A Convenient Access to 3-(Trihalomethyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazines/thiazines and Chlorinated 3-Phenyl-2,3-dihydro-1,5-benzoxazepines/thiazepines by an Aziridination–Selective-Ring-Opening Sequence

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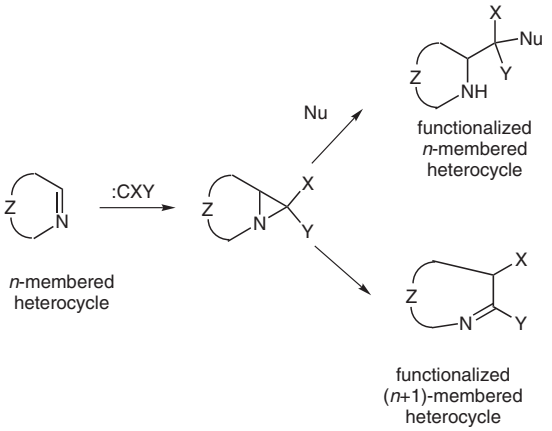
Abstract: Aziridine ring opening with N–C(1) bond breaking in 1,1-dichloro-1a-phenyl-1a,2-dihydro-1*H*-azirino[2,1-*c*][1,4]benzoxazine and -benzothiazine proceeds under the action of hydrohalo acid to give 3-trihalomethyl derivatives of 1,4-benzoxazine and thiazine. When the same compounds react with boron trifluoride etherate, the ring expansion with N–C(1a) bond breaking takes place with formation of 3,4-dichloro-3-phenyl-2,3-dihydro-1,5-benzoxazepine and -1,5-benzothiazepine. These are convenient precursors for the synthesis of 4-substituted 1,5-benzoxazepine and 1,5-benzothiazepine derivatives via reaction with nucleophiles.

Key words: fused haloaziridines, O,N-heterocycles, S,N-heterocycles, ring expansion, dihalocarbenes, acid catalysis

Derivatives of 1,4-benzoxazine,[1,2] 1,4-benzothiazine,[3] 1,5-benzoxazepine[4] and 1,5- benzothiazepine[4,5] have been reported to exhibit a wide range of biological activity and this has stimulated the search for new effective methods for their synthesis. The main synthetic strategies used in the preparation of these heterocyclic systems include cyclization reactions which form heterocycles and the introduction or modification of substituents in heterocyclic and benzene rings.[1,6,7]

A synthetic sequence consisting of cycloaddition of dichlorocarbene to a heterocycle with a C=N double bond leading to formation of a *gem*-dihaloaziridine fused with the heterocycle, which then undergoes subsequent ring enlargement, is a potentially simple and efficient approach to homologation and functionalization of nitrogenated heterocycles (Scheme 1). Utility of this approach takes advantage of the availability of starting materials, efficiency of carbenic methods of preparation of dihaloaziridines and the high reactivity of halogenated aziridines.[8]

However, the potential of this scheme has still not been investigated enough. The aziridine ring in 1,1-dichloro-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinolines, which are the products of cycloaddition of dichlorocarbene to 3,4-dihydroisoquinolines, could be opened by any C–N bond according to Scheme 1, providing routes to derivatives of benzazepine and tetrahydoisoquinoline-1-carboxylic acid.[9,10] Among the heterocyclic systems of such types



Scheme 1

containing two heteroatoms, transformations of 1,1-dihalogeno-1a,2,3,4-tetrahydro-1*H*-azirino[2,1-*e*][1,6]benzoxazocines and -thiazocines were investigated.[11]

Unlike azirinoisoquinolines, aziridine ring transformations into these azirino-fused eight-membered O,N- or S,N-heterocycles involve opening of the three-membered ring and contraction of the medium-sized ring via transannular reactions of endocyclic O or S atoms[11] to afford derivatives of functionalized 1,4-benzox(thi)azines or 1,3-benzox(thi)azoles.

In this work, ring transformations in azirinobenzoxazine **3** and azirinobenzothiazine **4** were examined to evaluate the influence of ring size on the reactivity of the three-membered ring in azirino-fused *n*-membered O,N- or S,N-heterocycles and the possibilities of using transformations according to Scheme 1 for functionalization and homologation of 2*H*-benzo-1,4-benzoxazine and 2*H*-1,4-benzothiazine.

Azirinobenzoxazine **3** and azirinobenzothiazine **4** were synthesized via cycloaddition of dichlorocarbene (generated by alkaline hydrolysis of chloroform or thermocatalytic decomposition of sodium trichloroacetate) to the C=N double bond of 3-phenyl-2*H*-1,4-benzoxazine (**1**) and 3-phenyl-2*H*-1,4-benzothiazine (**2**), respectively (Scheme 2). Alkaline hydrolysis of chloroform in the presence of compound **2** gave only tarry products. All the newly obtained compounds were fully characterized using standard spectral and analytical methods.

