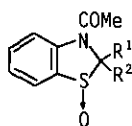
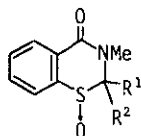
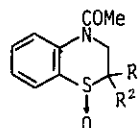


RING TRANSFORMATION OF SEVEN-MEMBERED HETEROCYCLIC SULFOXIDES,
2,2-DISUBSTITUTED 1,4- AND 1,5-BENZOTHAIAZEPINE SULFOXIDES

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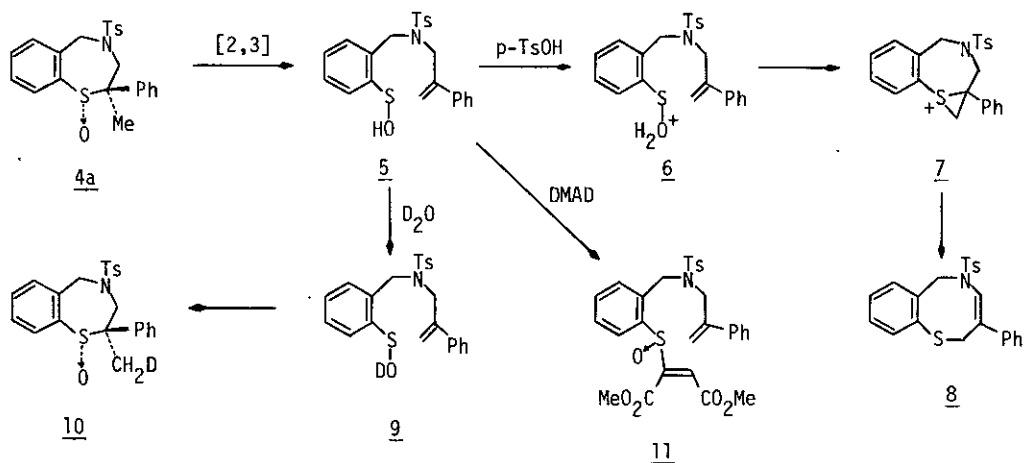
Abstract—— Thermal ring transformations of 2-methyl-2-phenyl-1,4- and 1,5-benzothiazepine 1-oxides in the presence of catalytic amount of p-toluenesulfonic acid are described. trans-Sulfoxides (having methyl group cis to the sulfoxide oxygen) underwent ring expansion to afford benzothiazocine derivatives, whereas cis isomers interestingly afforded ring contraction products, indicating that the ring transformations proceeded stereospecifically.

In our earlier papers,¹ we reported that benzothiazoline sulfoxides (1) or 1,3-benzothiazine sulfoxides (2) underwent non-stereospecific ring expansion via the mechanism involving sulfonium intermediate, and gave the corresponding benzothiazines or benzothiazepines, respectively, whereas 1,4-benzothiazine sulfoxides (3) did stereospecific ring expansion (via 2,3-sigmatropic rearrangement) to give benzothiazepines. The important factor for the stereospecificity of these ring expansions was proved to be the position of nitrogen atom relative to the sulfoxide moiety.

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In this communication, we wish to report the novel ring expansion or ring contraction reaction of seven-membered cyclic sulfoxides, 1,4- and 1,5-benzothiazepine sulfoxides and moreover, the stereospecificity of the reactions.

Refluxing of trans-2-methyl-2-phenyl-4-p-tosyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide (4a)^{2,3} in benzene for 10 h in the presence of 0.1 eq of p-toluenesulfonic acid (p-TsOH) caused ring expansion to afford 3-phenyl-5-p-tosyl-5,6-dihydro-2H-1,5-benzothiazocine (8) in 73% yield: colorless prisms (EtOH); mp 163.5-165.5 °C; ir (KBr) ν max cm^{-1} 1340, 1160 (SO_2); MS (m/e) 407 (M^+); ^1H -nmr (CDCl_3) δ 2.47 (3H, s, Me), 3.62 (2H, s, C_2 -2H), 4.92 (2H, s, C_6 -2H), 6.44 (1H, s, C_4 -H), 7.07-7.80 (13H, m, ArH). On refluxing a benzene solution for 24 h without acid catalyst, 4a was recovered unchanged in 91% yield. In order to examine the mechanism of the above ring expansion, the following experiments were carried out. When the sulfoxide (4a) was refluxed with a large excess of deuterium oxide in benzene for 5 h, deuterated sulfoxide (10) was obtained in 30% yield. This result indicates the formation of sulfenic acid (5) upon heating in benzene. The deuterium incorporation experiment of this type has been reported by Cooper et al. as the proof of the equilibrium between sulfoxide and sulfenic acid in penicillin sulfoxide chemistry.⁴ The sulfenic acid (5) was, in fact, trapped by the reaction with an electrophile. Refluxing of a solution of 4a and dimethyl acetylene-

