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

Hiroshi Shimizu, Norihiro Ueda, Tadashi Kataoka, and Mikio Hori[*]

Gifu College of Pharmacy, 6-1, Mitahora-higashi 5-chome,

Gifu 502, Japan

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 benzo-
thiazines 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 sul-
foxide moiety.
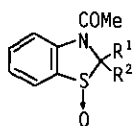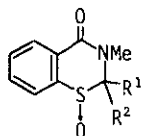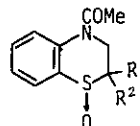
| 1 | 2 | 3 |

In this communication, we wish to report the novel ring expansion or ring contrac-
tion 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-benzo-thiazepine 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$^+$); ^{1}H-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-
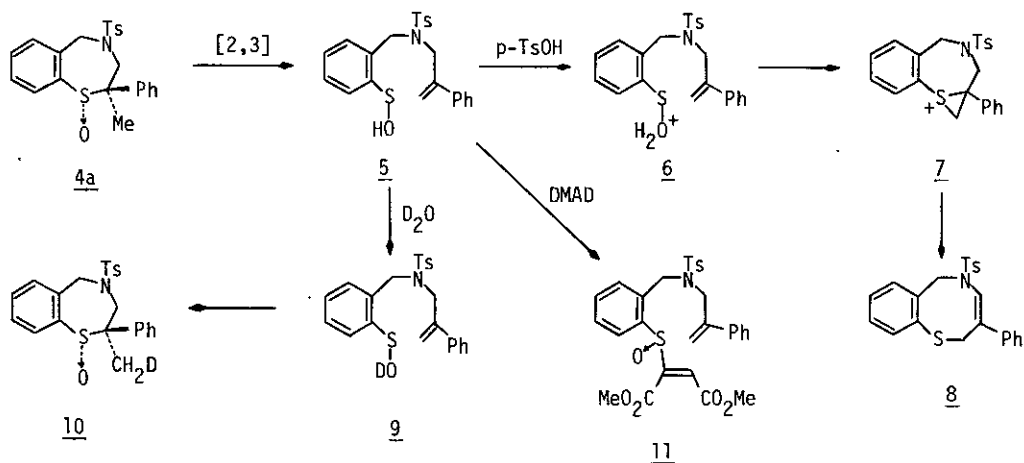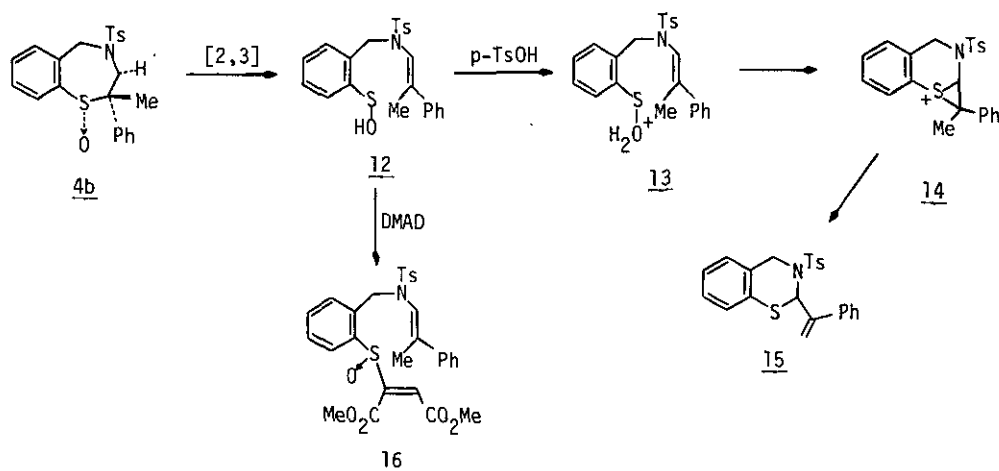

Scheme I

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$^+$); ^{1}H-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, =C$_H^H$), 5.39 (1H, s, =C$_H^H$), 6.99 (1H, s,

=CHCO$_2$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 recyclizes

to give episulfonium ion intermediate (**7**). Collapse of **7** leads to the ring expan-

sion 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-benzo-

thiazine (**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$^+$); ^{1}H-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, =C$_H$), 5.56 (1H, d, J=0.5

Hz, =C$_H^H$), 6.41 (1H, s, C$_2$-H), 6.86-7.54 (13H, m, ArH). The yield of **15** was rais-

ed 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$^+$); ^{1}H-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,
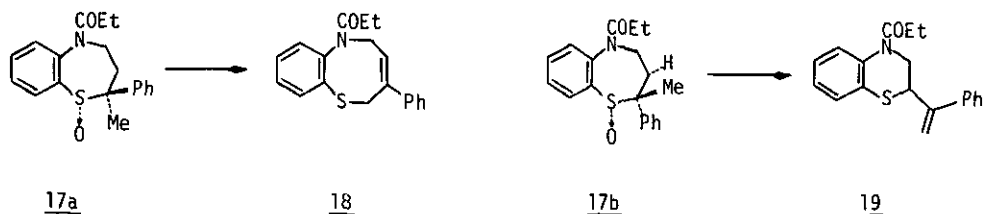

Scheme II

CH$_2$), 5.63 (1H, d, J=1.5 Hz, CH), 6.98 (1H, s, =C<u>H</u>CO$_2$Me), 7.15-7.98 (13H, m, ArH).