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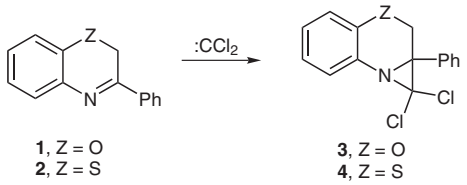
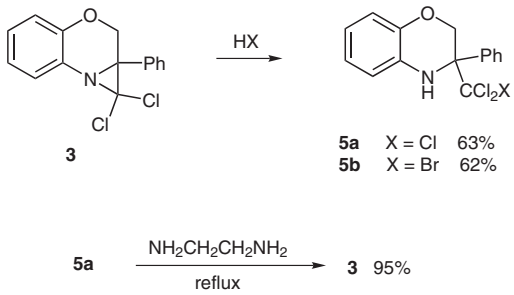


Scheme 2

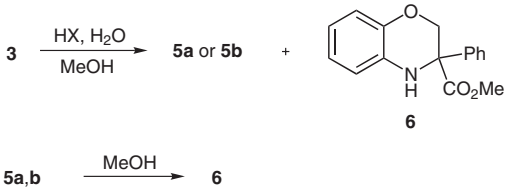
Unexpectedly, attempts to synthesize the corresponding chlorofluoro derivatives using reactions of chlorofluorocarbene (generated by alkaline hydrolysis of dichlorofluoromethane or thermocatalytic decomposition of sodium dichlorofluoroacetate) were unsuccessful, although corresponding cycloadducts were obtained under the same conditions from eight-membered rings with a C=N double bond.[11] Compounds **1** and **2** were unreactive in the presence of chlorofluorocarbene and recovered completely unchanged.

We found that the opening of the aziridine ring in **3** in the presence of nucleophilic halogenide ions proceeds with conservation of the benzoxazine ring. 3-(Trichloromethyl)- and 3-(bromodichloromethyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazines **5a**,**b** were obtained on heating compound **3** in hydrohalo acids (HCl, HBr) (Scheme 3). Under these conditions the aziridine ring opening with N–C(1) bond breaking occurs probably through a mechanism of nucleophilic substitution of the 'ammonium group' of the protonated aziridine. Trichloride **5a** can be transformed quantitatively back into aziridine **3** via reaction with base (Scheme 3). This type of transformation was earlier realized for acyclic 2,2,2-trichloroethylamines.[12,13]



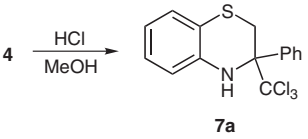
Scheme 3

Heating compound **3** in methanol with addition of hydrohalo acids afforded a mixture of **5** and **6** (Scheme 4). The ratio trihalide **5**/ester **6** depends on the added acid. Refluxing a solution of azirinobenzoxazine **3** in methanol in the presence of hydrofluoric acid gave 18% of compound **5a** and 34% of compound **6**. Under similar conditions, addition of aqueous hydrochloric or hydrobromic acid gave compounds **5a** or **5b** and **6** (43% of **5a** and 8% of **6**; 46% of **5b** and 14% of **6**, respectively). It was also found that compounds **5a**,**b** react on prolonged heating with methanol to form ester **6**.



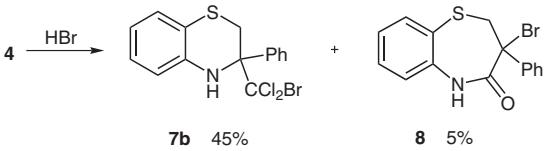
Scheme 4

In the presence of hydrogen chloride in anhydrous methanol, a faster and more selective reaction of azirinobenzoxazine **3** is observed. Thus, heating aziridine **3** in 5% solution of HCl in methanol for 0.5 hour gave trichloride **5a** in 76% yield. The trichloride **7a** was obtained from azirinobenzothiazine **4** in 81% yield under the same conditions (Scheme 5).



Scheme 5

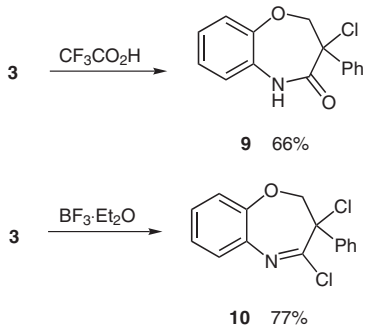
On heating azirinobenzothiazine **4** in concentrated hydrobromic acid, the 3-bromodichloromethyl derivative of benzoxazine **7b** was obtained as the main product. However, in contrast to the reaction of azirinobenzoxazine **3** under the same conditions, the product of ring enlargement, the 1,5-benzothiazepine **8** was also formed here in 5% yield (Scheme 6). This finding prompted us to look for reaction conditions for the transformation of azirino[*c*][1,4]benzoxazine and benzothiazine systems into derivatives of 1,5-benzoxazepine and benzothiazepine.