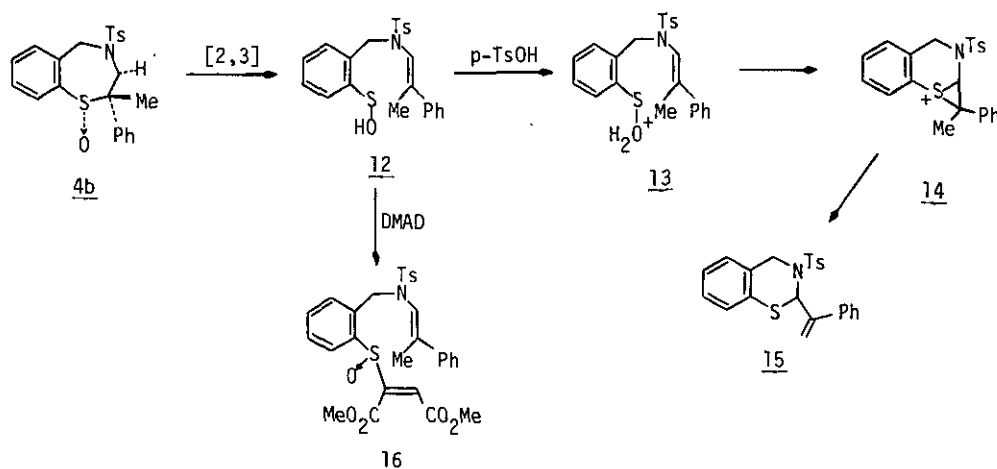


Scheme I

dicarboxylate (DMAD) in toluene for 2 h gave 89% yield of 1:1-adduct (11) as a white powder (hexane-dichloromethane): mp 112-114 °C; ir (KBr) ν max cm^{-1} 1730 (ester), 1340, 1160 (SO_2); MS (m/e) 567 (M^+); ^1H -nmr (CDCl_3) δ 2.38 (3H, s, Me), 3.55 (3H, s, OMe), 3.80 (3H, s, OMe), 4.30 (2H, ABq, $J=14.3$ Hz, CH_2), 4.53 (2H,

AB q, $J=16.5$ Hz, CH_2), 5.15 (1H, s, $=\text{C}-\text{H}$), 5.39 (1H, s, $=\text{C}-\text{H}$), 6.99 (1H, s, $=\text{CHCO}_2\text{Me}$), 7.05-7.95 (13H, m, ArH). From these results the ring expansion of 4a to 8 may be explained by the mechanism involving the sulfenic acid intermediate (5) generated by 2,3-sigmatropic rearrangement of the sulfoxide (4a) as shown in Scheme I. The intermediate (5) is protonated by p-TsOH to form 6 which recycles to give episulfonium ion intermediate (7). Collapse of 7 leads to the ring expansion product (8).

On the contrary, cis-sulfoxide (4b)² (having methyl group trans to the sulfoxide oxygen) afforded quite different results. Refluxing of 4b in benzene for 14 h in the presence of 0.1 eq of p-TsOH resulted in the recovery of 4b (80%) and gave ring contraction product, 2-(1-phenylvinyl)-3-p-tosyl-2,3-dihydro-4H-1,3-benzothiazine (15) as colorless prisms (EtOH) in 17% yield: mp 147-148 °C; ir (KBr) ν_{max} cm^{-1} 1340, 1160 (SO_2); MS (m/e) 407 (M^+); ^1H -nmr (CDCl_3) δ 2.30 (3H, s, Me), 4.37 (2H, AB q, $J=16.4$ Hz, CH_2), 5.54 (1H, d, $J=0.5$ Hz, $=\text{C}-\text{H}$), 5.56 (1H, d, $J=0.5$ Hz, $=\text{C}-\text{H}$), 6.41 (1H, s, C_2-H), 6.86-7.54 (13H, m, ArH). The yield of 15 was raised up to 34% when the refluxing was continued for 3 days. Treatment of 4b with DMAD in refluxing toluene for 10 h gave 1:1-adduct (16) as a white powder (hexane-dichloromethane) in 92% yield: mp 101-103 °C; ir (KBr) ν_{max} cm^{-1} 1740 (ester), 1350, 1170 (SO_2), 1080 (SO); MS (m/e) 567 (M^+); ^1H -nmr (CDCl_3) δ 1.99 (3H, d, $J=1.5$ Hz, Me), 2.48 (3H, s, Me), 3.53 (3H, s, OMe), 3.80 (3H, s, OMe), 4.69 (2H, s,



