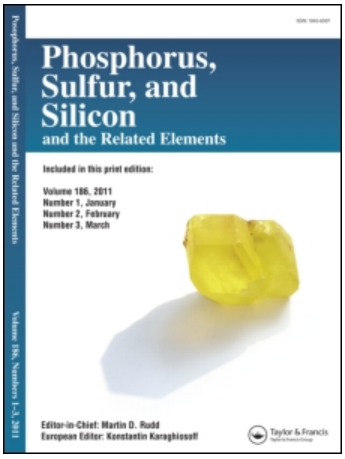

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SYNTHESIS OF 1,5-BENZOTHIAZEPINE-1-OXIDE/-1,1-DIOXIDE DERIVATIVES AND 1,2-OXAZIRINO[2,3-*a*] [1,5] BENZODIAZEPINE

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Three 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7-oxide derivatives, three 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide derivatives, and 1,5-benzothiazepine-1-oxide and 1,5-benzothiazepine-1,1-dioxide derivatives have been synthesized by oxidizing 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one and 1,5-benzothiazepine with *m*-chloroperbenzoic acid (MCPBA) as mimetics of benzodiazepinone for studies on relationship of structure and activity, respectively. One 1,2-oxazirino[2,3-*a*][1,5]benzodiazepine derivative also has been synthesized by the reaction of 1,5-benzodiazepine and *m*-chloroperbenzoic acid (MCPBA).

Keywords: 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7-oxide; 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide; 1,5-benzothiazepine-1-oxide; 1,5-benzothiazepine-1,1-dioxide; 1,2-oxazirino[2,3-*a*] [1,5]benzodiazepine; oxidation; *m*-chloroperbenzoic acid

Benzodiazepine and benzothiazepine derivatives are two of the most important classes of bioavailible therapeutic agents with widespread biological activities including anxiolytic, anticonvulsant, and antihypnotic activities[1], selective cholecystokinin (CCK) receptor subtype A and B antagonists[2], opioid receptor ligands[3], platelet-activating factor antagonists[4], human immunodeficiency virus trans-activator Tat/Tar antagonists[5], reverse transcriptase inhibitors[6], and ras farnesyltransferase inhibitors[7]. Recent years our research group has focused on the studies on the synthesis and stereostructure of novel 1,5-benzothiazepine and 1,5-benzodiazepine derivatives[8–12]. Most of benzodiazepine derivatives

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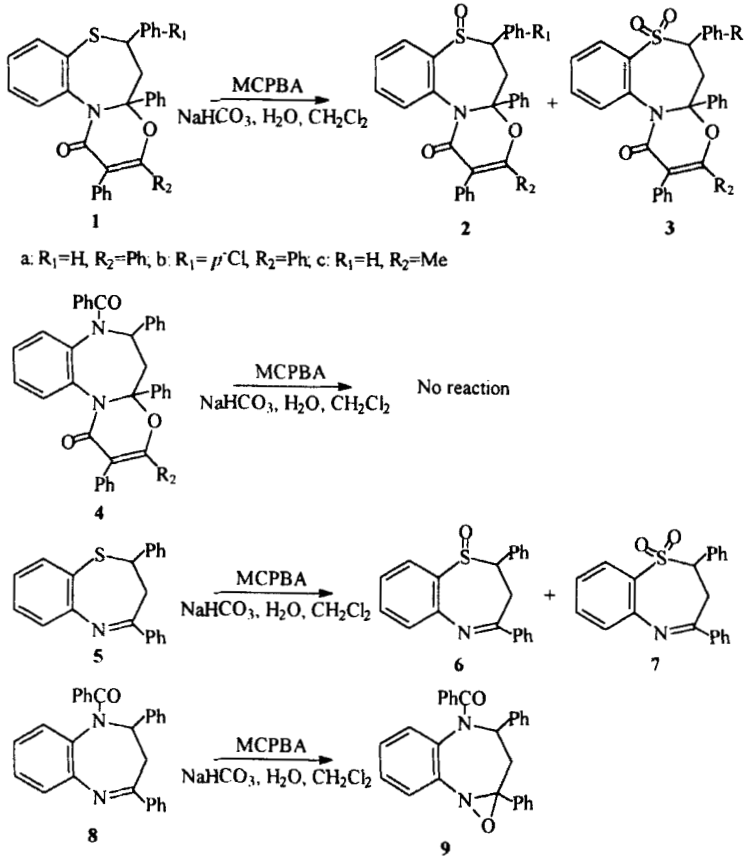
with the well-documented clinical value are their lactam derivatives, such as benzodiazepinone or benzodiazepinedione[13–15]. Herein we report the synthesis of 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7-oxide derivatives **2,** 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide derivatives **3**, and 1,5-benzothiazepine-1-oxide **6** and 1,5-benzothiazepine-1,1-dioxide **7** derivatives. They can be used as the mimetics of benzodiazepinone for studies on the relationship of structure and activity.