Scheme 6

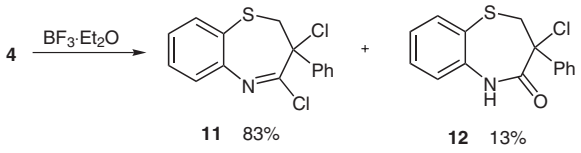
We investigated the chemical behavior of compounds **3** and **4** without addition of active nucleophiles, and under these conditions we succeeded in the ring expansion with breaking of N–C(1a) bond. Thus, reaction of the azirinobenzoxazine **3** with trifluoroacetic acid at room temperature proceeds with formation of 1,5-benzoxazepinone **9**. When compound **3** was treated with boron trifluoride etherate at room temperature the imidoyl chloride **10** was isolated as the sole product in 77% yield (Scheme 7).

Similarly, the azirinobenzothiazine **4** with boron trifluoride etherate at room temperature gave the imidoyl chloride **11**. This imidoyl chloride hydrolyzed more easily under purification on silica gel, than the oxazepine derivative **10**, forming 1,5-benzothiazepinone **12**. Thus, after chromatography on silica gel, 28% of compound **11** and



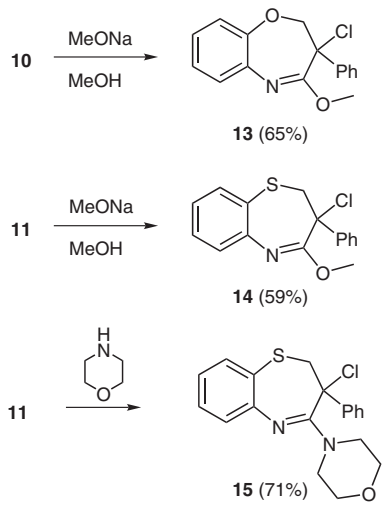
Scheme 7

44% of compound **12** were isolated whereas chromatography on alumina gave 83% of compound **11** and 13% of compound **12** (Scheme 8).



Scheme 8

The compounds **10** and **11** contain two chlorine atoms which could potentially be used for their modification via reactions with nucleophiles. We succeeded, however, in reacting only at the imidoyl chloride part of these molecules. According to simple PM3 computations, compounds **10** and **11** were unable to undergo S_N2 reactions due to steric reasons. When compounds **10** and **11** were heated with sodium methoxide in methanol, they were smoothly transformed into the corresponding methoxy derivatives **13** and **14**, respectively. Chloride **11** also reacts with morpholine to give amidine **15** in good yield (Scheme 9).



Scheme 9

In conclusion, we have developed a simple and efficient approach for the synthesis of 3-(trihalomethyl)-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazines (thiazines) and chlorinated 3-phenyl-2,3-dihydro-1,5-benzoxazepines (thiazepines) via a synthetic sequence consisting of cycloaddition of dichlorocarbene to the C=N double bond of 2*H*-benzo-1,4-benzoxazine and 2*H*-1,4-benzothiazine, leading to the formation of the *gem*-dihaloazirino-fused heterocycle, and subsequent selective C–N bond breaking.

Melting points were determined on a Boetius melting point apparatus; uncorrected values are given. The IR spectra were recorded on a Carl Zeiss UR-20 instrument. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR were measured with a Bruker DPX 300 spectrometer using $CDCl_3$ as the solvent, and are reported in ppm relative to the solvent peak of $CDCl_3$ (δ = 7.26 for ^{1}H NMR and δ = 77.0 for the central resonance in ^{13}C NMR). Mass spectral data were collected on MX-1303 and Finnigan MAT 95 LCQ instruments. The elemental compositions were determined on an HP-185B CHN analyzer. The progress of reactions was monitored by TLC using Silufol UV-254 plates. Silica gel Merck 60 was used for column chromatography. All solvents were purified according to standard procedures. Benzoxazine **1** and benzothiazine **2** were prepared according published procedures.[14,15]

1,1-Dichloro-1a-phenyl-1a,2-dihydro-1*H*-azireno[2,1-*c*][1,4]-benzoxazine (3)

Method a: Powdered KOH (2.1 g, 37.5 mmol) was added to a solution of 3-phenyl-2*H*-1,4-benzoxazine (**1**; 1 g, 4.785 mmol) and benzyltriethylammonium chloride (0.1 g, 0.44 mmol) in $CHCl_3$ (10 mL) under vigorous stirring, keeping the temperature of the mixture at 21–23 °C (water bath). The mixture was stirred at this temperature for 3 h and then filtered through a layer of Al_2O_3 (1 cm). After removal of the solvent on a rotary evaporator (bath temperature ≤ 30 °C) and crystallization of the residue from Et_2O–hexane, compound **3** (0.75 g, 54%) was obtained as white crystals; mp 83–84 °C.

