THERMAL RING TRANSFORMATION OF 2,2-DISUBSTITUTED BENZOTHIAZOLINE 1-OXIDES

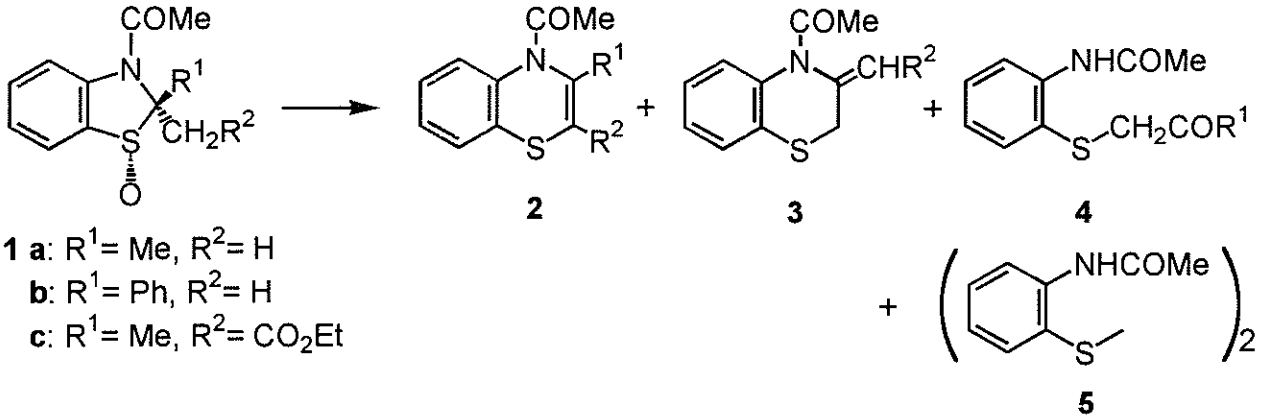
Hiroshi Shimizu,[a]* Michiko Kanematsu,[a] Kiyomi Hashimoto,[a] and Kazuhiro Kobayashi[b]

[a] *Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502-8585, Japan*
[b] *Taiho Pharmaceutical Co. Ltd., Hanno Research Center, 1-27, Misugidai, Hanno, Saitama 357-0041, Japan*

Abstract - Thermal rearrangement of 2,2-disubstituted benzothiazoline 1-oxides (**1**) in aprotic solvent afforded the corresponding 1,4-benzothiazines (**2**) and (**3**). The thermal reaction performed in the presence of electron-deficient acetylenic compounds produced new tricyclic compounds (**7**) whose structures have been established by an X-Ray crystal structure determination.

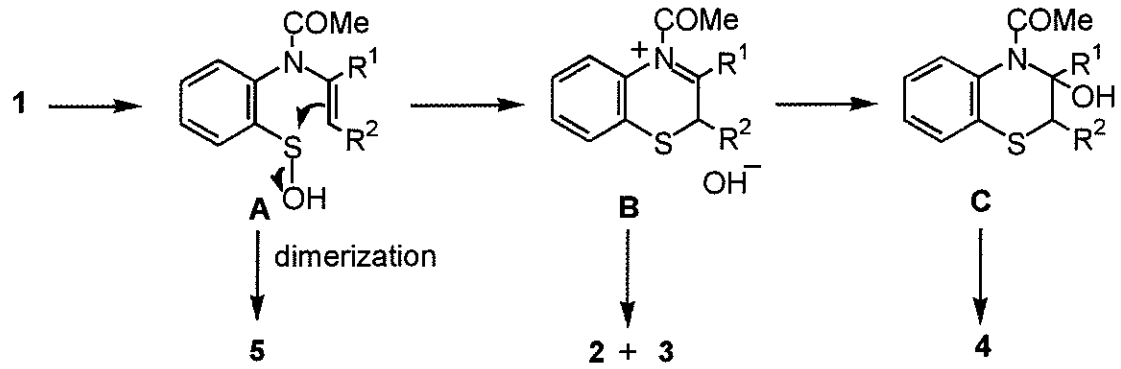
In our earlier papers, we reported the novel ring expansion reactions of benzothiazoline 1-oxides to benzothiazine derivatives by treatment with acetic anhydride.[1] Prota *et al.* also independently reported the similar ring expansion reactions by using a strong acid catalyst such as *p*-toluenesulfonic acid.[2] It was further clarified that above ring transformation needed electrophilic catalysts and proceeded non-stereospecifically to the sulfoxide geometry *via* sulfonium intermediate. Thus, it becomes very interesting to make the ring expansion to proceed without any electrophilic catalysts as above, because Prota *et al.* , in their report, described that attempts to achieve the ring expansion of benzothiazoline sulfoxides by thermal rearrangement in aprotic solvent were unsuccessful, although the analogous ring expansion of 1,3-dithiolane 1-oxides into dihydro-1,4-dithiins under thermal conditions were successful.[3] We now report the thermal rearrangement of several 2,2-disubstituted benzothiazoline 1-oxides to benzothiazines under the conditions of refluxing the sulfoxides in aprotic solvents such as xylene.

