1,2,4-Benzothiadiazine 1,1-Dioxides 3. Reactions of 2-Aminobenzenesulfonamide with Chloroalkyl Isocyanates [1].

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Reactions of 2-aminobenzenesulfonamide (**1**) with allyl, methyl, 2-chloroethyl aor 3-chloropropyl isocyanates gave 2-(methylureido)-, 2-(allylureido)-, 2-(2′-chloroethylureido)- and 2-(3′-chloropropylureido)-benzene sulfonamides **3a,b** and **7a,b** in excellent yields. Treatment of **3a,b** at refluxing temperature of DMF afforded 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (**4**) in good yield. However, when compounds **7a,b** were refluxed in 2-propanol, 3-(2′-aminoethoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**11a**) and 3-(3′-aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**11b**) were obtained in a form of the hydrochloride salts **10a,b** in 87% and 78% yields respectively. Heating **11b** in ethanol gave a dimeric form of 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide and 3-(3′-aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**12**) in 55% yield. Treating of **7a,b** or **11a,b** with triethylamine at the refluxing temperature of 2-propanol afforded 3-(2′-hydroxyethylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2a**) and 3-(3′-hydroxypropylamine)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2b**) *via* a Smiles rearrangement.

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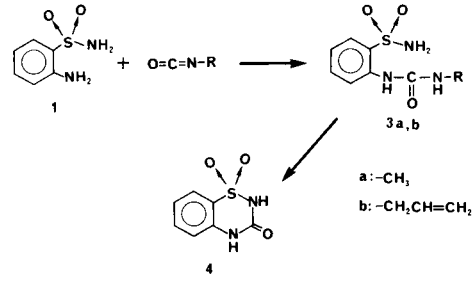
Chloroalkyl isocyanates have been employed as building blocks for the synthesis of some condensed quinazolines [2,3]. As a part of our studies on the synthesis of heterocyclic compounds, we recently reported a direct condensation of 2-aminobenzamide or 2-aminothiobenzamide with chloroalkyl isocyanates leading to the corresponding condensed quinazolinone ring systems [4,5]. We have extended our interest to examine the behavior of chloroalkyl isocyanates with 2-aminobenzenesulfonamide (**1**) and found that the reaction of these compounds proceeded smoothly and resulted in the formation of 3-(hydroxyalkylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides **2** in good yield. This paper will describe our efforts toward this investigation.

The 2*H*-1,2,4-benzothiadiazine 1,1-dioxide ring system has been the subject of much attention in the field of pharmaceutics, primarily due to the discovery of diuretic activity of chlorothiazide [6] and antihypertensive activity of diazoxide [7]. It has been reported that a reaction of 2-amino-4,4-dichloro-*N*-methylbenzenesulfonamide with phenyl isocyanate would afford a 37% yield of 6,7-dichloro-2-methyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide [8]. In order to study the scope of this methodology, 2-(allylureido)- and 2-(methylureido)benzenesulfonamides **3a,b** were prepared by a treatment of **1** with allyl or methyl isocyanate in 2-propanol. We found that when **3a,b** were refluxed in DMF, 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (**4**) was obtained in a good yield (Scheme 1). A perusal of literature revealed that 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide derivatives were generally synthesized either by direct condensation of 2-aminobenzenesulfonamide derivatives with urea at elevated temperature or by reaction of aniline derivatives with chlorosulfonyl isocyanate giving chlorosulfonylurea, followed by cyclization with Lewis acids [9]. Thus, the results described above provide an alternative approach for the preparation of 2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide derivatives.