^{1}H NMR ($CDCl_3$): δ = 4.36 and 4.76 (d, J = 11.7 Hz, 2 H, OCH_2), 6.99–7.18 (m, 3 H), 7.43–7.53 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 50.9 (*C*Ph), 66.4 (OCH_2), 82.7 (CCl_2), 117.6, 122.4, 125.8, 126.1, 127.3, 128.59, 128.62, 129.0, 136.9, 147.8.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.66; H, 3.80; N, 4.79. Found: C, 61.57; H, 3.94; N, 4.72.

Method b: A mixture of compound **5a** (0.16 g, 0.487 mmol) and anhyd 1,2-diaminoethane (2 mL) was refluxed for 0.25 h. After cooling, H_2O (10 mL) was added, the precipitated crystals were filtered, dried, and after crystallization from Et_2O–hexane, compound **3** (0.135 g, 95%) was obtained as white crystals; mp 83–84 °C.

1,1-Dichloro-1a-phenyl-1a,2-dihydro-1*H*-azireno[2,1-*c*][1,4]-benzothiazine (4)

Powdered sodium trichloroacetate (7 g, 37.7 mmol) was added in small portions with stirring to a mixture of the benzothiazine **2** (2 g, 8.89 mmol), and benzyltriethylammonium chloride (0.20 g, 0.879 mmol) in refluxing $CHCl_3$ (60 mL) over 3 h. After completion of the reaction, the mixture was filtered and the solvent distilled off on a rotary evaporator. The residue was chromatographed on a basic Al_2O_3 column using EtOAc–hexane as eluent to give compound **4** (0.70 g, 26%) as a white solid; mp 97–99 °C (hexane–Et_2O).

^{1}H NMR ($CDCl_3$): δ = 3.09 and 3.43 (d, J = 13.1 Hz, 2 H, SCH_2), 7.11–7.16 (m, 1 H), 7.30–7.51 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 30.3 (SCH_2), 55.6 (*C*Ph), 81.9 (CCl_2), 124.1, 124.2, 124.3, 127.0, 128.0, 128.4, 128.5, 129.5, 137.9, 138.0.

Anal. Calcd for $C_{15}H_{11}Cl_2NS$: C, 58.45; H, 3.60; N, 4.54. Found: C, 58.38; H, 3.99; N, 4.57.

3-Phenyl-3-(trichloromethyl)-3,4-dihydro-2*H*-1,4-benzoxazine (5a)

Method a: A mixture of compound **3** (57 mg, 0.196 mmol) and concd HCl (1 mL) was heated at 90 °C for 5.5 h. After cooling, the mixture was made alkaline with aq sat. Na_2CO_3 (pH 8), extracted with Et_2O (3 × 10 mL) and the combined Et_2O layers were dried (Na_2SO_4). After removal of the solvent and crystallization of the residue from Et_2O–CH_2Cl_2, compound **5a** (40 mg, 63%) was obtained as a white solid; mp 115–116 °C.

Method b: A mixture of compound **3** (0.301 g, 1.03 mmol) and 5% aq solution of HCl in anhyd MeOH (10 mL) was refluxed for 0.5 h. The solvent was removed under vacuum, and purification of the residue was performed by chromatography on silica gel using EtOAc–hexane as eluent to give **5a** (0.253 g, 76%) as a white solid.

IR (CCl_4): 3410 (NH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.72 and 5.16 (d, *J* = 10.9 Hz, 2 H, OCH_2), 5.13 (br s, 1 H, NH), 6.70–6.91 (m, 4 H), 7.40–7.42 (m, 3 H), 7.74–7.76 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 67.6 (*C*Ph), 68.3 (OCH_2), 103.6 (CCl_3), 115.5, 116.7, 119.5, 122.2, 127.9, 128.7, 129.5, 131.0, 135.2, 142.9.

MS (EI, 70 eV): *m*/*z* (%) = 329 (2.4), 327 (3, $[M]^+$), 220 (6), 210 (100), 182 (11), 180 (6), 165 (8), 132 (11), 117 (13).

Anal. Calcd for $C_{15}H_{12}Cl_3NO$: C, 54.82; H, 3.69; N, 4.26. Found: C, 54.76; H, 3.69; N, 4.18.

3-[Bromo(dichloro)methyl]-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine (5b)

A similar procedure starting from compound **3** (57 mg, 0.196 mmol) and concd HBr (1 mL) afforded the compound **5b** (45 mg, 62%) as a white solid; mp 113 °C (CH_2Cl_2–Et_2O).