3-Acetyl-2,2-dimethylbenzothiazoline 1-oxide (**1a**) was refluxed in anhydrous xylene for 4.5 h and the reaction mixture was purified by preparative thin layer chromatography on silica gel to afford two types of ring expansion products, 4-acetyl-3-methyl-4*H*-1,4-benzothiazine (**2a**) and 4-acetyl-3-methylene-2,3-dihydro-4*H*-1,4-benzothiazine (**3a**) in yields of 22 and 10 %, respectively together with ring-opened products (**4a**, 23%) and (**5**, 16%). Similarly, *trans*-3-acetyl-2-methyl-2-phenylbenzothiazoline 1-oxide (**1b**) underwent thermal rearrangement to yield 4-acetyl-3-phenyl-4*H*-1,4-benzothiazine (**2b**) in 58% yield with a small amount of ring-opened product (**4b**, 4%). *cis*-3-Acetyl-2-ethoxycarbonylmethyl-2-methylbenzothiazoline 1-oxide (**1c**) also afforded 4-acetyl-2-ethoxycarbonyl-3-methylbenzothiazine (**2c**) in 49% yield together with (**5**, 5%). These ring transformation is believed to proceed *via* the mechanism proposed for the well-documented example, the penam-cephem conversion of penicillin



Scheme 1

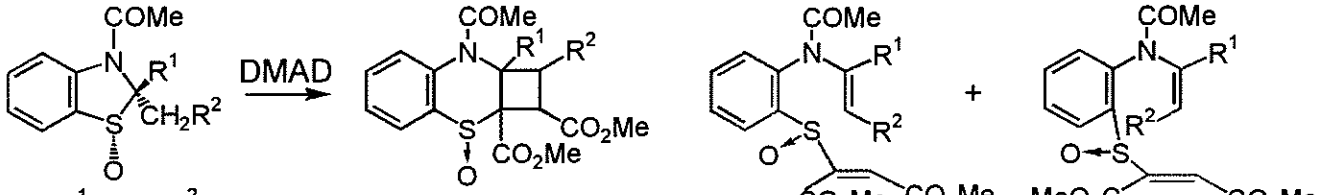
S-oxides;[4] the initial step of this reaction apparently is the thermal ring opening to a sulfenic acid intermediate (**A**) *via* an assumed β-*cis*-elimination process (Scheme 2). The subsequent electrophilic



Scheme 2

addition of the sulfenic acid to the olefinic center occurs to lead to the formation of six-membered ring intermediate (**B**), which is stabilized by a nitrogen atom substituent on the olefinic center. The intermediates (**A**) dimerizes to give the product (**5**), and the intermediate (**B**) leads to 1,4-thiazines (**2**) and (**3**). The intermediate (**B**) also affords a ring-opened product (**4**) *via* the intermediate (**C**).

