2*H*-1,2,4-Benzothiadiazine 1,1-Dioxides **2** [1]. A Condensation of 2-Aminobenzenesulfonamide with Chloroalkyl Isothiocyanates

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A reaction of 2-aminobenzenesulfonamide (**1**) with 2-chloroethyl or 3-chloropropyl isothiocyanate in isopropanol afforded 2-(2′-chloroethylthioureido)- and 2-(3′-chloropropylthioureido)benzenesulfonamides (**2a,b**) in 67% and 55% yield respectively. Treatment of **2a,b** with triethylamine in methanol at room temperature furnished 3-(2′-aminoethylthio)- and 3-(3′-aminopropylthio)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**9a,b**) in quantitative yield. Heating **2b** to reflux in methanol under neutral conditions gave **9b** but in the form of the hydrochloride **8b** which could be converted into the free base **9b** by treating with ammonia water. When compounds **2a,b** were treated with triethylamine in methanol at elevated temperature, 3-(2′-mercaptoethylamino)- and 3-(3′-mercaptopropylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (**10a,b**) were obtained in good yield. Alternatively, **10a,b** could also be prepared from **9a,b** in 95% and 77% yield respectively.

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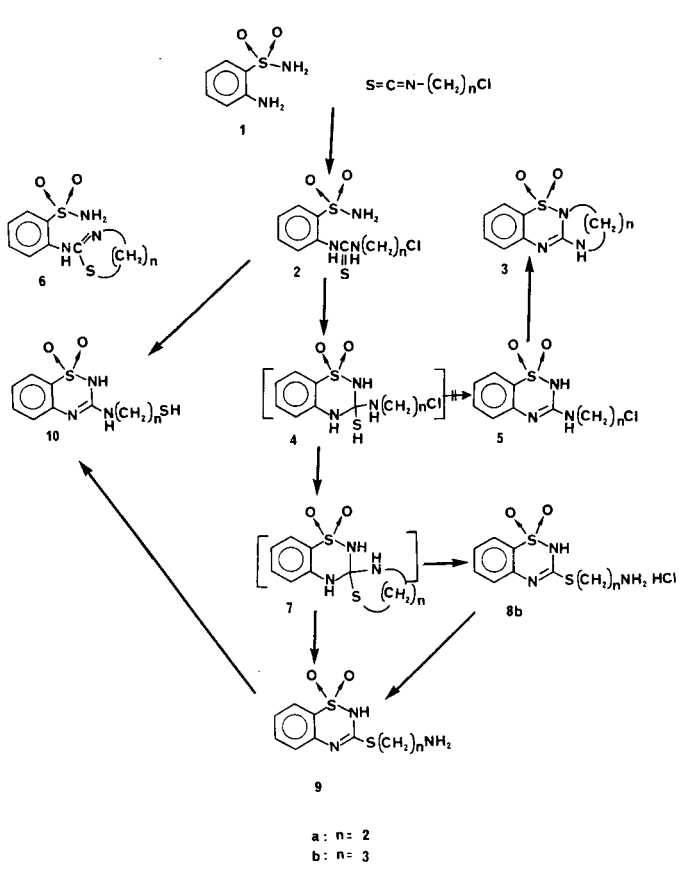
The 1,2,4-benzothiadiazine 1,1-dioxide ring system has drawn much attention since the discovery of the diuretic activity of chlorothiazide [2] and the antihypertensive activity of diazoxide [3]. It has been reported that a direct cyclocondensation of 2-aminobenzenesulfonamide (**1**) with an alkyl isothiocyanates neat [4] or under basic conditions [1] gave the corresponding 3-substituted amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides. A previous paper from this laboratory described a reaction of anthranilamide with 2-chloroethyl isothiocyanate resulting in the formation of 2,3-dihydro-5*H*-thiazolo[2,3,-*b*]quinazolin-5-one *via* a double ring closure reaction [5]. The present investigation was prompted by the expectation that an analogous condensed 3-(chloroalkylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5**) formed from **1** with the appropriate chloroalkyl isothiocyanates would undergo a second ring closure reaction to afford tricyclic heterocycles such as 2,3-dihydro-2*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**3a**) or 1,2,3,4-tetrahydropyrimido[1,2-*b*][1,2,4]benzothiadiazine 6,6-dioxide (**3b**), as a result of an intramolecular nucleophilic substitution of the initially cyclized compound **5**.