Scheme 1

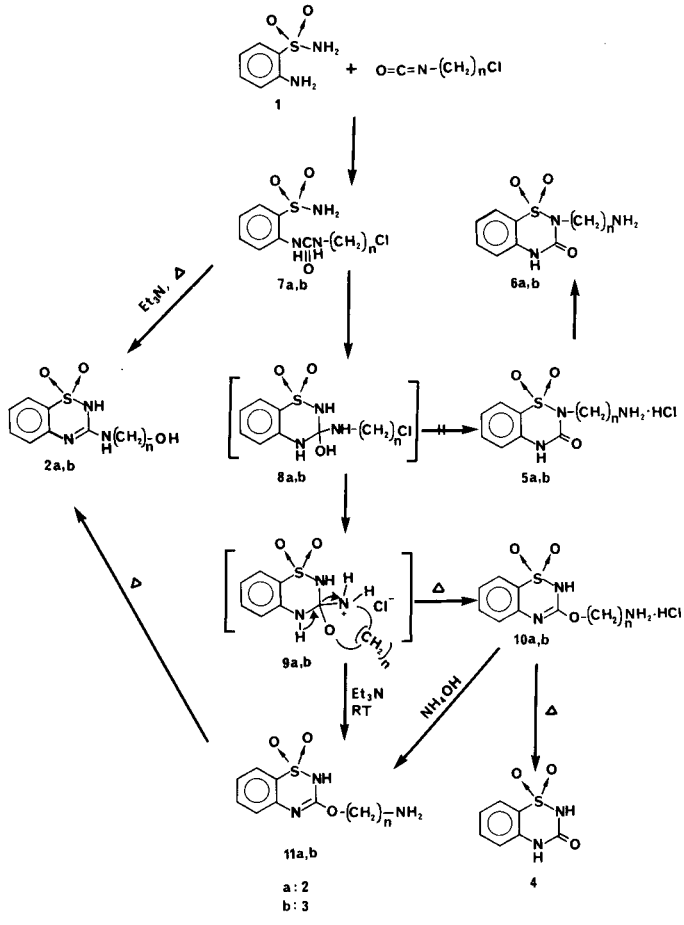


In view of the fact that 2-(alkylureido)benzenesulfonamide proceeded an elimination of alkyl amine *via* an initial attack of nitrogen atom of the sulfamido group to the carbonyl group of the ureido moiety, we reasoned that a reaction of **1** with an appropriate isocyanate containing a properly located suitable leaving group would allow alkylation at the 2-position of **4** leading to the formation of 2-(aminoalkyl)-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxides **6**, as a result of an intramolecular addition to form intermediate **8**, followed by alkylation and subsequent elimination of side chain from **8**. To examine this double ring closure and elimination, the starting material 2-(2′-chloroethylureido)benzenesulfonamide (**7a**) was obtained in 81% yield by reaction of **1** with 2-chloroethyl iso-

cyanate in 2-propanol at room temperature. However, when **7a** was refluxed in 2-propanol, a sole water soluble product was isolated in good yield. The mass spectra of the product illustrated a molecular ion peak at 277 indicative of a loss of hydrogen chloride from the starting material. The ^{1}H nmr spectrum of the product showed a strong broad singlet at δ 8.3 which corresponds to three protons and deuterium oxide exchangeable. On the basis of these data, it initially appeared to be the 2-(2′-aminoethyl)-2*H*-1,2,4-benzenethiadiazin-3(4*H*)-one 1,1-dioxide hydrochloride (**5a**). We realized that based upon these criteria alone the product could be not only **5a**, but also 3-(2′-aminoethoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide hydrochloride (**10a**). The infrared spectrum for the product showed a strong band at 1607 cm^{-1} for the C=N ring bond and no carbonyl absorption peak observed by a comparison with that of **3a**. Therefore, compound **5a** was rejected. On the basis of the ^{1}H nmr, ^{13}C nmr, ir and elemental analysis data, we have assigned the structure of this unexpected product as **10a**. Repeating the same reaction but in the presence of triethylamine, a sole product was isolated instead of the expected free base of **10a**, or 3-(2′-aminoethoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**11a**). The ^{1}H nmr spectrum of this product showed two triplets centered at δ 4.9 and δ 7.1 which are deuterium oxide exchangeable and correspond to OH and NH respectively. In addition to ^{1}H nmr, the ^{13}C nmr spectrum for this compound revealed that the chemical shifts of the carbons of the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide nucleus are in agreement with those values of the corresponding 3-alkylamino derivatives described in a recent report [10]. Thus, the structure of the product was determined to be 3-(2′-hydroxyethylamine)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2a**).

As shown in Scheme 2, the formation of **10a** from **7a** at elevated temperature under neutral conditions most probably involves the initial intramolecular nucleophilic attack of the nitrogen atom of the sulfamido group to the sp^2-hybridized-carbon atom of the ureido moiety of **7a** to form carbinol-intermediate **8** and subsequent loss of hydrogen chloride from **8** to give the spiro intermediate **9a**. The eliminated hydrogen chloride quarternized the nitrogen atom in the oxazolidine ring of the spiro intermediate **9a**. This protonated quaternary nitrogen atom might weaken the C-N bond and becomes a better leaving group. Thus, the ring opening of **9a** by proton transfer afforded **10a**. However, at elevated temperature and in the presence of triethylamine, **2a** can be formed either directly through C-O bond cleavage of the spiro intermediate **9a** or initially through C-N bond cleavage of the spiro intermediate **9a** furnishing **11a** which then subsequently underwent an intramolecular rearrangement. In order to classify the putative intramolecular rearrangement of **11a** to **2a**, compound **11a** obtained by dissolving **10a** in water and then neutralizing with ammonia water, was heated either in 2-propanol or in methanol with triethylamine giving **2a** in good yield. This lends support to the Smiles rearrangement [11] of compound **11a** involving in the synthesis of **2a** from **7a** at elevated temperature in the presence of triethylamine.

Scheme 2



Repeating the above reaction using 3-chloropropyl isocyanate instead of 2-chloroethyl isocyanate furnished 2-(3′-chloropropylureido)benzenesulfonamide (**7b**) in 93% yield and 3-(3′-aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide hydrochloride (**10b**) in 78% yield respectively. Similarly, 3-(3′-hydroxypropylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2b**) was obtained in good yield either by treatment of **7b** with triethylamine in 2-propanol at reflux temperature or by heating 3-(3′-aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**11b**) with triethylamine in methanol.

