Synthesis of 3-Substituted 4,1,2-Benzothiadiazine 4,4-Dioxides and 2 or 3-Substituted 1,4-Benzothiazine 1,1-Dioxides

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The title compounds were prepared starting from the synthones **6** using two different synthetic approaches: 3-substituted 1,4-benzothiazine 1,1-dioxides were synthesised by cyclisation with phosphorus oxychloride as the Vilsmeier reagent, while 4,1,2-benzothiadiazine 4,4-dioxides and 3-substituted 1,4-benzothiazine 1,1-dioxides were obtained by direct diazotisation or by cyclisation with triethyl orthoformate.

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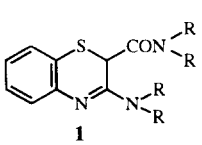
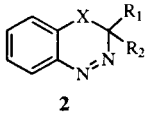
A new method for the preparation of substituted 1,4-benzothiazines 1 [1] and benzothiadiazines **2** (X = S or SO_2) [2] has been developed in our laboratories. The focal point being the preparation of suitable key intermediates **3**, which could lead to the desired compounds under appropriate cyclization.



1



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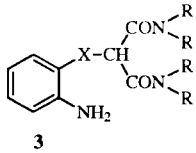
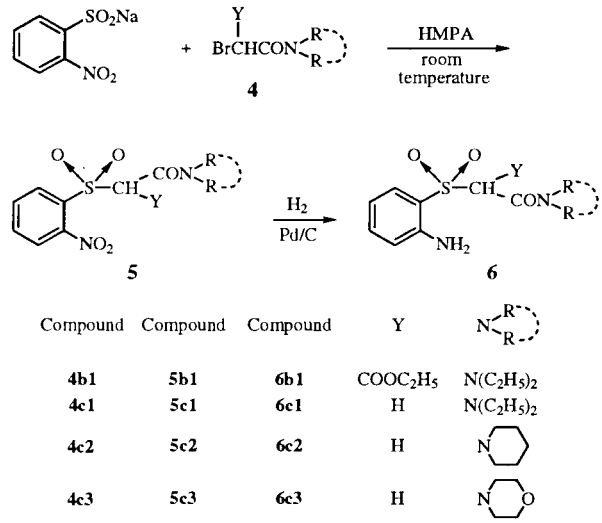


3

Compounds **1** were obtained from **3** (X = S) under Vilsmeier cyclisation, while compounds **2** were synthesised from **3** (X = S or SO_2) under a formal diazotisation [1, 2]. To further substantiate these findings, in an effort to generalize these reactions, additional studies were performed on the behaviour of synthones **6**, which could also pave the way toward new 1,4-benzothiazines and 4,1,2-benzothiadiazines, with potential pharmacological properties. The synthetic routes used to obtain the key intermediates **6** are outlined in Scheme 1: compounds **6b** (Y = $COOC_2H_5$) were prepared as previously reported for **6a** () [2], while **6c** (Y = H) were obtained by reducing the corresponding nitro derivatives **5**, which were synthesized by condensing 2-nitrobenzensulfinate with the suitable bromoacetamide **4** (Y = H) in hexamethylphosphoramide (HMPA) at room temperature (Scheme 1).

Taking our previous experience into account, the tertiary amide () of compounds **6**, reacting with phosphorus oxychloride, could be considered as a Vilsmeier reagent, which is subject to a intramolecular nucleophilic attack by the vicinal amino group providing a thiazine ring like **7**, without loss of the dialkylamino group itself (see Scheme 2). All attempts to obtain compounds **7** by treating compounds **6** () with phosphorus oxychloride under the same Vilsmeier conditions as we had successfully used to synthesise

Scheme 1



Compound	Compound	Compound	Y	
4b1	**5b1**	**6b1**	$COOC_2H_5$	$N(C_2H_5)_2$
4c1	**5c1**	**6c1**	H	$N(C_2H_5)_2$
4c2	**5c2**	**6c2**	H	
4c3	**5c3**	**6c3**	H	

