. Chem. Soc.*, **102**, 2693—2698 (1980).
17) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.
18) Structure solution methods: MITHRIL: Gilmore C. J., MITHRIL—an integrated direct methods computer program. *J. Appl. Crystallogr.*, **17**, 42—46, Univ. of Glasgow, Scotland, 1984. DIRDIF: Beurskens P. T., DIRDIF: direct methods for difference structures—an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed. Nijmegen, Netherlands.
19) Least-squares function minimized: $\Sigma w(|F_o|-|F_c|)^2$, where $w=4F_o^2/\sigma^2(F_o^2)$, $\sigma^2(F_o^2)=[S^2(C+R^2B)+(pF_o^2)^2]/Lp^2$, S=scan rate, C=total integrated peak count, R=ratio of scan time to background counting time, B=total background count, Lp=Lorentz-polarization factor, p=p-factor.
20) Standard deviation of an observation of unit weight: $[\Sigma w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}$, where: N_o=number of observations, N_v=number of variables.
21) Cromer D. T., Waber J. T., "International Tables for X-ray Crystallography," Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A, 1974.
22) Ibers J. A., Hamilton W. C., *Acta Crystallogr.*, **17**, 781—782 (1964).
23) Cromer D. T., "International Tables for X-ray Crystallography," Vol. IV, The Kynoch Press, Birmingham, England, Table 2.3.1, 1974.
24) TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).