The implication of **11a,b** in the reaction sequence is of interest in that a similar 3-(2′-aminoethylthio)- and 3-(3′-aminopropylthio)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide have also been found in the reaction of **1** with chloroalkyl isothiocyanates [1]. It shall be noted that when

Table 1
Crystallographic Data

Formula	$C_{17}S_2O_6N_5H_{20}$
Mol. Wt. (g mole^{-1})	454.5
Crystal size (mm)	0.2 x 0.3 x 0.3
Space Group	p -1
a	6.524 (3)
b Å	11.677 (4)
c	13.289 (4)
α	99.36 (3)
β (°)	101.39 (3)
γ	99.36 (3)
Vol (Å^3)	970.3 (6)
Z	2
Dc (g•cm^{-3})	1.56
Fooo	304
Radiation	Mok$_\alpha$(= .7107Å)
Scan Speed (deg/min)	16.48/2-16.48/12
2Θ Range (MoKα)	2- 50°
2Θ/2Θ Scan parameter	2(0.75 + 0.35 tan Θ)
abs coef (mm^{-1})	0.30
Total # of refl	3399
# of obs refl (>1.8σ)	2366
Quandrant collected	±h k ±1
R,R$_w$	0.050, 0.040
S	2.63

compound 10b was refluxed in concentrated hydrochloric acid, compound **4** was obtained in 59% yield. Interestingly, an attempt to crystallize **10b** in ethanol on a hot plate afforded a good yield of rod crystals. The ^{1}H and ^{13}C nmr spectrum for this product revealed a mixture of peaks for compounds **11b** and **4**. The elemental analysis for this product is consistent with an empirical composition of $C_{17}H_{20}N_5S_2O_6$ and indicated that this product existed as an equal amount of **11b** and **4**. Thus, we have assigned the structure of this product as a dimeric form of **4** and **11b** as **12**. An X-ray crystallographic study for this product was carried out and in agreement with this assignment and illustrates that in the solid state, **11b** and **4** form a dimeric salt by hydrogen bonding depicted in Figure 1. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer at room temperature using monochromated Mo-K_α radiation with $\theta/2\theta$ scan mode. Three reflections were chosen to monitor the intensity measurement every two hours throughout the data collection, the variation are less

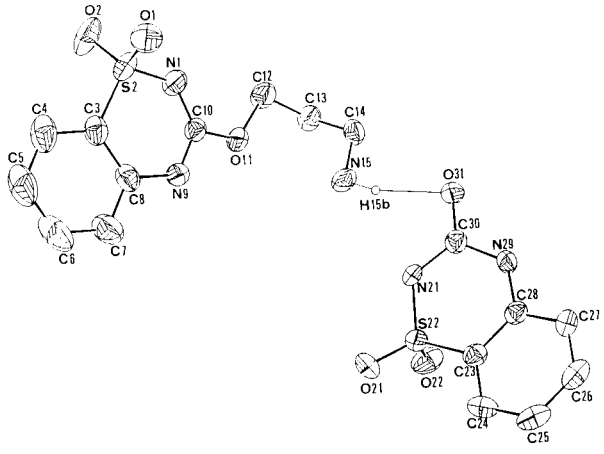


Figure 1. The crystallography of **12**.

Table 2
Atomic Parameters x,y,z and Biso. E.S.Ds. refer to the last digit printed

	x	y	z	Biso
N1	0.7943 (6)	0.3633 (3)	0.4882 (3)	3.43(18)
S2	0.65782(21)	0.30590(10)	0.58230(8)	3.44(5)
C3	0.5041 (7)	0.2199 (3)	0.5502 (3)	3.36(22)
C4	0.3995 (9)	0.1372 (4)	0.6196 (4)	5.0 (3)
C5	0.2687 (10)	0.0776 (4)	0.5855 (4)	6.1 (3)
C6	0.2370 (9)	0.1023 (4)	0.4833 (4)	6.2 (3)
C7	0.3414 (9)	0.1832 (4)	0.4140 (4)	5.0 (3)
C8	0.4787 (8)	0.2419 (3)	0.4470 (3)	3.38(22)
N9	0.5908 (6)	0.3204 (3)	0.37639(25)	3.32(18)
C10	0.7434 (7)	0.3697 (3)	0.3983 (3)	2.76(21)
O11	0.8490 (5)	0.42650(23)	0.31476(19)	3.01(14)
C12	1.0112 (7)	0.4929 (4)	0.3269 (3)	3.75(24)
C13	1.0895 (7)	0.5538 (4)	0.2209 (3)	3.35(21)
C14	0.9378 (7)	0.6546 (3)	0.1822 (3)	3.20(21)
N15	0.7497 (6)	0.6177 (3)	0.1546 (3)	3.48(18)
O1	0.5189 (5)	0.3981 (3)	0.64129(22)	4.35(17)
O2	0.7961 (6)	0.2338 (3)	0.65513(24)	5.80(20)
N21	0.5834 (6)	0.2854 (3)	0.99446(23)	2.93(17)
S22	0.68086(20)	0.32107(9)	1.08217(8)	2.89(5)
C23	0.8548 (7)	0.1970 (3)	1.1185 (3)	2.61(19)
C24	1.0296 (8)	0.2025 (4)	1.1616 (3)	3.55(22)
C25	1.1519 (8)	0.1006 (4)	1.1925 (3)	3.89(24)
C26	1.1019 (8)	-0.0061 (4)	1.1797 (3)	3.69(22)
C27	0.9322 (7)	-0.0121 (3)	1.1358 (3)	3.08(20)
C28	0.8055 (7)	0.0901 (3)	1.1037 (3)	2.49(20)
N29	0.6384 (6)	0.0848 (3)	1.05544(25)	2.84(16)
C30	0.5425 (7)	0.1769 (3)	0.9947 (3)	2.63(20)
O31	0.4244 (5)	0.15630(23)	0.93930(21)	3.25(15)
O21	0.8005 (5)	0.41834(23)	1.04171(22)	4.05(17)
O22	0.5209 (5)	0.3417 (3)	1.17263(20)	4.40(16)
H1	0.928	0.396	0.492	3.9
H4	0.421	0.120	0.697	5.2
H5	0.198	0.013	0.637	6.3
H6	0.138	0.054	0.459	6.9
H7	0.310	0.202	0.337	5.9
H9	0.553	0.344	0.303	4.0
H12A	0.953	0.552	0.376	4.4
H12B	1.131	0.438	0.357	4.4
H13A	1.229	0.581	0.221	4.0
H13B	1.118	0.493	0.171	4.0
H14A	1.014	0.703	0.120	3.7
H14B	0.889	0.707	0.239	3.7
H15A	0.802	0.537	0.106	3.2
H15B	0.673	0.682	0.122	3.2
H21	0.553	0.347	0.933	3.6
H24	1.070	0.282	1.170	4.2
H25	1.280	0.102	1.227	4.5
H26	1.199	-0.082	1.201	4.3
H27	0.899	-0.092	1.126	3.5
H29	0.582	0.006	1.065	3.4