This paper describes the preliminary results from the reaction of compound **1** and two representative chloroalkyl isothiocyanates, which leads to construction of the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide ring system bearing a side chain at C-3 capable of forming a fusion component. To perform this investigation, compound **1** was treated with 2-chloroethyl isothiocyanate in 2-propanol at room temperature to provide 2-(2′-chloroethylthioureido)benzenesulfonamide (**2a**) in 67% yield. Refluxing **2a** in methanol could not initiate the reaction. However, when **2a** was treated with triethylamine in the same medium, the white precipatated solid was obtained in good yield even by stirring at room temperature. The mass spectral analysis of this product exhibited a molecular ion peak at 257 (M^+), which showed that hydrogen chloride was eliminated from **2a** under these reaction conditions. Nevertheless, elimination of hydrogen chloride from **2a** might proceed *via* a different route leading to the formation of sulfonamide derivative **6a** and spiro compound **7a**. The ^1H nmr spectrum of this compound showed a downfield chemical shift at δ 6.8 corresponding to the two amino protons and this signal disappeared upon the addition of deuterium oxide. It thus

Scheme



excludes structure **7a**. In addition, the amino proton signal of this product appeared at a significantly higher field than that of the sulfonamide amino proton in **2a** (δ 7.8). Compound **6a** was therefore rejected. On the basis of ^{1}H nmr spectral and elemental analysis, we have assigned the structure of this product as 3-(2'-aminoethylthio)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**9a**) rather than the expected 3-(2'-chloroethylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5a**). However, when this reaction was performed at reflux temperature, it afforded a product which is quite different from **9a**. The ^{1}H, ^{13}C nmr spectrum and elemental analytical data provided strong support for the assignment of the structure of the product to be 2-(2'-mercaptoethyl)amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**10a**) rather than the tricyclic compounds, 2,3-dihydro-1*H*-imidazo[1,2-*b*][1,2,4]benzothiadiazine 5,5-dioxide (**3a**). Alternatively, **10a** was obtained in 95% yield by heating **9a** in methanol.

Repeating the above reactions using 3-chloropropyl isothiocyanate in place of 2-chloroethyl isothiocyanate furnished 2-(3'-chloropropylthioureido)benzenesulfonamide (**2b**) in 55% yield and 3-(3'-aminopropylthio)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**9b**) in 89% yield respectively. Similarly, 2-(3'-mercaptopropylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**10b**) was obtained in a quantitative yield either by heating **2b** with triethylamine or by heating **9b** under neutral conditions. The ^{13}C nmr spectra obtained for compound **9b** revealed that the chemical shift of the carbons of the benzene ring moiety has been changed when compared to the chemical shifts of the carbons atoms of starting material **2b** and are in agreement with values of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide [1]. This would indicate that the NH_2 proton in this compound is not incorporated in a conjugated electronic system and lend some support to the structure which has been assigned for compound **9a**. The ^{1}H nmr spectrum of **10b** showed the SH proton as a triplet δ 2.41. It must be pointed out that compound **9b** was readily converted into compound **10b**. In the ^{1}H nmr and ^{13}C nmr spectrum of **9b**, if **9b** was gently heated to dissolve in deuterium sulfoxide before it was run or allowed to stand for a while, two sets of peaks for the three carbons atoms of the propyl side chain which exists in **9b** and **10b** were observed. If we did not prepare the sample carefully, the spectrum of compound **10b** could be observed exclusively. In order to obtain in good nmr spectrum of **9b**, the nmr sample must be running as soon as it was ready without heating. This phenomena did not occur in the case of **9a**, it might be due to the strain transition state formed as a result of the nitrogen atom of 2-aminoethylthio displacing the sulfur atom. Therefore, compound **9a** is more stable than **9b**. However, it must be noted that when **2b** was refluxed in methanol under neutral conditions for 24 hours, a water soluble product was obtained in good yield. The ^{1}H nmr spectrum of this product showed a downfield chemical shift at δ 8.03 for three protons which is deuterium oxide exchangeable. This product was allowed to dissolve in water and then was neutralized with ammonia water giving a white solid which is similar to **9a** in many respects. However, the same reaction did not proceed in the case of **2a** probably due to poor solubility in methanol.

The results described herein illustrate that 3-(mercaptoalkylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides **10** are readily synthesized from **2** under basic conditions. The mechanism for this formation might proceed *via* an initial intramolecular attack of the nitrogen atom of the sulfamido group to the sp^2 carbon atom of the thioureido side chain in **2** to form intermediate **4**. Subsequently an intramolecular nucleophilic attack of the sulfur atom of the sulhydryl group to the chloroalkyl side chain of **4** formed a spiro intermediate **7** rather than an elimination hydrogen sulfide to give compound **5** as observed in the synthesis of 3-alkylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides prepared from a direct condensation of compound **1** and alkyl isothiocyantes [4]. A ring opening of **7** afforded compound **9** which is readily transformed to **10** in good yield. It would appear that this methodology may provide a new and novel general route for the preparation of **10** for the synthesis of tricyclic compounds in our laboratory.