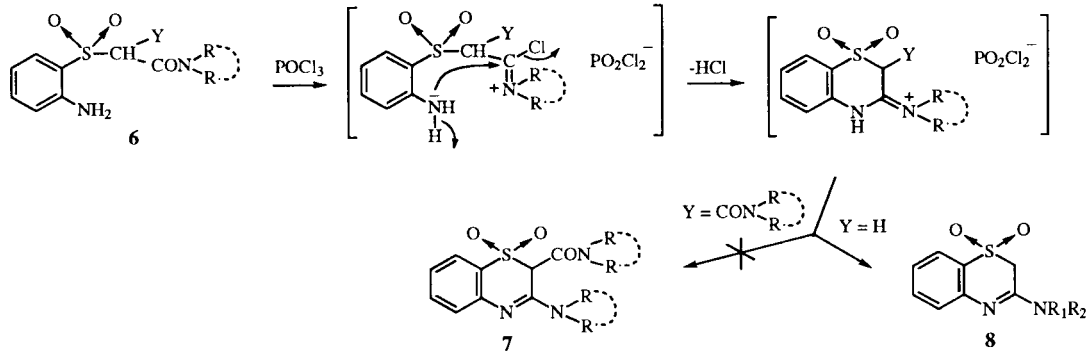
2*H*-1,4-benzothiazines [1], have failed, thus resulting in a complex mixture of unidentified products.

Only when we started with compound **6** (Y = H), therefore simplifying the molecule, were we able to isolate the desidered benzothiazines **8** in satisfactory yields. Whether this success was due to lower steric hindrance or to electronic properties, is still under investigation.

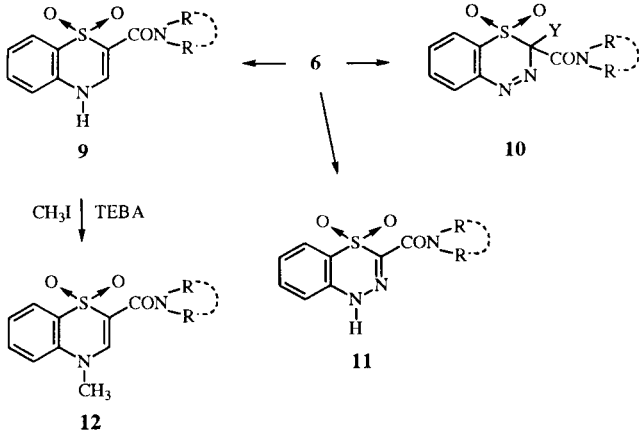
The second aim of this work was to verify if the methyne or methylene groups of the new synthones **6** promoted the cyclization by diazotisation according to the behaviour of compounds **3**. Therefore compounds **6** were treated with acetic acid and sodium nitrite, and, as expected, the ethyl 3-(diethylcarbamoyl)-3*H*-4,1,2-benzothiadiazine-3-carboxylate 4,4-dioxide **10b** or the *N,N*-dialkyl-1*H*-4,1,2-benzothiadiazine-3-carboxamide 4,4-dioxides **11** were obtained (Scheme 3). Moreover the cyclization of **6** with triethyl orthoformate at 130° led to the benzothiazines **9** in good yield. These were finally transformed into the *N*-methyl derivative **12** by reaction with methyl iodide and benzyltriethylammonium bromide (TEBA).

It is interesting to note that the coupling of the diazonium salt at the active CH_2 or CH groups of **6a** (Y = $CONR_2$),

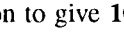
Scheme 2



Scheme 3



Compound	Compound	Compound	Y	N(R)(R)
–	**10b**	–	$COOC_2H_5$	$N(C_2H_5)_2$
9a	–	**11a**	–	$N(C_2H_5)_2$
9b	–	**11b**	–	
9c	–	–	–	

6b (Y = COOEt) and **6c** (Y = H) replaces a hydrogen in a formal substitution to give **10a** (Y = ) [2], **10b**, **6** or **11** in all cases. Evidently, also when there is a better leaving group (COOEt compared with $CONR_2$) the substitution prevails on the Japp-Klingmann reaction.