We next focused our attention on the intermolecular addition of the assumed sulfenic acid intermediate (**A**) to the acetylenic compounds such as dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate (MP), and found the novel ring formation reaction along with the expected addition reaction. Thus, refluxing a mixture of sulfoxide (**1a**) and 1.5 eq of DMAD in xylene for 2 h afforded 1:1-adduct (**7a**) as a new ring system, mp 166-167 °C as colorless prisms in 54% yield. Microanalytical and MS spectral data (M^+, *m/z* 365) indicated a molecular formula $C_{17}H_{19}NO_6S$ for this new compound.[5] It showed ^{1}H-NMR peaks at δ 2.65 and 2.99 attributable to each of the two different methylene protons of four-membered ring as doublet of doublet signals, respectively, and at δ 3.95 due to methine proton as doublet of doublet (J= 4.7 and 13.3 Hz). The ^{13}C-NMR spectrum showed two sp^3 quaternary carbon signals at δ 64.2 and 74.3, which are assignable to the two carbons of 1,4-thiazine skeleton, respectively, and sp^3 secondary and tertiary carbon signals assigned to methylene and methine carbons of four-membered ring at δ 35.4 and 36.6, respectively. Similarly, *trans*-3-acetyl-2-ethoxycarbonylmethyl- (or 2-methoxycarbonylmethyl-) 2-methylthiazoline 1-oxide (**1d**) or (**1e**) gave the corresponding tricyclic



1 a: R^1= Me, R^2= H
d: R^1= CH_2CO_2Et, R^2= H
e: R^1= CH_2CO_2Me, R^2= H
f: R^1= Me, R^2= CO_2Me
g: R^1= CH_2Ph, R^2= Ph

7 **8** **9**

Scheme 3

compound (**7d**) or (**7e**) in 59% or 56% yield, respectively, on refluxing in toluene for 7 h, while *cis*-sulfoxide (**1f**) afforded only addition products (**8f**) and (**9f**) in 57% and 47% yields, respectively under similar conditions. The structures of the compounds (**7**) were confirmed by an X-Ray analysis of **7d** (Figure 1). Crystallographic data are summarized in Table 1. Selected bond distances and angles are provided with an ORTEP drawing in Figure 1. 2,2-Dibenzyl substituted sulfoxide (**1g**), unfortunately,

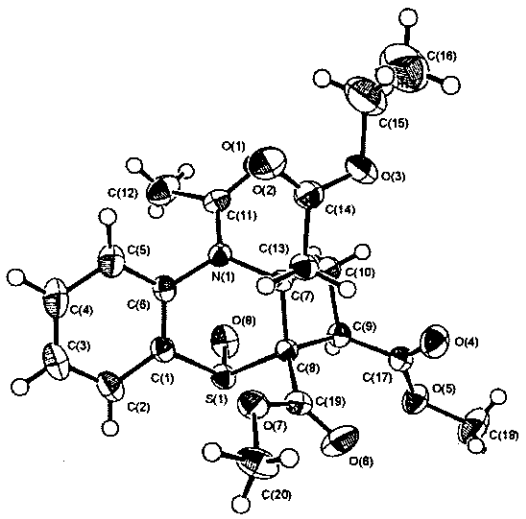


Figure 1. Molecular structure of compound (**7d**). Selected bond distances (Å) and angles (°) are: S(1)-O(8)=1.480 (3), S(1)-C(8)=1.862(3), N(1)-C(6)=1.423(4), N(1)-C(7)= 1.482(4), N(1)-C(11)=1.385(4), C(7)-C(8)=1.581(4), C(7)-C(10)=1.549(4), C(7)-C(13)=1.531(4), C(8)-C(9)=1.558 (4), C(9)-C(10)=1.540(5), O(8)-S(1)-C(1)=107.9(2), O(8)-S(1)-C(8)=107.1(2), C(1)-S(1)-C(8)=95.0(2), S(1)-C(8)-C(7)=114.3(2), C(6)-N(1)-C(7)=118.7(3),N(1)-C(7)-C(8) =113.0(3), C(7)-C(8)-C(9)= 90.3(2), C(8)-C(7)-C(10)= 87.8(2), C(7)-C(10)-C(9)=92.2(2), C(8)-C(9)-C(10)= 88.9 (2), C(7)-C(13)-C(14)=114.4(3), C(8)-C(7)-C(13)= 111.7 (3), N(1)-C(7)-C(13)=112.4(3), C(7)-C(8)-C(19)= 121.8 (3), C(8)-C(9)-C(17)=116.1(3), C(10)-C(7)-C(13)= 115.7 (3), N(1)-C(7)-C(10)=114.1(3), C(9)-C(8)-C(19)=117.2(3)