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table 2 (continued)

Table of u(i,j) or values *100.

E.S.Ds. refer to the last digit printed

	u11 (U)	u22	u33	u12	u13	u23
N1	4.1 (3)	5.36(24)	3.80(21)	-1.68(21)	-1.03(19)	0.33(18)
S2	4.92(8)	4.52(7)	3.08(6)	0.03(6)	-0.73(6)	0.46(5)
C3	4.7 (3)	3.31(25)	4.2 (3)	-0.36(24)	0.43(24)	-0.53(21)
C4	7.5 (4)	4.9 (3)	5.1 (3)	-1.3 (3)	1.9 (3)	-0.2 (3)
C5	8.5 (5)	6.2 (4)	7.6 (4)	-3.7 (4)	2.8 (4)	-0.7 (3)
C6	7.8 (5)	7.3 (4)	9.1 (4)	-4.6 (4)	1.6 (4)	-2.8 (3)
C7	7.2 (4)	6.6 (4)	5.9 (3)	-3.5 (3)	-0.1 (3)	-1.5 (3)
C8	5.1 (3)	3.30(24)	4.3 (3)	-1.02(24)	0.36(25)	-1.00(21)
N9	5.3 (3)	4.43(22)	3.30(20)	-1.93(21)	-1.02(19)	-0.12(17)
C10	4.1 (3)	3.12(23)	3.10(23)	-0.06(22)	-0.53(22)	-0.41(19)
O11	4.46(20)	3.99(17)	2.89(15)	-1.29(16)	-0.40(15)	0.28(13)
C12	4.3 (3)	5.6 (3)	4.7 (3)	-1.7 (3)	-1.6 (3)	0.52(24)
C13	3.6 (3)	4.7 (3)	4.3 (3)	-1.03(24)	-0.70(23)	0.15(22)
C14	5.0 (3)	3.25(24)	3.8 (3)	-1.31(24)	-0.02(24)	-0.15(20)
N15	5.2 (3)	3.95(22)	4.18(22)	0.91(20)	-2.35(21(	-0.71(17)
O1	6.2 (3)	5.51(21)	4.54(19)	-0.14(19)	0.05(18)	-1.82(16)
O2	7.3 (3)	7.8 (3)	6.01(23)	-0.19(23(	-2.65(21)	2.77(20)
N21	5.6 (3)	2.91(19)	3.03(19)	-0.60(19)	-2.28(19)	0.41(15)
S22	4.89(8)	3.10(6)	3.32(6)	-0.47(6)	-1.37(6)	-0.65(5)
C23	3.5 (3)	3.63(24)	2.74(22)	-0.26(22)	-0.52(21)	-0.59(19)
C24	4.8 (3)	5.1 (3)	4.4 (3)	-1.3 (3)	-1.40(25)	-1.59(23)
C25	4.2 (3)	7.1 (3)	3.8 (3)	-0.1 (3)	-1.69(24)	-1.09(25)
C26	4.6 (3)	5.6 (3)	3.4 (3)	0.6 (3)	-1.22(24)	0.04(23)
C27	4.4 (3)	3.44(25)	3.7 (3)	-0.33(23)	-1.07(23)	0.21(20)
C28	3.0 (3)	3.66(24)	2.77(22)	-0.71(21)	-0.56(20)	-0.04(19)
N29	3.96(3)	2.65(18)	4.62(22)	-1.16(18)	-1.90(19)	0.31(16)
C30	3.6 (3)	3.34(24)	2.99(23)	-0.52(21)	-0.45(21)	-0.23(19)
O31	4.82(21)	3.55(17)	4.68(18)	-0.77(16)	-2.55(16)	-0.31(14)
O21	7.5 (3)	3.28(17)	5.49(20)	-2.23(18)	-1.99(19)	0.48(15)
O22	5.13(23)	6.42(22)	3.63(18)	1.06(19)	-0.93(17)	-1.88(16)
H1	5.0					
H4	6.6					
H5	8.0					
H6	8.7					
H7	7.5					
H9	5.0					
H12A	5.5					
H12B	5.5					
H13A	5.0					
H13B	5.0					
H14A	4.7					
H14B	4.7					
H15A	4.1					
H15B	4.1					
H21	4.6					
H24	5.4					
H25	5.8					
H26	5.4					
H27	4.5					
H29	4.3					

Anisotropic Temperature Factors are of the form
Temp = 2*Pi*Pi*(h*h*ull*astar*astar+---+2*h*k*ul2*astar*bstar+---)

than ±3%. The structure was solved by the direct method and refined by the full matrix least squares process. The atomic scattering factors were based on an analytical expression taken from the International Tables for X-ray crystallography IV [12]. All the calculations were made on a microvax computer with NRCVAX programs [13].