IR (CCl_4): 3410 (NH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.39 and 5.00 (d, *J* = 11 Hz, 2 H, OCH_2), 5.08 (br s, 1 H, NH), 6.61–6.90 (m, 4 H), 7.26–7.40 (m, 3 H), 7.69–7.75 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 67.4 (*C*Ph), 68.7 (OCH_2), 101.7 (CCl_2Br), 115.5, 116.7, 119.5, 122.2, 127.9, 128.7, 129.8, 131.1, 135.0, 142.9.

MS (EI, 70 eV): *m*/*z* (%) = 373 (1), 371 (1, $[M]^+$), 227 (2), 220 (4), 212 (16), 210 (100, $[M - CCl_2Br]^+$), 208 (2), 182 (4), 132 (5), 117 (5), 103 (8), 91 (8), 77 (10), 65 (4).

Anal. Calcd for $C_{15}H_{12}BrCl_2NO$: C, 48.29; H, 3.25; N, 3.75. Found: C, 48.73; H, 3.45; N, 3.59.

Methyl 3-Phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-3-carboxylate (6)

Method a: A solution of compound **3** (0.05 g, 0.172 mmol) in MeOH (2 mL) was refluxed for 17.5 h (92% conversion). The solvent was removed under vacuum and the residue treated with aq sat. Na_2CO_3 (2 mL), extracted with Et_2O (3 × 10 mL) and chromatographed on silica gel using EtOAc–hexane as eluent to give compounds **5a** (13 mg, 31%) and **6** (18 mg, 34%).

Method b: A mixture of compound **3** (1 g, 3.44 mmol), 80% HF (6 mL) and MeOH (30 mL) was refluxed for 3 h. By following the above-mentioned work-up, compounds **5a** (0.211 g, 18%) and **6** (0.312 g, 34%) were isolated.

Method c: A mixture of compound **3** (100 mg, 0.344 mmol), concd HCl (0.5 mL) and MeOH (3 mL) was refluxed for 6 h. By following the above-mentioned work-up, compounds **5a** (48 mg, 43%) and **6** (7 mg, 8%) were isolated.

Method d: A mixture of compound **3** (300 mg, 1.03 mmol), concd HBr (1.4 g) and MeOH (10 mL) was refluxed for 2 h. By following the above-mentioned work-up, compounds **5b** (171 mg, 46%) and **6** (38 mg, 14%) were isolated.

Method e: A solution of compound **5a** (0.05 g, 0.152 mmol) in MeOH (1.5 mL) was refluxed for 14 h (66% conversion). By following the above-mentioned work-up, compound **6** (13 mg, 48%) was isolated.

Method f: A solution of compound **5b** (0.03 g, 0.081 mmol) in MeOH (1.5 mL) was refluxed for 8 h (80% conversion). By following the above-mentioned work-up, compound **6** (16 mg, 92%) was isolated.

6

White solid; mp 81–82 °C (hexane–Et_2O).

IR (CCl_4): 3390 (NH), 1745 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 4.17 and 4.66 (d, *J* = 11 Hz, 2 H, OCH_2), 4.78 (s, 1 H, NH), 6.69–6.90 (m, 4 H), 7.52–7.58 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 53.0 (OCH_3), 62.4 (*C*Ph), 70.4 (OCH_2), 115.9, 116.8, 119.5, 122.0, 125.7, 128.6, 131.9, 137.5, 143.0, 172.2 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 269 (13, $[M]^+$), 211 (16), 210 (100, $[M - CO_2Me]^+$), 182 (10), 180 (4).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.63; N, 5.20. Found: C, 71.38; H, 5.71; N 5.39.

3-Phenyl-3-(trichloromethyl)-3,4-dihydro-2*H*-1,4-benzothiazine (7a)

A solution of compound **4** (0.202 g, 0.649 mmol) and a 5% solution of HCl in anhyd MeOH (10 mL) was refluxed for 2 h. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel using EtOAc–hexane as eluent. Compound **7a** (0.183 g, 81%) was obtained as a white solid; mp 132–134 °C (CH_2Cl_2–Et_2O).

IR ($CHCl_3$): 3420 cm^{-1} (NH).

^{1}H NMR ($CDCl_3$): δ = 3.72 and 3.87 (d, *J* = 13.1 Hz, 2 H, SCH_2), 5.19 (br s, 1 H, NH), 6.71–6.74 (m, 1 H), 6.82–6.85 (m, 1 H), 7.01–7.07 (m, 2 H), 7.39–7.41 (m, 3 H), 7.69–7.74 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 31.8 (SCH_2), 70.9 (*C*Ph), 106.3 (CCl_3), 115.9, 116.1, 119.0, 126.4, 127.6, 127.8, 128.6, 129.7, 137.5, 140.1.

Anal. Calcd for $C_{15}H_{11}Cl_3NS$: C, 52.27; H, 3.51; N, 4.06. Found: C, 52.18; H, 3.60; N, 3.96.