Scheme 11

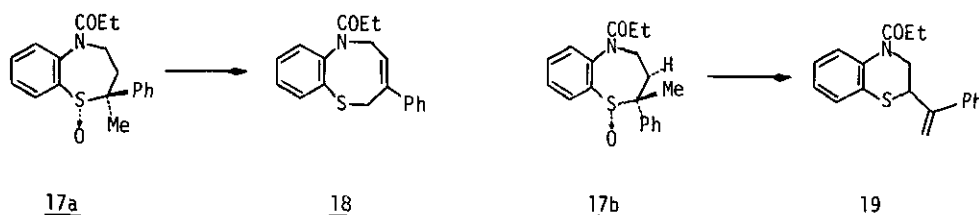
CH₂), 5.63 (1H, d, J=1.5 Hz, CH), 6.98 (1H, s, =CHCO₂Me), 7.15-7.98 (13H, m, ArH).

Formation of the compound (16) is reasonably explained by the mechanism that the sulfoxide (4b) initially undergoes thermal 2,3-sigmatropic rearrangement to give sulfenic acid (12) which was subsequently trapped with DMAD. The 2,3-sigmatropic rearrangement of 2-methyl group of 4b is highly retarded because of its trans configuration, indicating the recovery of large amounts of 4b and as a result, other β-proton, namely one of C₃-protons of the ring which occupies syn position with the sulfoxide oxygen, undergoes 2,3-sigmatropy (probably higher energy is necessary for the rearrangement compared to that of cis-methyl group as in the case of 4a) to give 12. Thus, the formation of the ring-contracted product (15) is explained by the mechanism via the intermediate (12) as depicted in Scheme II.

We next examined the ring transformation of 1,5-benzothiazepine sulfoxides. Refluxing of trans-2-methyl-2-phenyl-5-propionyl-2,3,4,5-tetrahydro-1,5-benzothiazepine 1-oxide (17a)⁵ in benzene for 10 h in the presence of 0.1 eq of p-TsOH afforded ring-expanded product (18) as colorless prisms (EtOH) in 57% yield: mp 117-118 °C; ir (KBr) ν max cm⁻¹ 1640 (CO); MS (m/e) 309 (M⁺); ¹H-nmr (CDCl₃) δ 1.13 (3H, dd, J=7.6, 7.3 Hz, CH₂CH₃), 1.93-2.24 (2H, m, CH₂CH₃), 3.42 (1H, d, J=12.7 Hz, C₂-H), 3.70 (1H, dd, J=15.6, 6.4 Hz, C₅-H), 4.39 (1H, d, J=12.7 Hz, C₂-H), 5.67 (1H, dd, J=15.6, 3.4 Hz, C₄-H), 5.75 (1H, dd, J=6.4, 3.4 Hz, C₄-H), 7.14-7.39 (9H, m, ArH). On the other hand, cis-sulfoxide (17b)⁵ afforded 10% yield of ring-contracted product (19) along with the recovery of 17b (81%) just as in the case of the cis-sulfoxide (4b), after refluxing in benzene for 20 h with 0.1 eq of p-TsOH. 19: colorless oil; ir (neat) ν max cm⁻¹ 1660 (CO); MS (m/e) 309 (M⁺); ¹H-nmr (CDCl₃) δ 1.13 (3H, dd, J=7.6, 7.3 Hz, CH₂CH₃), 2.37-2.52 (2H, m, CH₂CH₃), 3.05-3.30 (1H, m, C₃-H), 4.69-4.90 (2H, m, C₂-H, C₃-H), 5.48 (1H, s, olefinic H), 5.51 (1H, s, olefinic H), 7.05-7.49 (9H, m, ArH). In the thermal ring transformation of 1,5-benzothiazepine sulfoxides we also observed the corresponding sulfenic acid intermediates by the deuterium-incorporation experiments as mentioned in the case of the sulfoxide (4). Consequently, the ring expansion and contraction reactions of the 1,5-benzothiazepine sulfoxides could be explained by the mechanism involving sulfenic acid intermediates similar to those of 4.