The molecular structure of **12** with the thermal ellipsoids are shown in Figure 1. Figure 1 shows that there are two parts in the molecule connected through a H-bond (N15-H15b-O31). Crystal data, coordinates, bond distances and angles are available in Tables 1, 2 and 3. All bond lengths and angles are normal. There is hydrogen bonding between amine nitrogen atom (N15) and oxygen atom (O31) of the ketone group with N15-O31 distance of 2.886(4) (shown in Figure 1). Two other intermolecular H-bondings exist between N15 and O21 (sulfone); N9-O22 with N-O distance of 2.910 (4), 2.799 (4) Å respectively.

Table 3

Bond Distances and Angles of Compound

Bond Distances

N(1)-S(2)	1.601(4)	C(13)-C(14)	1.502(6)
N(1)-C(10)	1.289(5)	C(14)-N(15)	1.492(6)
S(2)-C(3)	1.749(5)	N(21)-S(22)	1.573(3)
S(2)-O(1)	1.443(3)	N(21)-C(30)	1.336(5)
S(2)-O(2)	1.429(3)	S(22)-C(23)	1.753(4)
C(3)-C(4)	1.387(6)	S(22)-O(21)	1.454(3)
C(3)-C(8)	1.391(6)	S(22)-O(22)	1.452(3)
C(4)-C(5)	1.366(8)	C(23)-C(24)	1.388(6)
C(5)-C(6)	1.391(8)	C(23)-C(28)	1.391(6)
C(6)-C(7)	1.373(7)	C(24)-C(25)	1.372(6)
C(7)-C(8)	1.385(7)	C(25)-C(26)	1.383(7)
C(8)-N(9)	1.387(5)	C(26)-C(27)	1.365(6)
N(9)-C(10)	1.328(6)	C(27)-C(28)	1.393(6)
C(10)-O(11)	1.325(5)	C(28)-N(29)	1.384(5)
O(11)-C(12)	1.456(5)	N(29)-C(30)	1.377(5)
C(12)-C(13)	1.502(6)	C(30)-O(31)	1.240(5)
N(15)-O(31)	2.886(4)	N(15)-O(21)'	2.910(4)
N(9)-O(22)'	2.799(4)		

Bond Angles

S(2)-N(1)-C(10)	122.7(3)	C(12)-C(13)-C(14)	144.4(4)
N(1)-S(2)-C(3)	104.59(19)	C(13)-C(14)-N(15)	113.5(3)
N(1)-S(2)-O(1)	1.08.66(19)	S(22)-N(21)-C(30)	122.9(3)
N(1)-S(2)-O(2)	109.38(21)	N(21)-S(22)-C(23)	104.44(18)
C(3)-S(2)-O(1)	108.40(21)	N(21)-S(22)-O(21)	110.59(17)
C(3)-S(2)-O(2)	110.15(21)	N(21)-S(22)-O(22)	111.32(20)
O(1)-S(2)-O(2)	115.12(20)	C(23)-S(22)-O(21)	108.86(20)
S(2)-C(3)-C(4)	120.6(4)	C(23)-S(22)-O(22)	107.32(18)
S(2)-C(3)-C(8)	118.2(3)	O(21)-S(22)-O(22)	113.79(19)
C(4)-C(3)-C(8)	121.0(4)	S(22)-C(23)-C(24)	123.0(3)
C(3)-C(4)-C(5)	119.0(4)	S(22)-C(23)-C(28)	116.0(3)
C(4)-C(5)-C(6)	120.2(4)	C(24)-C(23)-C(28)	121.0(4)
C(5)-C(6)-C(7)	121.1(5)	C(23)-C(24)-C(25)	119.3(4)
C(6)-C(7)-C(8)	119.2(5)	C(24)-C(25)-C(26)	120.1(4)
C(3)-C(8)-C(7)	119.4(4)	C(25)-C(26)-C(27)	120.9(4)
C(3)-C(8)-N(9)	121.1(4)	C(26)-C(27)-C(28)	120.1(4)
C(7)-C(8)-N(9)	119.5(4)	C(23)-C(28)-C(27)	118.5(4)
C(8)-N(9)-C(10)	123.4(3)	C(23)-C(28)-N(29)	121.1(4)
N(1)-C(10)-N(9)	126.4(4)	C(27)-C(28)-N(29)	120.4(4)
N(1)-C(10)-O(11)	121.3(4)	C(28)-N(29)-C(30)	125.1(3)
N(9)-C(10)-O(11)	112.2(3)	N(21)-C(30)-N(29)	119.6(4)
C(10)-O(11)-C(12)	118.9(3)	N(21)-C(30)-O(31)	121.6(3)
O(11)-C(12)-C(13)	106.3(3)	N(29)-C(30)-O(31)	118.8(3)

This will provide further evidence for the structural assignment of **11a-b**.

It would appear that the above reactions might provide a new route for the preparation of a biologically interesting hetero-bicyclic ring system 2*H*-1,2,4-benzothiodiazine 1,1-dioxide containing functionalized aza and oxa-alkyl side chain, though compounds **10a-b** showed no antihypertensive activity on spotaneous hypertensive rats at an intravenious administration of 10 mg/Kg.

EXPERIMENTAL

General Methods.

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

2-(Allylureido)benzenesulfonamide (**3a**).