Replacement of the lactam group in 1,5-benzothiazepines by the sulfoxide group leads to sulfoxide analogues of benzodiazepinone, by the sulfone group leads to a novel analogue of benzodiazepinone or benzodiazepincdione. They would show novel biological and pharmaceutical activity. They can be used to research the relationship of structure and activity.

In the realm of peroxy-acids, the *m*-chloroperoxybenzoic acid (MCPBA) is the most largely used to oxidize sulfide to sulfoxide or sulfone with reactions carried out in organic solvents[16], such as dichloromethane or chloroform. The basic buffered aqueous medium seems specially suitable for acid-sensitive starting materials or products[17–19]. Both the enolic ethers in 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one **1** and 1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-one **4,** and the imines in 1,5-benzothiazepine **5** and 1,5-benzodiazepine **8** are acid-sensitive. Thus, we carried out our experiments in a basic biphasic oxidation medium in a mixture of dichloromethane and saturated aqueous sodium bicarbonate by applying a phase transfer catalyst benzyltriethylammonium chloride (TEBA).

When the equivalence of MCPBA was used in oxidation, the sulfone product, both 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide **3** and 1,5-benzothiazepine-1,1-dioxide **7** derivatives were main products for the 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one **1** and 1,5-benzothiazepine **5,** respectively. It is difficult to avoid oxidizing further sulfoxides **2** and **6** to sulfones **3** and **7** in our experiments. When the amout of MCPBA was increased to 3.3 equivalence of sulfides **1** and **5,** the yields of sulfones **3** and **7** increased, too. But no epoxidation reaction occured for our starting materials **1, 4** and **5**. Even though sulfone products, 1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide **3** and 1,5-benzothiazepine-1,1-dioxide **7** were caused to react with MCPBA, neither epoxidation product or oxaziridation product was obtained. The results are shown in Table I.



SCHEME 1

The compound **3c** with small hindrance group Me instead of Ph in 3-position in the compound **3a** does not give an epoxidation product, either. In addition, 7-benzoyl-2,3,4a,6-tetraphenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*a*][1,5]benzodiazepin-1-one didnt react with MCPBA. However, 1-benzoyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine did react with MCPBA to yield an oxaziridation product, 4-benzoyl-1a,3-diphenyl-1a,2,3,9-tetrahydro-4*H*-1,2-oxazirino[2,3-*a*][1,5] benzodiazepine.

The epoxidation of alkene with peroxycarboxylic acid is an electrophilic addition mechanism. The C = C double bonds in compounds **1** and **4** did not take part in the epoxidation reactions under these conditions. It maybe presumed that these alkenes are electron-deficient due to the attachment of the electron-withdrawing group C = O, and steric hindrance with phenyl group(s).

According to our knowledge all products are unknown compounds. They were characterized by IR, ^{1}HNMR, MS spectrometries and elemental analysis. In the MS of compounds 2 and 3, it is an obvious characteristic that they underwent a retro-Diels-Alder reaction to release α-carbonyl-β-ketene, benzyl phenyl ketene (m/z 223 in FAB) or acetyl phenyl ketene (m/z 161 in FAB).