3-[Bromo(dichloro)methyl]-3-phenyl-3,4-dihydro-2*H*-1,4-benzothiazine (7b) and 3-Bromo-3-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (8)

A mixture of compound **4** (0.381 g, 1.23 mmol) and concd HBr (3 mL) was heated at 90 °C for 12 h (79% conversion). The solvent was removed under vacuum and the residue was treated with aq sat. Na_2CO_3 (2 mL), and extracted with CH_2Cl_2 (3 × 40 mL). The residue obtained on removal of solvent was chromatographed on silica gel using EtOAc–hexane as eluent to give compounds **7b** (0.170 g, 45%) and **8** (0.020 g, 5%).

7b

White solid; mp 155–157 °C (CH_2Cl_2–Et_2O).

IR ($CHCl_3$): 3420 cm^{-1} (NH).

^{1}H NMR ($CDCl_3$): δ = 3.73 and 3.89 (d, *J* = 13.1 Hz, 2 H, SCH_2), 5.21 (br s, 1 H, NH), 6.69–6.74 (m, 1 H), 6.83–6.86 (m, 1 H), 7.01–7.09 (m, 2 H), 7.38–7.41 (m, 3 H), 7.70–7.73 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 32.2 (SCH_2), 70.9 (*C*Ph), 92.0 (CCl_2Br), 115.9, 116.1, 119.0, 126.4, 127.5, 127.8, 128.6, 129.9, 137.2, 140.2.

Anal. Calcd for $C_{15}H_{12}BrCl_2NS$: C, 46.30; H, 3.11; N, 3.60. Found: C, 46.40; H, 3.18; N, 3.49.

8

White solid; mp 183–184 °C (CH_2Cl_2–hexane).

IR ($CHCl_3$): 1690 (C=O), 3390 cm^{-1} (NH).

^{1}H NMR ($CDCl_3$): δ = 3.90 and 4.28 (d, *J* = 10.2 Hz, 1 H, CH), 6.72–6.85 (m, 1 H), 6.92–7.45 (m, 7 H), 7.57–7.68 (m, 2 H), 8.86 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 36.8 (SCH_2), 56.1 (*C*BrPh), 116.6, 119.2, 124.1, 127.0, 127.5, 128.0, 128.56, 128.62, 135.2, 135.6, 166.7 (C=O).

MS (EI): *m*/*z* (%) = 336 (4), 335 (34, $[M + 2]^+$), 333 (35, $[M]^+$), 242 (6), 241 (17), 240 (100, $[M - CH_2Br]^+$), 212 (27), 152 (45), 103 (92), 77 (37).

Anal. Calcd for $C_{15}H_{12}BrNOS{\cdot}0.25C_6H_{14}$: C, 55.70; H, 3.94; N, 4.39. Found: C, 55.62; H, 4.27; N, 4.03.

3-Chloro-3-phenyl-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one (9)

A mixture of compound **3** (0.13 g, 0.445 mmol) and 95% trifluoroacetic acid (2 mL) was kept overnight at 20 °C. Trifluoroacetic acid was removed under vacuum and purification of the residue was performed by chromatography on silica gel using EtOAc–hexane as eluent. Compound **9** (0.080 g, 66%) was obtained as a white solid; mp 153–155 °C (Et_2O).

IR ($CHCl_3$): 1680 (C=O), 3380 cm^{-1} (NH).

^{1}H NMR ($CDCl_3$): δ = 4.48 and 4.70 (d, *J* = 13.1 Hz, 2 H, OCH_2), 6.99–7.02 (m, 3 H), 7.10–7.12 (m, 1 H), 7.38–7.44 (m, 3 H), 7.64–7.66 (m, 2 H), 9.87 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 72.4 (*C*ClPh), 74.8 (OCH_2), 120.7, 121.1, 124.0, 124.9, 127.1, 128.6, 129.0, 137.36, 137.39, 148.3, 171.1 (C=O).

MS (EI, 70 eV): *m*/*z* (%) = 275 (26, $[M + 2]^+$), 273 (83, $[M]^+$), 224 (48), 210 (12), 138 (25), 126 (100), 120 (25), 103 (90), 77 (28), 52 (19).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.89; H, 4.59; N, 5.03.

3,4-Dichloro-3-phenyl-2,3-dihydro-1,5-benzoxazepine (10)

$BF_3{\cdot}OEt_2$ (1.38 g, 9.72 mmol) was added dropwise to a stirred solution of compound **3** (0.71 g, 2.44 mmol) in anhyd CH_2Cl_2 (10 mL) and the mixture was kept overnight at r.t.. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel using EtOAc–hexane as eluent. Compound **10** (0.551 g, 77%) was obtained as a pale yellow oil.