A mixture of **1** (0.5 g, 3 mmoles) and allyl isocyanate (0.3 ml, 3 mmoles) in 2-propanol (10 ml) was stirred at room temperature for 4 hours. The solid was then collected by filtration and recrystallized from 2-propanol to give 0.65 g (85%) of **3a**, mp 155°; ir (potassium bromide): 3372 (N-H), 3065 (=C-H), 1684 (C=O), 1172 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 3.8 (d, 2H, CH_2), 5.1 (q, 1H, =CH), 5.2 (q, 1H, =CH), 5.8 (m, 1H, =CH), 6.9 (t, 1H, Ar-H), 7.4-7.8 (m, 5H, Ar-H + NH_2), 8.1 (d, 1H, NH), 8.3 (s, 1H, NH); ms: m/z, 255 (M^+).

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.09; N, 16.47. Found: C, 47.07; H, 5.01; N, 16.46.

2-(Methylureido)benzenesulfonamide (**3b**).

A mixture of **1** (1.0 g, 6 mmoles) and methyl isocyanate (0.34 ml, 6.0 mmoles) in acetonitrile (20 ml) was stirred at room temperature for 24 hours. The solid was collected and recrystallized from acetonitrile to afford 1.04 g (78%) of **3b**, mp 170°; ir (potassium bromide): 3310 (N-H), 1697 (C=O), 1165, 751 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 2.7 (d, 3H, CH_3), 7.0 (t, 1H, NH), 7.5 (m, 6H, Ar-H + NH_2), 8.2 (s, 1H, NH); ms: m/z 229 (M^+).

Anal. Calcd. for $C_8H_{11}N_3O_3S$: C, 41.92; H, 4.80; N, 18.34. Found: C, 41.93; H, 4.61; N, 18.24.

2-(2'-Chloroethylureido)benzenesulfonamide (**7a**).

To a solution of **1** (5.0 g, 29 mmoles) in 2-propanol (50 ml) was added 2-chloroethyl isocyanate (4 ml, 47 mmoles). The mixture was stirred at room temperature for 4 hours and then evaporated to oily residue *in vacuo*. The solid formed by treating with ether (30 ml) was collected by filtration to afford 6.5 g (81%) of **7a**. An analytical sample was recrystallized from acetonitrile, mp 150°; ir (potassium bromide): 2959 (C-H), 1671 (C=O), 1172 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 3.39 (t, 2H, CH_2), 3.63 (t, 2H, CH_2), 7.01-7.17 (m, 1H, NH, deuterium oxide exchangeable), 7.57 (s, 2H, NH_2, deuterium oxide exchangeable), 7.40-7.82 (m, 4H, Ar-H + NH, deuterium oxide exchangeable), 8.32 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 41.44, 43.80, 119.66, 119.89, 125.71, 128.42, 130.61, 134.92, 152.12; ms: m/z 277 (M^+).

Anal. Calcd. for $C_9H_{12}N_3O_3SCl$: C, 38.92; H, 4.36; N, 15.13. Found: C, 38.91; H, 4.28; N, 15.01.

2-(3'-Chloropropylureido)benzenesulfonamide (**7b**).

Compound **7b** was prepared in 93% yield using a procedure similar to that which afforded **7a**, mp 120°; ir (potassium bromide): 3361 (NH), 3254, 3103 (=C-H), 2969 (C-H), 1675 (C=O), 1639 (C=C), 1572, 1497, 1437, 1311, 1292, 1229, 1166, 920 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 1.91 (q, 2H, CH_2), 3.31 (q, 2H, CH_2), 3.70 (t, 2H, CH_2), 7.01-7.15 (m, 1H, NH, deuterium oxide exchangeable), 7.53 (s, 2H, NH_2, deuterium oxide exchangeable), 7.39-8.12 (m, 4H, Ar-H + NH, deuterium oxide exchangeable), 8.25 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 32.52, 36.80, 43.07, 120.94, 121.41, 127.32, 129.90, 132.30, 136.99, 154.33; ms: m/z 291 (M^+), 255, 211, 172, 155.

Anal. Calcd. for $C_{10}H_{14}N_3O_3SCl$: C, 41.17; H, 4.84; N, 14.40. Found: C, 41.18; H, 4.86; N, 14.39.

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

A mixture of **7a** (1.5 g, 5.4 mmoles) in 2-propanol (30 ml) was heated at reflux for 20 hours. After the mixture was cooled to room temperature, the white solid was collected by filtration and washed with warm 2-propanol (10 ml about 40°) to furnish 1.3 g (87%) of **10a**. An analytical sample was recrystallized from ethanol, mp 230°; ir (potassium bromide): 3171 (N-H), 3037 (=C-H), 2856 (C-H), 1627 (C=C), 1607 (C=N), 1582 (C=C), 1541, 1481, 1446, 1360, 1317, 1293, 1259, 1176, 1161, 1075, 1015, 978, 870, 761, cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6): δ 3.2 (t, 2H, CH_2), 4.5 (t, 2H, CH_2), 7.5 (m, 5H, Ar-H + NH, deuterium oxide exchangeable), 8.3 (br s, 3H, NH_2 + HCl, deuterium oxide exchangeable); ^{13}C nmr (75 MHz, DMSO-d_6): δ 37.60, 64.60, 117.11, 121.32, 123.34, 125.11, 133.24, 134.33, 153.09.