TABLE I Oxidation of 1,5-benzothia/diazepine derivatives

Entry	*Starting Materials*	*Starting: MCPBA (mmol)*	*Sulfoxide (%) **2** or **6***	*Sulfone (%) **3** or **7***	*Epoxide (%) or oxaziridine **9***
1	**1a**	1:1.1	12	35	no
2	**1a**	1:3.3	trace	99	no
3	**1b**	1:3.3	12	80	no
4	**1c**	1:3.3	10	60	no
5	**3a**	1:1.5	-	-	no
6	**3c**	1:1.5	-	-	no
7	**4**	1:1.5	-	-	no
8	**5**	1:1.1	30	29	-
9	**5**	1:3.3	10	80	-
10	**7**	1:1.5	-	-	no
11	**8**	1:1.1	–	-	60

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and uncorrected. Elemental analyses were carried out on a Perkin-Elmer 240C or an Elemenlar Vario EL analyzers. The ^{1}HNMR spectra were recorded on a Varian mercury 200 or a Varian FT-80 spectrometer with TMS as an internal standard in $CDCl_3$. The IR spectra were taken on a Nicolet

5MX-S spectrometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer.

Oxidation of 1,5-benzothiazepine derivatives (general procedure)

In a 100 mL three-necked flask equipped with magnetic stirrer and dropping funnel were placed 1.5 mmol of the appropriate 1,5-benzothiazepine derivative, **1, 5** or **8,** in 7 mL of CH_2Cl_2, 20 mL of saturated aqueous $NaHCO_3$ and 0.1 g (0.5 mmol) of TEBA (benzyltriethylammonium chloride). The solution was cooled to 0°C in an ice bath and rapidly stirred. 1.7 to 5.0 mmol of MCPBA (*m*-chloroperbenzoic acid) in 9 to 25 mL of CH_2Cl_2 was added dropwise over 1 h. After the addition was complete the solution was stirred for an additional 4 h at room temperature and the CH_2Cl_2 solution was washed with water (50 mL), 10% Na_2SO_3 (3 × 50 mL), 10% $NaHCO_3$ (3 × 50 mL) and water (50 mL). After the solution was dried over anhydrous K_2CO_3 the solvent was removed on the rotatory evaporator keeping the bath temperature below 35°C to give sulfoxide and/or sulfone mixed products. After silica gel column separation with a mixture of ethyl acetate and petroleum ether (1:1) as eluent pure sulfoxide and sulfone products were obtained, respectively. An oxaziridine product **9** also was obtained from 1,5-benzodiazepine **8** in this procedure.

2,3,4a,6-Tetraphenyl-4a,5,6,12-tetrahydro-1,3-oxazino[3,2-*d*][1,5] benzothiazepin-1-one-7-oxide 2a

Colorless crystals, mp 145–6°C. IR (KBr) ν (cm^{-1}): 1665 (C = O), 1300, 1065 (SO). MS/FAB m/z: 554 $(M+H)^+$, 332 $(M+H\text{-}PhCO(Ph)C=C=O)^+$, 228 $(M+H\text{-}PhCO(Ph)C=C=O\text{-}PhCH=CH_2)^+$, 223 $(PhCO(Ph)C=C=O+H)^+$. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.60 (dd, J = 12.4, 16.2 Hz, 1H), 3.12 (dd, J = 4.0, 16.2 Hz, 1H), 5.25 (dd, J = 4.0, 12.4 Hz, 1H), 6.96–8.07 (m, ArH, 24H). Anal. Cald. For $C_{36}H_{27}NO_3S$ (553.68): C, 78.10; H, 4.92; N, 2.53. Found: C, 77.97; H, 5.18; N, 2.39.