EXPERIMENTAL

Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Model 983 G spectrophotometer. The ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Joel FX-100 spectrometer from the National Taiwan Normal University or on a Bruker Model AM 300 spectrometer from the National Taiwan University, Taipei, using DMSO-d_6 as the solvent and as internal standard. Mass spectra were obtained on a Finnigan MAT TSQ-46C GC/MS spectrometer from the National Taiwan University. Elemental analysis was carried out either on Heraeus Elemental Analyzer from the Cheng-Kong University, Tainan, or on Perkin-Elmer 240 Elemental Analyzer from the National Taiwan University, Taipei.

2-(2'-Chloroethylthioureido)benzenesulfonamide (**2a**).

To a solution of 2-aminobenzenesulfonamide (2.0 g, 12.0 mmoles) in 2-propanol (30 ml) was added 2-chloroethyl isothiocyanate (2.5 ml, 15.0 mmoles). The mixture was stirred at room temperature for 24 hours and the precipitate was collected by filtration and then recrystallized from 2-propanol to give 2.9 g (67%) of **2a**, mp 196-197°; ir (potassium bromide): 3287, 3020, 2875, 1626, 1585, 1343, 1308, 1165, 1056 cm^{-1}; ^{1}H nmr (DMSO-d_6): 100 MHz, δ 3.5 (q, 2H, CH_2), 3.9 (t, 2H, CH_2), 7.8 (m, 6H, Ar-H, NH_2), 9.6 (br s, 1H, NH); ^{13}C nmr (DMSO-d_6): 25 MHz, δ 30.93, 48.98, 128.20, 128.96, 133.47, 139.57, 171.97; ms: m/z 257, 223, 197, 156, 133.

Anal. Calcd. for $C_9H_{12}N_3ClO_2S_2$ (293.8): C, 36.79; H, 4.12; N, 14.30. Found: C, 36.76; H, 3.92; N, 14.20.

2-(3'-Chloropropylthioureido)benzenesulfonamide (**2b**).

Compound **2b** was prepared in 55% yield using a procedure similar to that which afforded **2a**, mp 185-186°; ^{1}H nmr (DMSO-d_6): 100 MHz, δ 2.0 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 7.2-8.1 (m, 6H, Ar-H and NH_2, deuterium oxide exchangeable), 9.6 (br s, 1H, NH, deuterium oxide exchangeable), 11.4 (br s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (DMSO-d_6): 25 MHz, δ 166.2, 140.7, 133.2, 131.1, 130.8, 129.4, 128.4, 39.1, 26.4, 20.6.

Anal. Calcd. for $C_{10}H_{14}N_3O_2SCl$ (307.8): C, 39.02; H, 4.58; N, 13.65. Found: C, 38.96; H, 4.61; N, 13.68.

3-(3'-Aminopropylthio)-2*H*-1,2,4-benzothiazine 1,1-Dioxide Hydrochloride (**8b**).

A mixture of **2b** (0.5 g, 1.6 mmoles) in methanol (25 ml) was refluxed in an oil bath for 24 hours. After the mixture was cooled to room temperature, the solid was collected by filtration and recrystallization from methanol to afford 0.46 g (92%) of **8b**, mp 255°; ^{1}H nmr (DMSO-d_6): 300 MHz, δ 2.01 (p, 2H, CH_2), 2.90 (br s, 2H, CH_2), 3.19 (t, 2H, CH_2), 7.41 (t, 2H, Ar-H), 7.67 (q, 1H, Ar-H), 7.71 (d, 1H, J = 8.0 Hz, Ar-H), 8.03 (s, 3H, NH_3, deuterium oxide exchangeable) 12.91 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (DMSO-d_6): 25 MHz, δ 26.89, 27.48, 37.44, 116.89, 121.58, 123.10, 126.79, 132.95, 135.46, 159.72.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S_2$·HCl (307.83): C, 39.02; H, 4.59; N, 13.65. Found: C, 39.05; H, 4.53; N, 13.42.

3-(2'-Aminoethylthio)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**9a**).

To a mixture of **2a** (0.6 g, 2.0 mmoles) was added triethylamine (1 ml) to obtain a white precipitate. The mixture was stirred at room temperature for 40 minutes. The solid was then collected by filtration and recrystallized from acetonitrile to afford 0.42 g (80%) of **9a**, mp 159-160°; ir (potassium bromide): 3293, 2868, 1625, 1578, 1467, 1305, 1140 cm^{-1}; ^{1}H nmr (DMSO-d_6): 100 MHz δ 3.3 (t, 2H, CH_2), 3.6 (t, 2H, CH_2), 6.8 (s, 2H, NH_2, deuterium oxide exchangeable), 7.0 (m, 2H, Ar-H), 7.1 (m, 1H, Ar-H), 7.4 (m, 1H, Ar-H), 7.6 (s, 1H, NH, deuterium oxide exchangeable); ms: m/z 257 (M^+).