Anal. Calcd. for $C_9H_{11}N_3O_3S{\cdot}HCl$: C, 38.92; H, 4.36; N, 15.13. Found: C, 38.93; H, 4.35; N, 15.14.

3-(2'-Aminoethoxy)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**11a**).

A solution of **10a** (0.16 g, 0.57 mmole) in water (5.5 ml) was neutralized with ammonia water to *p*H 8 to get a white precipitate. After standing for 30 minutes, the solid was collected by filtration and recrystallized from ethanol to give 0.13 g (94%) of **11a**, mp 203-204°; ir (potassium bromide): 3364, 3306 (N-H), 2981 (C-H), 1630 (C=C), 1610 (C=N), 1579 (C=C), 1548, 1482, 1442, 1398, 1375, 1336, 1282, 1253, 1172, 1163, 1073, 1059, 947, 761 cm^{-1}.

Anal. Calcd. for $C_9H_{11}N_3O_3S$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.53; H, 4.36; N, 17.10.

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

Compound **10b** was prepared in 78% yield using a procedure similar to that which afforded **10a**, mp 210°; ir (potassium bromide): 3180, 3104 (N-H), 3070 (=C-H), 2928 (C-H), 1627 (C=C), 1604 (C=N), 1578 (C=C), 1534, 1482, 1360, 1317, 1292,

1282, 1264, 1124, 1059, 854 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 1.98 (p, 2H, CH_2), 2.97 (q, 2H, CH_2), 4.38 (t, 2H, CH_2), 6.88-7.79 (m, 4H, Ar-H), 8.28 (br s, 3H, NH_2 + HCl, deuterium oxide exchangeable), 9.6 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 26.13, 35.98, 65.62, 116.89, 121.11, 123.10, 124.80, 132.94, 134.23, 153.10.

Anal Calcd. for $C_{10}H_{13}N_3O_3S$·HCl: C, 41.17; H, 4.83; N, 14.40. Found: C, 41.14; H, 4.62; N, 14.21.

2H-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-Dioxide (**4**).

Method A.

A solution of **3a** (1.0 g, 4 mmoles) in *N*,*N*-dimethylformamide (10 ml) was refluxed in an oil bath for 30 minutes. The solvent was evaporated *in vacuo* and the residue was treated with water (20 ml). The solid was collected by filtration and recrystallized from DMF and water to give 0.7 g (90%) of **4**, mp 299-300° [lit [9], 300-302°]; ^1H nmr (100 MHz, DMSO-d_6): δ 7.28 (t, 2H, Ar-H), 7.74 (q, 2H, Ar-H), 11.23 (s, 1H, NH, deuterium oxide exchangeable), 11.58 (br s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 116.86,121.88, 122.46, 123.28, 133.78, 134.91, 150.42.

Method B.

Compound **4** was prepared from **3b** in 80% yield using a procedure similar to that which described in method A.

Method C.

A solution of **10b** (0.25 g, 0.85 mmole) in water (20 ml) and concentrated hydrochloric acid was refluxed for 24 hours. The solid was collected by filtration after the mixture was cooled to room temperature to afford 0.1 g (59%) of **4**. The ^1H and ^{13}C nmr spectra are similar to those obtained from method A.

Dimeric Form **4** and **11b** as **12**.

Compound **10b** (0.82 g, 2.8 mmoles) was heated in ethanol (30 ml) affording a rod crystalline compound **12** (0.7 g, 55%), mp 217-218°; ^1H nmr (300 MHz, DMSO-d_6): δ 2.03 (p, 2H, CH_2), 2.98 (t, 2H, CH_2), 4.37 (t, 2H, CH_2), 6.94 (t, 2H, Ar-H), 7.30 (t, 2H, Ar-H), 7.36 (m, 1H, Ar-H), 7.46 (d, 1H, Ar-H), 7.63 (q, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 9.50 (s, 1H, NH); ^{13}C nmr (25 NHz, DMSO-d_6): δ 26.2, 36.0, 65.7, 115.0, 117.0, 120.4, 122.1, 121.2, 122.9, 123.1, 124.9, 130.8, 133.0, 134.3, 137.8, 153.2, 154.9.

Anal. Calcd. For $C_{17}H_{20}N_5S_2O_6$: C, 44.92; H, 4.43; N, 15.41. Found: C, 44.87; H, 4.22; N, 15.38.

3-(3′-Aminopropoxy)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**11b**).

Compound **11b** was prepared in 33% yield using a procedure similar to that which afforded **11a**, mp 185°; ^1H nmr (300 MHz, DMSO-d_6): δ 1.66 (p, 2H, CH_2), 3.28 (t, 2H, CH_2), 3.40 (br s, 2H, NH_2), 3.48 (t, 2H, CH_2), 7.06 (br s, 1H, NH), 7.13-7.25 (m, 2H, Ar-H), 7.49-7.54 (q, 1H, Ar-H), 7.63 (d, 1H, J = 7.68 Hz, Ar-H); ^{13}C nmr (100 MHz, DMSO-d_6): δ 31.81, 38.71, 58.55, 116.28, 122.46, 122.65, 123.38, 132.13, 135.59, 150.90.

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46. Found: C, 46.74; H, 4.83; N, 16.27.

3,2′-Hydroxyethylamino)-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (**2a**).

Method A.