6-(4-Chlorophenyl)-2,3,4a-triphenyl-4a,5,6,12-tetrahydro-1,3-oxazino [3,2-*d*][1,5]benzothiazepin-1-one-7-oxide 2b

Colorless crystals, mp 177–8°C. IR (KBr) ν (cm^{-1}): 1665 (C = O), 1320, 1070 (SO). MS/FAB m/z: 588 $(M+H)^+$, 366 $(M+H\text{-}PhCO(Ph)C=C=O)^+$,

228 (M+H-PhCO(Ph)C = C = O-p-ClPhCH = CH_2)$^+$, 223 (PhCO(Ph)C = C = O+H)$^+$. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.49 (dd, J = 12.2, 16.0 Hz, 1H), 3.11 (dd, J = 4.0, 16.0 Hz, 1H), 5.24 (dd, J = 4.0, 12.2 Hz, 1H), 6.94–8.07 (m, ArH, 23H). Anal. Cald. For $C_{36}H_{26}ClNO_3S$ (588.12): C, 73.53; H, 4.46; N, 2.38. Found: C, 73.42; H, 4.56; N, 2.53.

6-Methyl-2,3,4a-triphenyl-4a,5,6,12-tetrahydro-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one-7-oxide 2c

Colorless crystals, mp 272–3°C. IR (KBr) ν (cm^{-1}): 2930 (Me), 1665 (C = O), 1321, 1070 (SO). MS/FAB m/z: 492 (M+H)$^+$, 332 (M+H-MeCO(Ph)C = C = O)$^+$, 228 (M+H-PhCO(Ph)C = C = O-PhCH = CH_2)$^+$, 161 (MeCO(Ph)C = C = O+H)$^+$. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 1.88 (s, CH_3, 3H), 2.52 (dd, J = 12.0, 16.2 Hz, 1H), 3.15 (dd, J = 4.0, 16.2 Hz, 1H), 4.93 (dd, J = 4.0, 12.0 Hz, 1H), 6.70–8.08 (m, ArH, 19H). Anal. Cald. For $C_{31}H_{25}NO_3S$ (491.60): C, 75.74; H, 5.13; N, 2.85. Found: C, 75.99; H, 5.00; N, 3.01.

2,3,4a,6-Tetraphenyl-4a,5,6,12-tetrahydro-1,3-oxazino[3,2-*d*][1,5] benzothiazepin-1-one-7,7-dioxide 3a

Colorless crystals, mp 181–2°C. IR (KBr) ν (cm^{-1}): 1665 (C = O), 1322, 1155 (SO_2). MS/FAB m/z: 570 (M+H)$^+$, 348 (M+H-PhCO(Ph)C = C = O)$^+$, 223 (PhCO(Ph)C = C = O+H)$^+$. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.62 (dd, J = 12.4, 16.2 Hz, 1H), 3.14 (dd, J = 4.0, 16.2 Hz, 1H), 5.27 (dd, J = 4.0, 12.4 Hz, 1H), 6.90–8.07 (m, ArH, 24H). Anal. Cald. For $C_{36}H_{27}NO_4S$ (569.67): C, 75.90; H, 4.78; N, 2.46. Found: C, 76.11; H, 4.82; N, 2.60.

6-(4-Chlorophenyl)-2,3,4a-triphenyl-4a,5,6,12-tetrahydro-1,3-oxazino [3,2-*d*][1,5]benzothiazepin-1-one-7,7-dioxide 3b

Colorless crystals, mp 171–2°C. IR (KBr) ν (cm^{-1}): 1665 (C = O), 1320, 1150 (SO_2). MS/FAB m/z: 604 (M+H)$^+$, 382 (M+H-PhCO(Ph)C = C = O)$^+$, 223 (PhCO(Ph)C = C = O+H)$^+$. ^{1}H NMR ($CDCl_3$/TMS) δ (ppm): 2.57 (dd, J = 12.0, 16.2 Hz, 1H), 3.11 (dd, J = 3.6, 16.2 Hz, 1H), 5.25 (dd, J = 3.8, 12.0 Hz, 1H), 6.95–8.08 (m, ArH, 23H).