IR ($CHCl_3$): 1670 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$): δ = 4.38 and 4.48 (d, *J* = 12.9 Hz, 2 H, OCH_2), 7.02–7.05 (m, 1 H), 7.17–7.30 (m, 2 H), 7.43–7.47 (m, 3 H), 7.58–7.62 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 76.8 (*C*ClPh), 78.0 (OCH_2), 120.2, 124.3, 126.9, 128.7, 129.2, 130.2, 132.1, 133.7, 136.7, 150.2, 153.5 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 293 (34, $[M + 2]^+$), 291 (53, $[M]^+$), 258 (6, $[M - Cl + 2]^+$), 256 (19, $[M - Cl]^+$), 244 (6), 242 (21), 221 (15), 220 (50), 210 (14), 207 (10), 155 (18), 153 (57), 140 (23), 138 (75), 103 (59), 88 (11), 86 (64), 84 (100), 77 (24), 47 (14).

HRMS: *m*/*z* calcd for $C_{15}H_{11}Cl_2NO$: 291.0218; found: 291.0218.

3,4-Dichloro-3-phenyl-2,3-dihydro-1,5-benzothiazepine (11) and 3-Chloro-3-phenyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (12)

$BF_3{\cdot}OEt_2$ (0.400 g, 2.82 mmol) was added dropwise to a stirred solution of the compound **4** (0.145 g, 0.471 mmol) in anhyd CH_2Cl_2 (10 mL) and the mixture was kept at r.t. overnight. The solvent was removed under vacuum and purification of the residue was performed by chromatography on silica gel using EtOAc–hexane as eluent. Compounds **11** (0.041 mg, 28%) and **12** (0.060 mg, 44%) were isolated. The yield of dichlorobenzothiazepine **11** was increased (83%) and that of its hydrolysis product **12** decreased (13%) when alumina was used instead of silica gel for chromatography.

11

White solid; mp 94–96 °C (hexane).

IR ($CHCl_3$): 1620 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$): δ = 4.12 and 4.31 (d, *J* = 11.6 Hz, 2 H, SCH_2), 7.15–7.23 (m, 2 H), 7.29–7.39 (m, 5 H), 7.64–7.67 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 47.9 (SCH_2), 56.4 (*C*ClPh), 122.7, 126.4, 127.2, 127.5, 127.6, 128.3, 128.5, 128.9, 136.5, 140.1, 151.2 (C=N).

Anal. Calcd for $C_{15}H_{11}Cl_2NS$: C, 58.45; H, 3.60; N, 4.54. Found: C, 58.47; H, 3.85; N, 4.58.

12

White solid; mp 195–197 °C (Et_2O).

IR ($CHCl_3$): 1680 (C=O), 3400 cm^{-1} (NH).

^{1}H NMR ($CDCl_3$): δ = 4.06 and 4.41 (d, *J* = 11.6 Hz, 2 H, SCH_2), 6.79–6.82 (m, 1 H), 6.96–7.13 (m, 2 H), 7.25–7.40 (m, 4 H), 7.61–7.64 (m, 2 H), 9.28 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 48.7 (SCH_2), 56.7 (*C*ClPh), 116.8, 118.9, 124.0, 127.5, 127.9, 128.5, 128.6, 135.0, 135.6, 167.2 (C=O).

Anal. Calcd for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17; N, 4.83. Found: C, 62.00; H, 4.34; N, 4.79.

3-Chloro-4-methoxy-3-phenyl-2,3-dihydro-1,5-benzoxazepine (13)

A solution of chloride **10** (0.55 g, 1.884 mmol) in MeOH (5 mL) was added to a solution of MeONa [prepared from Na (0.201 g) and MeOH (5 mL)] and the mixture was refluxed for 0.5 h. The solvent was removed in vacuum and the residue was partitioned between H_2O (20 mL) and EtOAc (30 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL) and dried (Na_2SO_4). Purification of the residue obtained on removal of the solvent was performed by chromatography on silica gel using EtOAc–hexane as eluent. Compound **13** (0.350 g, 65%) was obtained as a pale yellow oil.

IR ($CHCl_3$): 1670 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 4.33 and 4.43 (d, *J* = 12.7 Hz, 2 H, OCH_2), 6.97–7.00 (m, 1 H), 7.11–7.14 (m, 2 H), 7.40–7.53 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 54.0 (OCH_3), 71.4 (*C*ClPh), 77.3 (OCH_2), 119.8, 123.9, 126.7, 126.8, 128.5, 128.7, 131.5, 132.3, 138.1, 153.4, 157.2 (C=N).

MS (EI, 70 eV): *m*/*z* (%) = 289 (32, $[M + 2]^+$), 287 (100, $[M]^+$), 252 (18), 238 (71), 220 (16), 149 (97), 134 (34), 103 (75), 77 (39), 51 (15).

HRMS: *m*/*z* calcd for $C_{16}H_{14}ClNO_2$: 287.0713; found: 287.0713.