A mixture of **7a** (1.0 g, 6 mmoles) in 2-propanol (20 ml) and triethylamine (1 ml) was refluxed in an oil bath for 12 hours. After the mixture was cooled to room temperature, the white solid was collected by filtration and recrystallized from ethanol to afford 1.0 g (74%) of **2a**, mp 229-230°; ir (potassium bromide): 3512 (O-H), 3319, 3112 (N-H), 3071 (=C-H), 2975, 2955 (C-H), 1618 (C=N), 1570 (C=C), 1500, 1480, 1431, 1396, 1326, 1283, 1254, 1219, 1161, 1104, 1059, 861, 764 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 3.3 (t, 2H, CH_2), 3.5 (t, 2H, CH_2), 4.9 (t, 1H, OH, deuterium oxide exchangeable), 7.1 (t, 1H, NH, deuterium oxide exchangeable), 7.2-7.3 (m, 2H, Ar-H), 7.5-7.7 (m, 2H, Ar-H), 10.5 (s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 43.00, 59.23, 103.18, 116.19, 122.40, 123.45, 132.19, 135.47, 150.99; ms: m/z 242 (M^+), 223, 211, 197, 155, 91.

Anal. Calcd. for $C_9H_{11}N_3O_3S$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.79; N, 4.42; N, 17.34.

Method B.

A suspension of **11a** (0.18 g, 0.74 mmole) in 2-propanol (10 ml) was heated under reflux in an oil bath for 40 hours. The solvent was then evaporated *in vacuo* and the residue was treated with ethanol (5 ml). The solid was collected by filtration and recrystallized from ethanol to furnish 0.13 g (72%) of **2a**, mp 227-230°. The ^1H and ^{13}C nmr spectra are similar to those obtained from method A.

Method C.

A mixture of **11a** (50 mg, 0.2 mmole) in methanol (15 ml) and triethylamine (0.04 ml) was refluxed in an oil bath for 16 hours and the solvent was then evaporated *in vacuo*. The residue was treated with water (10 ml) and the solid was collected by filtration and washed with ether (10 ml) and recrystallized from ethanol to afford 38 mg (76%) of **2a**, mp 232°. The ^1H and ^{13}C nmr spectra are similar to those obtained from method A.

3-(3′-Hydroxypropylamino)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**2b**).

Method A.

Compound **2b** was prepared in 80% yield using a procedure similar to that which afforded **2a** describing in Method A, mp 210°; ir (potassium bromide): 3345 (O-H), 3201, 3121 (N-H), 2998, 2966, 2882 (C-H), 1633 (C=C), 1608 (C=N), 1568 (C=C), 1429, 1269, 1197, 1170, 1160, 1115, 1074, 1024, 870 cm^{-1}; ^1H nmr (100 MHz, DMSO-d_6): δ 1.70 (p, 2H, CH_2), 3.29 (q, 2H, CH_2), 3.49 (q, 2H, CH_2), 4.60 (t, 1H, OH, deuterium oxide exchangeable), 7.10 (t, 1H, NH, deuterium oxide exchangeable), 7.21 (m, 2H, Ar-H), 7.52 (q, 2H, Ar-H), 10.5 (br s, 1H, NH, deuterium oxide exchangeable); ^{13}C nmr (25 MHz, DMSO-d_6): δ 31.93, 45.46, 58.42, 116.01, 122.34, 122.63, 123.28, 132.12, 135.59, 151.17.

Anal. Calcd. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.13; N, 16.46. Found: C, 47.09; H, 5.14; N, 16.44.

Method B.

Compound **2b** was prepared in 76% yield using a procedure similar to that which afforded **2a** described Method C, mp 209-210°.

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REFERENCES AND NOTES

[1] Part 2. J.-W. Chern, Y.-H. Wu, and K.-C. Liu, *J. Heterocyclic Chem.*, **27**, 1485 (1990).

[2] L. G. Payne, J. Przytycki, A. A. Patchett, and M. T. Wu, *J. Heterocyclic Chem.*, **16**, 391 (1979).

[3] E. P. Papadopoulos, *J. Heterocyclic Chem.*, **17**, 1553 (1980).

[4] J.-W. Chern, F.-J. Shish, C.-D. Chang, C.-H. Chan and K.-C. Liu, *J. Heterocyclic Chem.*, **25**, 1103 (1988).

[5] C.-Y. Shiau, J.-W. Chern, J.-H. Tien, and K.-C. Liu, *J. Heterocylic Chem.*, **26**, 595 (1989).

[6] F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2038 (1957).

[7] A. A. Rubin, F. E. Roth, M. W. Winburg, J. G. Topliss, M. H. Sherlock, N. Sperber, and J. Blenk, *Science,* **133**, 2067 (1961).

[8] J. C. Topliss and L. M. Konzelman, *J. Org. Chem.*, **28**, 2655 (1963).

[9] Y. Girard, J. G. Atkinson, and J. Rokach, *J. Chem. Soc., Perkin Trans. I*, 1043 (1979).

[10] J.-W. Chern. C.-P. Ho, Y.-H. Wu, C.-H. Chan, M.-H. Yen, and K.-C. Liu, *Chin. Pharm. J.*, **42**, 233 (1990).

[11] N. E. Truce, E. M. Kreider and W. W. Brand, *Org. React.*, **18**, 99 (1970).

[12] D. T. Cromer, International Tables for X-ray Crystallography, Vol **IV**, The Kynoch Press, Birmingham, England, 1974.

[13] E. J. Gabe, F. L. Lee and Y. LePage, Crystallographic Computing 3, Clarenden Press, Oxford, 1985, p 167.