Anal. Cald. For $C_{36}H_{26}ClNO_4S$ (604.12): C, 71.57; H, 4.34; N, 2.32. Found: C, 71.30; H, 4.50; N, 2.22.

6-Methyl-2,3,4a-triphenyl-4a,5,6,12-tetrahydro-1,3-oxazino [3,2-d][1,5]benzothiazepin-1-one-7,7-dioxide 3c

Colorless crystals, mp 174–5°C. IR (KBr) ν (cm^{-1}): 1670 (C = O), 1320, 1155 (SO_2). MS/FAB m/z: 508 $(M+H)^+$, 348 $(M+H\text{-}MeCO(Ph)C=C=O)^+$, 161 $(MeCO(Ph)C=C=O+H)^+$. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 1.88 (s, CH_3, 3H), 2.54 (dd, J = 12.2, 16.0 Hz, 1H), 3.17 (dd, J = 3.8, 16.0 Hz, 1H), 4.98 (dd, J = 3.8, 12.2 Hz, 1H), 6.70–8.08 (m, ArH, 19H). Anal. Cald. For $C_{31}H_{25}NO_4S$ (507.60): C, 73.35; H, 4.96; N, 2.76. Found: C, 73.08; H, 5.14; N, 2.80.

2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine-1-oxide 6

Colorless crystals, mp 122–3°C. IR (KBr) ν (cm^{-1}): 1620 (C = N), 1320, 1155 (SO). MS/EI m/z: 331 (M^+), 238 $(M^+\text{-O-Ph})$, 227 $(M^+\text{-PhCH=CH}_2)$, 211 $(M^+\text{-O-PhCH=CH}_2)$, 108 $(C_6H_4S^+)$. ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.54 (dd, J = 12.2, 16.0 Hz, 1H), 3.17 (dd, J = 3.8, 16.0 Hz, 1H), 4.98 (dd, J = 3.8, 12.2 Hz, 1H), 6.70–8.08 (m, ArH, 19H). Anal. Cald. For $C_{21}H_{17}NOS$ (331.43): C, 76.10; H, 5.17; N, 4.23. Found: C, 75.88; H, 5.26; N, 4.01.

2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine-1,1-dioxide 7

Colorless crystals, mp 172–4°C. IR (KBr) ν (cm^{-1}): 1620 (C = N), 1310, 1130 (SO_2). MS/EI m/z: 347 (M^+). ^1H NMR ($CDCl_3$/TMS) δ (ppm): 3.38 (dd, J = 12.2, 14.0 Hz, 1H), 3.57 (dd, J = 4.4, 14.0 Hz, 1H), 5.50 (dd, J = 4.4, 12.2 Hz, 1H), 6.90–7.92 (m, ArH, 10H). Anal. Cald. For $C_{21}H_{17}NO_2S$ (347.43): C, 72.60; H, 4.93; N, 4.03. Found: C, 72.80; H, 4.94; N, 3.91.

4-Benzoyl-1a,3-diphenyl-1a,2,3,4-tetrahydro-1,2-oxazirino [2,3-*a*] [1 ,5]benzodiazepine 9

Colorless crystals, mp 192–4°C. IR (KBr) ν (cm^{-1}): 1640 (C = O). MS/EI m/z: 418 (M^+), 402 $(M^+\text{-O})$, 325 $(M^+\text{-O-Ph})$, 313 $(M^+\text{-PhCO})$, 297

(M^+-O-PhCO), 105 ($PhCO^+$). ^1H NMR ($CDCl_3$/TMS) δ (ppm): 2.42 (dd, J = 13.0, 14.6 Hz, 1H), 2.83 (dd, J = 4.4, 14.6 Hz, 1H), 5.27 (dd, J = 4.4, 13.0 Hz, 1H), 6.98–7.60 (m, ArH, 19H). Anal. Cald. For $C_{28}H_{22}N_2O_2$ (418.49): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.02; H, 5.20; N, 6.78.

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