Table 1. Crystallographic Data for compound (**7d**)

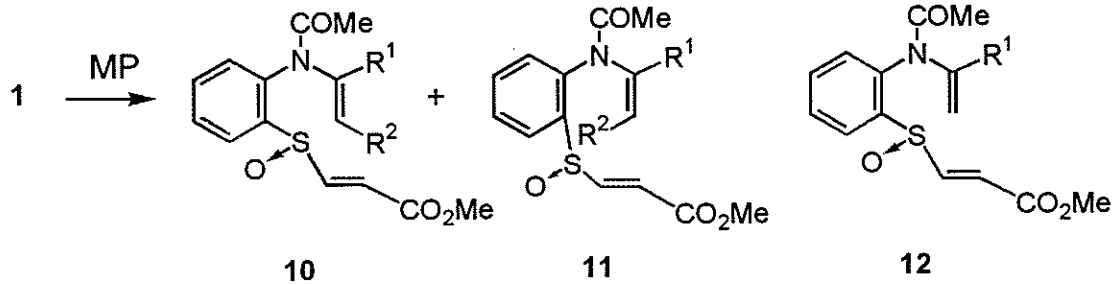
(a) Crystal parameters
formula: $C_{20}H_{23}NO_8S$ M=437.46 size(mm): 0.25 x 0.20 x 0.30 color: colorless
crystal system: triclinic space group: P1(#2) T: 20.2 ℃
a= 10.809(4) Å α= 92.97(5)° V= 1034.9(9) $Å^3$
b= 11.437(8) Å β= 105.07(3)° Z= 1.80
c= 9.331(2) Å γ= 68.47(4)° Dc= 1.263 g/cm^3 F_{000}= 414.00 μ(CuKα)= 16.34 cm^{-1}

(b) Data collection
diffractometer: Rigaku AFC5R radiation: CuKα(λ=1.54178 Å) graphite monochromated
scan range: $37.27 < 2\theta < 42.79°$
number of reflections measured: Total: 5001 Unique: 4750(R_{int}= 0.025)

(c) Refinement
R: 0.048 Rw: 0.063 GOF: 1.73

afforded only an inseparable complex mixture under similar conditions.