Anal. Calcd. for $C_9H_{11}N_3O_2S_2$ (257.3): C, 42.02; H, 4.31; N, 16.33. Found: C, 42.17; H, 4.47; N, 16.38.

3-(3'-Aminopropylthio)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**9b**).

Method A.

Compound **9b** was prepared from **2b** in 89% yield using a procedure similar to that which afforded **9a**, mp 140-142°; ^{1}H nmr (DMSO-d_6): 100 MHz, δ 1.92 (m, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.29 (q, 2H, CH_2), 6.72 (br s, 2H, NH_2, deuterium oxide exchangeable), 7.03-7.73 (m, 4H, Ar-H), 7.86 (br s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (DMSO-d_6): 25 MHz, δ 21.16, 26.41, 39.10, 116.28, 122.46, 122.60, 123.43, 132.09, 135.49, 150.90.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S$ (271.37): C, 44.26; H, 4.83; N, 15.49. Found: C, 44.29; H, 4.85; N, 15.49.

Method B.

Compound **8b** (0.48 g, 1.6 mmoles) was dissolved in water (20 ml) and the resulting solution was made to *p*H 8 with 23% ammonia water, then the solution was titrated back to *p*H 6 by acetic acid to get precipitate. The solid was collected by filtration, washed with water (10 ml), ether (5 ml) and recrystallization from ethanol affording 0.36 g (86%) of **9b**, mp 137-139°. The ^{1}H and ^{13}C nmr are identical to those obtained from method A.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S$ (271.37): C, 44.26; H, 4.83; N, 15.49. Found: C, 44.23; H, 4.57; N, 15.38.

3-(2'-Mercaptoethylamino)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**10a**).

Method A.

To a mixture of **2a** (0.65 g, 2.0 mmoles) in methanol (10 ml) was added triethylamine (1 ml) to get precipitate. The mixture was refluxed in an oil bath for 12 hours and then evaporated *in vacuo* to oil residue. The residue was treated with water (20 ml) and the solid formed was then collected by filtration and washed with ether (20 ml) to furnish 0.33 g (65%) of **10a**. An analytical sample was recrystallized from ethanol, mp 201-203°; ir (potassium bromide): 3117, 1627, 1164, 754 cm^{-1}; ^{1}H nmr (DMSO-d_6): 100 MHz, δ 2.95 (t, 1H, SH), 3.3 (q, 2H, CH_2), 3.6 (q, 2H, CH_2), 7.1-7.6 (m, 5H, Ar-H + NH, deuterium oxide exchangeable), 10.56 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (DMSO-d_6): 25 MHz, δ 36.68, 38.96, 116.31, 122.34, 122.79, 123.64, 132.24, 135.41, 150.76.

Anal. Calcd. for $C_9H_{11}N_3O_2S_2$ (257.34): C, 42.02; H, 4.31; N, 16.33. Found: C, 42.01; H, 4.09; N, 16.13.

Method B.

A solution of **9a** (100 mg, 0.4 mmole) in methanol (10 ml) was refluxed in an oil bath for 24 hours and the solvent was then evaporated *in vacuo*. The residue was dissolved in acetone (5 ml) and then ether was added (10 ml). A precipitate was obtained which was recrystallized from methanol furnishing 95 mg (95%) of **10a**, mp 200-203°. The ^{1}H and ^{13}C nmr spectrum are identical to those obtained from method A.

3-(3'-Mercaptopropylamino)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**10b**).

Method A.

Compound **10b** was prepared in 88% yield using a procedure similar to that which afforded **10a** described in method A, mp 215-217°; ^{1}H nmr (DMSO-d_6): 300 MHz, δ 1.78 (p, 2H, CH_2), 2.41 (t, 1H, SH), 2.50 (m, 2H, CH_2), 3.31 (m, 2H, CH_2), 7.13 (br s, 1H, NH, deuterium oxide exchangeable), 7.17 (d, 1H, Ar-H), 7.23 (t, 1H, Ar-H), 7.53 (t, 1H, Ar-H), 7.64 (d, 1H, Ar-H), 10.55 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (DMSO-d_6): 75 MHz, δ 28.46, 35.08, 39.14, 116.47, 122.59, 122.78, 123.65, 132.32, 135.67, 151.10; ms: m/z 271 (M^+), 253, 191, 163.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S_2$ (271.37): C, 44.26; H, 4.83; N, 15.49. Found: C, 44.37; H, 4.75; N, 15.40.

Method B.

A solution of **9b** (200 mg, 0.37 mmole) in methanol (25 ml) was refluxed in an oil bath for 18 hours. After the mixture was cooled to room temperature, the solid formed was collected by filtration and recrystallized from methanol to afford 153 mg (77%) of **10b**, mp 215-217°. The ^{1}H and ^{13}C nmr spectrum are identical to that obtained from method A.

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