3-Chloro-4-methoxy-3-phenyl-2,3-dihydro-1,5-benzothiazepine (14)

Chloride **11** (0.12 g, 0.390 mmol) was added to a solution of MeONa [prepared from sodium (0.10 g) and MeOH (7 mL)] and the mixture was refluxed for 4 h. The solvent was removed under vacuum and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (40 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed and the residue was purified by chromatography on silica gel using EtOAc–hexane as eluent. Compound **14** (0.071 g, 59%) was obtained as a white solid; mp 81–82 °C (hexane).

IR ($CHCl_3$): 1640 cm^{-1} (C=N).

^1H NMR ($CDCl_3$): δ = 4.08 (s, 3 H, OCH_3), 4.04 and 4.30 (d, J = 11.6 Hz, 2 H, SCH_2), 6.98–7.03 (m, 1 H), 7.10–7.32 (m, 6 H), 7.52–7.55 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 48.0 (SCH_2), 53.0 (*C*ClPh), 54.6 (OCH_3), 121.4, 124.9, 125.5, 126.6, 126.9, 127.2, 128.26, 128.29, 136.8, 141.1, 159.3 (C=N).

Anal. Calcd for $C_{16}H_{14}ClNOS$: C, 63.25; H, 4.64; N, 4.61. Found: C, 63.32; H, 4.60; N, 4.68.

4-(3-Chloro-3-phenyl-2,3-dihydro-1,5-benzothiazepin-4-yl)morpholine (15)

A mixture of chloride **11** (0.085 g, 0.276 mmol) and morpholine (distilled from NaOH) was refluxed for 0.5 h. The excess of morpholine was removed under vacuum and the residue was partitioned between H_2O (10 mL) and EtOAc (30 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), and dried (Na_2SO_4). Purification of the residue obtained after removal of the solvent was performed by chromatography on silica gel using EtOAc–hexane as eluent to give **15** (0.071 g, 71%) as a white solid; mp 154–156 °C (Et_2O).

^1H NMR ($CDCl_3$): δ = 3.19–3.33 (m, 4 H), 3.48–3.51 (m, 4 H), 3.79 and 4.08 (d, J = 12.3 Hz, 2 H, SCH_2), 6.96–7.02 (m, 1 H), 7.21–7.25 (m, 2 H), 7.37–7.50 (m, 4 H), 7.67–7.70 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 44.2 (SCH_2), 47.0 (*C*ClPh), 49.2 (CH_2N), 66.2 (OCH_2), 120.3, 123.1, 125.3, 127.0, 128.3, 128.4, 128.6, 137.4, 141.8, 154.7 (C=N).

Anal. Calcd for $C_{19}H_{19}ClN_2OS$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.40; H, 5.48; N, 7.66.

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References

(1) Ilaš, J.; Štefanič, A. P.; Sollner, D. M.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325.
(2) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449.
(3) Fringuelli, R.; Milanese, L.; Schiaffella, F. *Mini-Rev. Med. Chem.* **2005**, *5*, 1061.
(4) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1986**, *34*, 2078.
(5) Atwal, K. S.; Bergey, J. L.; Hedberg, A.; Moreland, S. *J. Med. Chem.* **1987**, *30*, 635.
(6) Teller, J. In *Houben-Weyl Methods of Organic Chemistry*, Vol. E 9a; Schaumann, E., Ed.; Thieme: Stuttgart, **1997**, 141.
(7) (a) Ulrich, H. In *Science of Synthesis*, Vol. 17; Weinreb, S. M., Ed.; Thieme: Stuttgart, **2003**, 55. (b) Herr, R. J. In *Science of Synthesis*, Vol. 17; Weinreb, S. M., Ed.; Thieme: Stuttgart, **2003**, 929.
(8) Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Russ. Chem. Rev.* **2005**, *74*, 171.
(9) Khlebnikov, A. F.; Nikiforova, T. Yu.; Novikov, M. S.; Kostikov, R. R. *Russ. J. Org. Chem.* **1997**, *33*, 885.
(10) Khlebnikov, A. F.; Nikiforova, T. Yu.; Novikov, M. S.; Kostikov, R. R. *Synthesis* **1997**, 677.
(11) Khlebnikov, A. F.; Novikov, M. S.; Shinkevich, E. Yu.; Vidovich, D. *Org. Biomol. Chem.* **2005**, *3*, 4040.
(12) Takamatsu, M.; Sekiya, M. *Chem. Pharm. Bull.* **1980**, *28*, 3098.
(13) Khlebnikov, A. F.; Kostik, E. I.; Kostikov, R. R. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1991**, *27*, 636.
(14) Sabitha, G.; Rao, A. V. S. *Synth. Commun.* **1987**, *17*, 341.
(15) Fujii, K. *Yakugaku Zasshi* **1957**, *77*, 347; *Chem. Abstr.* **1957**, *51*, 66636.