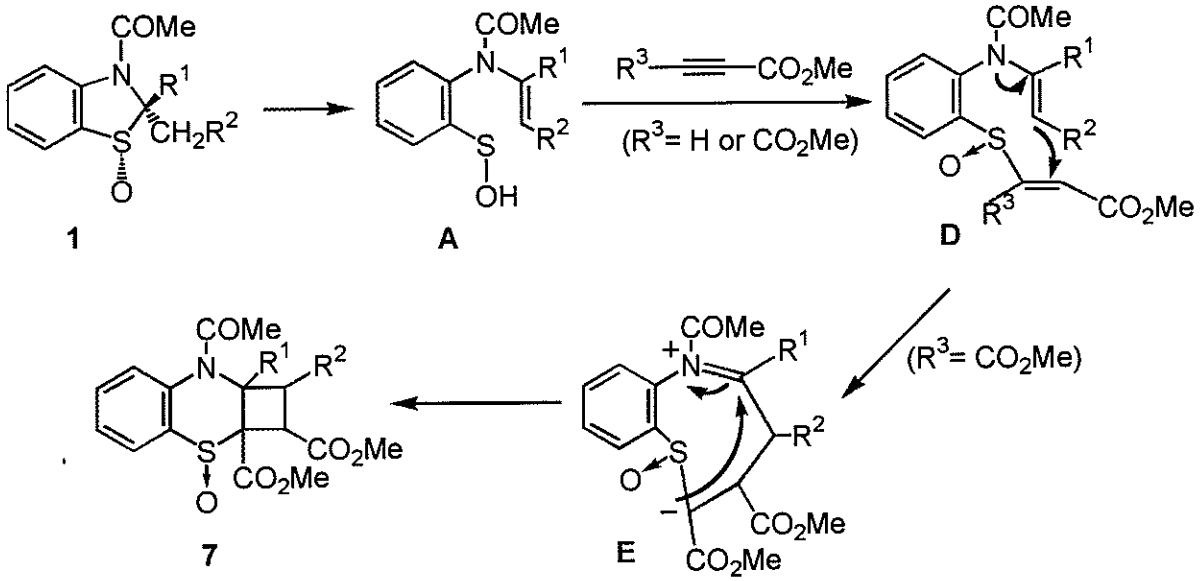
We next examined the thermal reaction of the sulfoxides (**1**) with MP (Scheme 4). Refluxing of 3-acetyl-2,2-dimethylbenzothiazoline 1-oxide (**1a**) with MP in xylene resulted in the formation of inseparable complex mixtures, meanwhile, *cis*-2-ethoxycarbonylmethyl- (or 2-methoxycarbonylmethyl-) 2-methyl sulfoxide (**1c**) or (**1f**) afforded two isomeric addition products (**10c** and **11c**) or (**10f** and **11f**), respectively, but not any tricyclic products as above. *trans*-Sulfoxide (**1d**) or (**1e**) afforded only an addition product (**12d**) or (**12e**) in 65% or 41% yield, respectively. Further, 2,2-dibenzyl substituted



Scheme 4

sulfoxide (**1g**) also gave only addition products (**10g**) and (**11g**) in 31% and 56% yields, respectively.

We propose a plausible mechanism for the formation of the novel tricyclic compounds (**7**) as shown in Scheme 5. A thermal ring opening of sulfoxides (**1**) affords a sulfenic acid intermediate (**A**) *via* a β-*cis*-elimination process as described above. The subsequent addition of the sulfenic acid intermediate (**A**) to acetylenic compound takes place to form a sulfoxide (**D**), which then undergoes intramolecular Michael-type addition of the β-carbon of alkenyl amide moiety to the sulfinyl alkene center to lead to the intermediate (**E**). A sulfinyl carbanion of the intermediate (**E**) attacks intramolecularly the iminium carbon to construct simultaneously both 1,4-thiazine and condensed cyclobutane skeletons, yielding the compound (**7**).



Scheme 5

The present results indicate that the formation of tricyclic compounds (**7**) *via* the reaction with DMAD is

preferable to the sulfoxides whose configurations take cis to 2-methyl substituents as seen in the reaction of sulfoxides (**1a**,**1d** and **1e**). Moreover, no formation of the similar tricyclic products was observed with all the sulfoxides investigated with MP. These observations would be explained in terms of the combination of the nucleophilicity of the β-carbon of alkenyl amide moiety and electrophilicity of sulfinyl alkene moiety in the intermediate (**D**) in Scheme 5. The nucleophilicity of β-carbon of alkenyl amide moiety of the intermediate (**D**) derived from the sulfoxides (**1c**) or (**1f**) with DMAD is decreased by the stabilization with electron-withdrawing ester group, respectively, and subsequent nucleophilic attack to the sulfinyl alkene moiety would not proceed, the intermediate (**D**) being isolated as addition product (**8**) or (**9**).[6] Further, the electrophilicity of β-carbon of sulfinyl alkene moiety of the intermediate (**D**) formed from the reaction of all sulfoxides with MP is very low because of the absence of strong electron-withdrawing ester group at the α-carbon, and therefore subsequent cyclization reaction would not proceed, the intermediate (**D**) being isolated as stable product (**10**), (**11**), or (**12**).