The ring closure reaction was confirmed, for example, by the disappearance of the infrared amine absorption band present in **6** at 3475 and 3380 cm^{-1} (average values) proving that the cyclisation concerned the amino group itself. In addition, compounds **9** and **11** show the NH stretching at 3230 cm^{-1} (average values). On the other hand, in the ^1H nmr spectra, compounds **8** show the characteristic CH_2 singlet at δ = 4.0 (average values) and **9** and **12** the CH singlet at 6 = 7.4. All products had elemental microanalysis and spectral data consistent with the proposed structures. Detailed nmr and ir are given in the experimental.

In conclusion, the cyclisation of synthones **6** provides a new variety of benzothiadiazine and benzothiazine derivatives in one step: the former were obtained by simple diazotisation, the latter were prepared either by direct cyclisation with triethyl orthoformate (2-substituted 1,4-benzothiazine **9**) or by phosphorus oxychloride in a formal Vilsmeier reaction (3-substituted 1,4-benzothiazine **8**).

Further compounds can be obtained using the above procedures from synthones **6** by changing Y or the malonic moiety.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded in chloroform or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^1H-nmr spectra were obtained on a Hitachi Perkin-Elmer R 600 (60 MHz) or a Varian Gemini 200 (200 MHz) spectrometers with TMS as the internal standard (δ = 0). The purity of all compounds was checked by thin-layer chromatography on silica gel 60-F-254 pre-coated plates and the spots were located in uv light or by iodine vapor. Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyzer in the Microanalysis Laboratory in our Institute.

Sulfonylamides **5**. General Procedure.

A solution of 1.05 g (5 mmoles) of sodium *o*-nitrobenzensulfinate, prepared as indicated in [3], and 5 mmoles of a suitable 2-bromoamide **4** in 5 ml of hexamethylphosphoramide was left stirring at the temperature and for the amount of time indicated below for each compound. The reaction mixture was poured onto crushed ice and allowed to stand at room temperature. The precipitated solid was then collected and crystallized from a suitable solvent as indicated below to give **5** as a faint yellow solid.

Ethyl 2-[(2-Nitrophenyl)sulfonyl]-*N,N*-diethylmalonamate **5b1**.

By the general method, the title compound was prepared from *N,N*-diethylethylmalonamate **4b1** [4] after stirring for 5 hours at room temperature. The precipitated solid was collected and crystallized from ethyl acetate:cyclohexane (1:1) to give **5b1** (0.75

g, 40%), mp 129-130°; ir (potassium bromide): ν 1745 (CO), 1655 (NCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (m, 9H, CH_3), 3.50 (m, 4H, N-CH_2), 4.25 (q, 2H, O-CH_2), 6.05 (s, 1H, CH), 7.70-8.60 (m, 4H, arom H).

Anal. Calcd. for $C_{15}H_{20}N_2O_7S$: C, 48.38; H, 5.41; N, 7.52; S, 8.61. Found: C, 48.18; H, 5.35; N, 7.42; S, 8.53.

2-[(2-Nitrophenyl)sulfonyl]-*N,N*-diethylacetamide **5c1**.

By the general method from 2-bromo-*N,N*-diethylacetamide **4c1** [5] after stirring for 6 hours at room temperature, the product which we obtained, collected and crystallized from ethyl acetate:cyclohexane (1:1) was **5c1** (0.68 g, 45%), mp 98-99°; ir (chloroform): ν 1640 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.18 (q, 6H, CH_3), 3.42 (m, 4H, CH_2), 4.72 (m, 2H, CH_2), 7.70-8.40 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{16}N_2O_5S$: C, 47.99; H, 5.37; N, 9.33; S, 10.67. Found: C, 47.75; H, 5.25; N, 9.28; S, 10.52.