From the present studies described above, it was clarified that the seven-membered cyclic sulfoxides containing nitrogen atom at γ-, or δ-position relative to sulfur atom underwent ring transformation stereospecifically.

The ring transformation reactions of benzothiazepine sulfoxide derivatives contain-



Scheme III

ing heteroatom at β -position are now under way.

REFERENCES AND NOTES

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 - H. Shimizu, N. Ueda, T. Kataoka, and M. Hori, *Chem. Pharm. Bull.*, 1984 in press.
- The sulfoxide (4) was prepared via four steps from 2-phenyl-3,5-dioxo-2,3,4,5-tetrahydro-1H-1,4-benzothiazepine synthesized by the reaction of thiosalicylamide with α -chlorophenylacetyl chloride. The separation of the cis (4b) and trans isomers (4a) was performed by column chromatography on silica gel using ethyl acetate-hexane (1:1). The configurational assignments of cis-trans stereoisomers were achieved by nmr spectral analysis. The details will be reported in a full paper.
4a: mp 157-158 °C (dec); ir (KBr) ν max cm^{-1} 1330, 1150 (SO_2), 1030 (SO); MS (m/e) 425 (M^+); ^1H -nmr (CDCl_3) δ 1.45 (3H, s, $\text{C}_2\text{-Me}$), 2.42 (3H, s, Me), 4.08 (2H, s, $\text{C}_3\text{-2H}$), 4.49 (2H, AB q, $J=15$ Hz, $\text{C}_5\text{-2H}$), 7.1-7.87 (12H, m, ArH), 7.9 (1H, m, ArH). 4b: mp 168-169 °C (dec); ir (KBr) ν max cm^{-1} 1330, 1160 (SO_2), 1030 (SO); MS (m/e) 425 (M^+); ^1H -nmr (CDCl_3) δ 1.58 (3H, s, $\text{C}_2\text{-Me}$), 2.49 (3H, s, Me), 4.27 (2H, AB q, $J=14.3$ Hz, $\text{C}_3\text{-2H}$), 4.84 (2H, AB q, $J=15$ Hz, $\text{C}_5\text{-2H}$), 7.10-7.93 (13H, m, ArH).
- All new compounds had satisfactory analytical data to support the assignment.
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- The sulfoxide (17) was prepared through four steps from 2-phenyl-4-oxo-2,3,4,5-tetrahydro-5H-1,5-benzothiazepine,⁶ and two stereoisomers (17a and 17b) were

separated by column chromatography.

17a: mp 129-130 °C; ir (KBr) ν max cm^{-1} 1680 (CO), 1040 (SO); MS (m/e) 327 (M^+); ^1H -nmr (CDCl_3) δ 1.10 (3H, t, $J=7.5$ Hz, CH_2CH_3), 1.38 (3H, s, $\text{C}_2\text{-Me}$), 1.5-3.5 (5H, m, CH_2CH_3 , $\text{C}_3\text{-2H}$, $\text{C}_4\text{-H}$), 4.38-4.88 (1H, m, $\text{C}_4\text{-H}$), 7.0-7.55 (8H, m, ArH), 7.55-8.05 (1H, m, ArH). 17b: mp 144-146 °C; ir (KBr) ν max cm^{-1} 1680 (CO), 1040 (SO); MS (m/e) 327 (M^+); ^1H -nmr (CDCl_3) δ 1.05 (3H, t, $J=7.5$ Hz, CH_2CH_3), 1.88 (3H, s, $\text{C}_2\text{-Me}$), 1.65-3.45 (5H, m, CH_2CH_3 , $\text{C}_3\text{-2H}$, $\text{C}_4\text{-H}$), 4.4-5.08 (1H, m, $\text{C}_4\text{-H}$), 6.83-7.85 (9H, m, ArH).

6 W. H. Mills and J. B. Whitworth, J. Chem. Soc., 1927, 2738.

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