Further work is in progress to apply this interesting ring transformation to other heterocyclic compounds such as 2,2-disubstituted 1,3-dithiolane sulfoxides or 1,3-oxathiolane sulfoxides.

REFERENCES AND NOTES

1. H. Shimizu, N. Ueda, T. Kataoka, and M. Hori, *Chem. Pharm. Bull.*, 1984, **32**, 2571.
2. F. Chioccara, L. Oliva, G. Prota, and E. Novellino, *Synthesis*, **1978**, 744.
3. C. H. Chen, *Tetrahedron Lett.*, **1976**, 25.
4. For reviews, see (a) R. D. G. Cooper and D. O. Spry in "Cephalosporins and Penicillins", ed. by E. H. Flynn, Academic Press, New York, N. Y., 1972, p. 183; (b) R. J. Stoodley, *Tetrahedron*, 1975, **31**, 2321: (c) P. G. Sammes, *Chem. Rev.*, 1976, **76**, 113.
5. All new compounds had satisfactory analytical data to support the assignment. Data for the selected compounds. **7a**: white prisms (ether); mp 166-167 °C; IR(KBr) cm^{-1}: 1730(CO_2), 1660(COMe), 1055(SO); MS *m/z*: 365(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.71(3H, s, Me), 2.11(3H, s, COMe), 2.65(1H, dd, J=11.1, 4.7 Hz, C*H*H), 2.99(1H, dd, J=13.3, 11.1 Hz, CH*H*), 3.51(3H, s, OMe), 3.75(3H, s, OMe), 3.95(1H, dd, J=13.3, 4.7 Hz, CH), 7.20-7.69(4H, m, ArH); ^{13}C-NMR($CDCl_3$) δ: 22.0(q), 23.9(q), 35.4(t), 36.6(d), 52.3(q), 52.6(q), 64.2(s), 74.3(s), 126.8(d), 128.6(d), 129.5(d), 134.2(d), 135.0(s), 137.3(s), 165.3(s), 168.6(s), 172.7(s). Anal. Calcd for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.98; H, 5.27; N, 3.82. **7d**: colorless prisms (ether); mp 161-162 °C; IR(KBr) cm^{-1}: 1720(CO_2), 1675(COMe), 1040(SO); MS *m/z*: 437(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.22(3H, t, J=7.0 Hz, CH_2CH_3), 2.06(3H, s, Me), 3.02(1H, d, J=14.2 Hz, C*H*HCO$_2$Et), 3.06(2H, d, J=8.3 Hz, CH_2 of cyclobutane ring), 3.29(1H, d, J=14.2 Hz, CH*H*CO$_2$Et), 3.51(3H, s, OMe), 3.76(3H, s, OMe), 3.92-4.02(3H, m, CH_2Me and CH of cyclobutane ring), 7.21-7.81(4H, m, ArH). ^{13}C-NMR($CDCl_3$) δ: 13.9(q), 23.8(q), 33.0(t), 36.3(d), 40.0(t), 52.4(q), 52.7(q), 60.7(t), 64.5(s), 73.8(s), 126.9(d), 129.1(d), 129.5(d), 133.9(d), 135.0(s), 137.6(s), 165.2(s), 169.2(s), 169.6(s), 172.3(s). Anal. Calcd for $C_{20}H_{23}NO_8S$: C, 54.91; H, 5.26; N, 3.20. Found: C, 54.84; H, 5.40; N, 3.02. **7e**: colorless prisms (ether-CH_2Cl_2); mp 139-141 °C; IR(KBr) cm^{-1}: 1740(CO_2), 1670(COMe), 1060(SO); MS *m/z*:

423(M^+); ^{1}H-NMR($CDCl_3$) δ: 2.06(3H, s, COMe), 2.97-3.11(2H, br m, CH_2 of cyclobutane ring), 3.03(1H, d, J=14.1 Hz, C*H*HCO_2Me), 3.35(1H, d, J=14.1 Hz, CH*H*CO_2Me), 3.51(3H, s, OMe), 3.56(3H, s, OMe), 3.76(3H, s, OMe), 3.93(1H, dd, J=9.8, 6.0 Hz, CH of cyclobutane ring), 7.29-7.71(4H, m, ArH). ^{13}C-NMR($CDCl_3$) δ: 23.9(q), 33.2(t), 36.8(d), 39.8(t), 51.8(q), 52.5(q), 52.7(q), 64.4(s), 73.8(s), 127.1(d), 129.3(d), 129.5(d), 134.0(d), 135.0(s), 137.6(s), 165.2(s), 169.2(s), 170.1(s), 172.5(s). Anal. Calcd for $C_{19}H_{21}NO_8S$: C, 53.89; H, 5.00; N, 3.31. Found: C, 53.64; H, 4.98; N, 3.25. **8f**: colorless oil; IR(neat) cm^{-1}: 1720 and 1690 (CO_2), 1635(COMe), 1080(SO); MS *m/z*: 423(M^+); ^{1}H-NMR($CDCl_3$) δ: 2.06(3H, s, Me), 2.47(3H, s, COMe), 3.61(3H, s, OMe), 3.63(3H, s, OMe), 3.81(3H, s, OMe), 5.58(1H, s, olefinic H), 7.00(1H, s, olefinic H), 7.18-7.88(4H, m, ArH). HRMS *m/z* Calcd for $C_{19}H_{21}NO_8S$: 423.0987; Found: 423.0964. **9f**: colorless oil; IR(neat) cm^{-1}: 1730 and 1690(CO_2), 1650(COMe), 1080(SO); MS *m/z*: 423(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.96(3H, s, Me), 2.11(3H, s, COMe), 3.69(3H, s, OMe), 3.72(3H, s, OMe), 3.80(3H, s, OMe), 6.00(1H, s, olefinic H), 6.95(1H, s, olefinic H), 7.20-7.85(4H, m, ArH). HRMS *m/z* Calcd for $C_{19}H_{21}NO_8S$: 423.0987; Found: 423.0958. **10c**: colorless prisms (ether-CH_2Cl_2); mp 149-151 °C; IR(KBr) cm^{-1}: 1730 and 1710(CO_2), 1640(COMe), 1620(C=C), 1060(SO); MS *m/z*: 379 (M^+); ^{1}H-NMR($CDCl_3$) δ: 1.30(3H, t, J=7.0 Hz, CH_2CH_3), 2.24(3H, s, COMe), 2.38(3H, d, J=1.0 Hz, Me), 3.77(3H, s, OMe), 4.21(2H, q, J=7.0 Hz, CH_2Me), 5.85(1H, q, J=1.0 Hz, olefinic H), 6.80(1H, d, J=15.2 Hz, olefinic H), 7.71(1H, d, J=15.2 Hz, olefinic H), 7.13-7.88(4H, m, ArH). Anal. Calcd $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.76; H, 5.61; N, 3.63. **10f**: colorless prisms (hexane-CH_2Cl_2); mp 110-112 °C; IR(KBr) cm^{-1}: 1730 and 1720(CO_2), 1660(COMe), 1630(C=C), 1060(SO); MS *m/z*: 365(M^+); ^{1}H-NMR($CDCl_3$) δ: 2.21(3H, br s, Me), 2.38(3H, s, COMe), 3.72(3H, s, OMe), 3.75(3H, s, OMe), 5.88(1H, br s, olefinic H), 6.81(1H, d, J=15.5 Hz, olefinic H), 7.73(1H, d, J=15.5 Hz, olefinic H), 7.14-7.98(4H, m, ArH). Anal. Calcd for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.93; H, 5.26; N, 3.87. **10g**: colorless prisms (hexane-CH_2Cl_2); mp 137-139 °C; IR(KBr) cm^{-1}: 1723(CO_2), 1655(COMe), 1072(SO); MS *m/z*: 459(M^+); ^{1}H-NMR($CDCl_3$) δ: 2.14(3H, s, COMe), 3.68(2H, ABq, J=15.0 Hz, CH_2Ph), 3.74(3H, s, OMe), 6.84(1H, s, olefinic H), 6.82(1H, d, J=15.0 Hz, olefinic H), 7.91(1H, d, J=15.0 Hz, olefinic H), 7.00-7.90(14H, m, ArH). Anal. Calcd for $C_{27}H_{25}NO_4S$: C, 70.57; H, 5.48; N, 3.05. Found: C, 70.72; H, 5.56; N, 3.01. **11c**: colorless prisms (ether-CH_2Cl_2); mp 143-145 °C; IR(KBr) cm^{-1}; 1720 and 1705(CO_2), 1655(COMe), 1620(C=C), 1040(SO); MS *m/z*: 379(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.29(3H, t, J=7.0 Hz, CH_2CH_3), 2.00(3H, d, J=1.5 Hz, Me), 2.19(3H, s, COMe), 3.77(3H, s, OMe), 4.24(2H, q, J=7.0 Hz, CH_2Me), 6.50(1H, q, J=1.5 Hz, olefinic H), 6.81(1H, d, J=15.2 Hz, olefinic H), 7.87(1H, d, J=15.2 Hz, olefinic H), 7.15-7.84(4H, m, ArH). Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 57.09; H, 5.63; N, 3.65. **11f**: colorless prisms (hexane-CH_2Cl_2); mp 137-138 °C; IR(KBr) cm^{-1}: 1740 and 1720(CO_2), 1675(COMe), 1625(C=C), 1045(SO); MS *m/z*: 365(M^+); ^{1}H-NMR($CDCl_3$) δ: 2.00(3H, br s, Me), 2.19(3H, s. COMe), 3.76(6H, s, 2xOMe), 6.12(1H, br s, olefinic H), 6.83(1H, d, J=15.0 Hz, olefinic H), 7.90(1H, d, J=15.0 Hz, olefinic H), 7.13-8.01(4H, m, ArH). Anal. Calcd for $C_{17}H_{19}NO_6S$: C, 55.88; H, 5.24; N, 3.83. Found: C, 55.71; H, 5.23; N, 3.88. **11g**: colorless needles (hexane-CH_2Cl_2); mp 146-148 °C; IR(KBr) cm^{-1}: 1725(CO_2), 1670(COMe), 1050(SO); MS *m/z*: 459(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.68(3H, s, COMe),