Formation of the compound (<u>16</u>) is reasonably explained by the mechanism that the sulfoxide (<u>4b</u>) initially undergoes thermal 2,3-sigmatropic rearrangement to give sulfenic acid (<u>12</u>) which was subsequently trapped with DMAD. The 2,3-sigmatropic rearrangement of 2-methyl group of <u>4b</u> is highly retarded because of its trans configuration, indicating the recovery of large amounts of <u>4b</u> and as a result, other β-proton, namely one of C$_3$-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 <u>4a</u>) to give <u>12</u>. Thus, the formation of the ring-contracted product (<u>15</u>) is explained by the mechanism via the intermediate (<u>12</u>) 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-benzo-thiazepine 1-oxide (<u>17a</u>)[5] in benzene for 10 h in the presence of 0.1 eq of p-TsOH afforded ring-expanded product (<u>18</u>) as colorless prisms (EtOH) in 57% yield: mp 117-118 °C; ir (KBr) ν max cm^{-1} 1640 (CO); MS (m/e) 309 (M$^+$); [1]H-nmr (CDCl$_3$) δ 1.13 (3H, dd, J=7.6, 7.3 Hz, CH$_2$C<u>H</u>$_3$), 1.93-2.24 (2H, m, C<u>H</u>$_2$CH$_3$), 3.42 (1H, d, J=12.7 Hz, C$_2$-H), 3.70 (1H, dd, J=15.6, 6.4 Hz, C$_5$-H), 4.39 (1H, d, J=12.7 Hz, C$_2$-H), 5.67 (1H, dd, J=15.6, 3.4 Hz, C$_4$-H), 5.75 (1H, dd, J=6.4, 3.4 Hz, C$_4$-H), 7.14-7.39 (9H, m, ArH). On the other hand, cis-sulfoxide (<u>17b</u>)[5] afforded 10% yield of ring-contracted product (<u>19</u>) along with the recovery of <u>17b</u> (81%) just as in the case of the cis-sulfoxide (<u>4b</u>), after refluxing in benzene for 20 h with 0.1 eq of p-TsOH. <u>19</u>: colorless oil; ir (neat) ν max cm^{-1} 1660 (CO); MS (m/e) 309 (M$^+$); [1]H-nmr (CDCl$_3$) δ 1.13 (3H, dd, J=7.6, 7.3 Hz, CH$_2$C<u>H</u>$_3$), 2.37-2.52 (2H, m, C<u>H</u>$_2$CH$_3$), 3.05-3.30 (1H, m, C$_3$-H), 4.69-4.90 (2H, m, C$_2$-H, C$_3$-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 (<u>4</u>). 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 <u>4</u>.

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

1 a) M. Hori, T. Kataoka, H. Shimizu, and N. Ueda, Tetrahedron Lett., 1981, 1701.

   b) H. Shimizu, N. Ueda, T. Kataoka, and M. Hori, Chem. Pharm. Bull., 1984 in

   press.

2 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 thiosalicyl-

   amide 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 re-

   ported 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^+); ^{1}H-nmr $(CDCl_3)$ δ 1.45 (3H, s, C_2-Me), 2.42 (3H, s, Me), 4.08

   (2H, s, C_3-2H), 4.49 (2H, AB q, J=15 Hz, C_5-2H), 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^+); ^{1}H-nmr $(CDCl_3)$ δ 1.58 (3H, s, C_2-Me), 2.49 (3H,

   s, Me), 4.27 (2H, AB q, J=14.3 Hz, C_3-2H), 4.84 (2H, AB q, J=15 Hz, C_5-2H),

   7.10-7.93 (13H, m, ArH).

3 All new compounds had satisfactory analytical data to support the assignment.

4 R. D. G. Cooper, J. Am. Chem. Soc., 1970, 92, 5010.

5 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^{+}); ^{1}H-nmr (CDCl$_{3}$) δ 1.10 (3H, t, J=7.5 Hz, CH$_{2}$CH$_{3}$), 1.38 (3H, s, C$_{2}$-Me), 1.5-3.5 (5H, m, CH$_{2}$CH$_{3}$, C$_{3}$-2H, C$_{4}$-H), 4.38-4.88 (1H, m, C$_{4}$-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^{+}); ^{1}H-nmr (CDCl$_{3}$) δ 1.05 (3H, t, J=7.5 Hz, CH$_{2}$CH$_{3}$), 1.88 (3H, s, C$_{2}$-Me), 1.65-3.45 (5H, m, CH$_{2}$CH$_{3}$, C$_{3}$-2H, C$_{4}$-H), 4.4-5.08 (1H, m, C$_{4}$-H), 6.83-7.85 (9H, m, ArH).

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