3.56(2H, ABq, J=15.0 Hz, C*H*$_2$Ph), 3.80(3H, s, OMe), 6.65(1H, s, olefinic H), 6.94(1H, d, J=15.0 Hz, olefinic H), 8.12(1H, d, J=15.0 Hz, olefinic H), 7.12-8.04(14H, m, ArH). Anal. Calcd for $C_{27}H_{25}NO_4S$: C, 70.57; H, 5.48; N, 3.05. Found: C, 70.29; H, 5.45; N, 2.99. **12d**: colorless plates (hexane-CH_2Cl_2); mp 102-103 °C; IR(KBr) cm^{-1}: 1735 and 1720(CO_2), 1660(COMe), 1060(SO); MS *m/z*: 379(M^+); ^{1}H-NMR($CDCl_3$) δ: 1.25(3H, t, J=7.0 Hz, CH_2CH_3), 2.35(3H, s, COMe), 3.20(2H, br s, C*H*$_2$$CO_2$Et), 3.78(3H, s, OMe), 4.18(2H, q, J=7.0 Hz, C*H*$_2$$CH_3$), 5.45(2H, br s, =$CH_2$), 6.83(1H, d, J=15.0 Hz, olefinic H), 7.85(1H, d, J=15.0 Hz, olefinic H), 7.10-8.10(4H, m, ArH). Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.75; H, 5.52; N, 3.55.

6. Further refluxing a solution of the isolated **8f** or **9f** in xylene for 4 h resulted in the decomposition to yield 1,4-benzothiazine derivatives (**2**, R^1= Me, R^2= CO_2Me) in 20% or 24% yield, respectively.

Received, 24th February, 1999