2-[(2-Nitrophenyl)sulfonyl]-1-(1-piperidinyl)ethanone **5c2**.

By the general method from 1-(bromoacetyl)piperidine **4c21** [6] after stirring at 40° for 24 hours, the solid which was separated out, collected and crystallized from ethyl acetate:cyclohexane (1:1), was **5c2** (0.74 g, 47%), mp 149-150°; ir (chloroform): ν 1640 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62 (broad s, 6H, β-CH_2), 3.51 (sl, 4H, α-CH_2), 4.28 (s, 2H, CH_2), 7.68-8.35 (m, 4H, arom H).

Anal. Calcd. for $C_{13}H_{16}N_2O_5S$: C, 49.99; H, 5.16; N, 8.97; S, 10.26. Found: C, 49.85; H, 5.02; N, 8.90; S, 10.15.

2-[(2-Nitrophenyl)sulfonyl]-1-(4-morpholinyl)ethanone **5c3**.

By the above procedure, the title compound was prepared from 4-(bromoacetyl)morpholine **4c3** [7]. The product was finally crystallized from cyclohexane:ethyl acetate (2:1) (0.76 g, 48%), mp 142-143°; ir (chloroform): ν 1640 (CO) cm^{-1}. ^1H nmr (deuteriochloroform): δ 3.63 (broad s, 8H, α and β-CH_2), 4.30 (s, 2H, CH_2), 7.70-8.50 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{14}N_2O_6S$: C, 45.86; H, 4.49; N, 8.91; S, 10.20. Found: C, 45.69; H, 4.40; N, 8.85; S, 10.12.

Reduction of Nitrocompounds **5**. General Procedure.

Using a Parr apparatus, 0.1 g of 5% palladium on charcoal were added to a solution of 3.3 mmoles of **5b** or **5c** in 50 ml of tetrahydrofuran and the mixture was shaken with hydrogen at 60 psi until gas uptake ceased. The catalyst was filtered off and washed with THF, the filtrate was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The resulting oil or solid was dissolved in hot cyclohexane:ethyl acetate (1:1) and charcoal and then filtered. After cooling to room temperature, a pure white solid which separated out, was **6b** or **6c** as indicated below:

Ethyl 2-[(2-Aminophenyl)sulfonyl]-*N,N*-diethylmalonamate **6b1**.

Compound **6b1** was obtained in 46% yield (0.48 g), mp 115-117° after recrystallization from cyclohexane: ethyl acetate (1:1); ir (potassium bromide): ν 3454 and 3342 (NH_2), 1750 (CO), 1650 (NCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (m, 9H, CH_3), 3.40 (m, 4H, N-CH_2), 4.30 (q, 2H, O-CH_2), 5.38 (broad s, 3H, CH and NH_2, deuterium oxide exchangeable), 6.60-7.80 (m, 4H, arom H).

Anal. Calcd. for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18; S, 9.36. Found: C, 52.42; H, 6.43; N, 8.08; S, 9.22.

2-[(2-Aminophenyl)sulfonyl]-*N,N*-diethylacetamide **6c1**.

Compound **6c1** was obtained in 56% yield (0.50 g), mp 113-4°, after recrystallization from cyclohexane:ethyl acetate (1:1); ir (chloroform): ν 3480 and 3380 (NH_2), 1640 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (m, 6H, CH_3), 3.40 (m, 4H, CH_2), 4.22 (s, 2H, CH_2), 5.20 (s, 2H, NH_2, deuterium oxide exchangeable), 6.60-7.80 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36; S, 11.86. Found: C, 53.28; H, 6.67; N, 10.18; S, 11.80.

2-[(2-Aminophenyl)sulfonyl]-1-(1-piperidinyl)ethanone **6c2**.

Compound **6c2** was obtained in 74% yield (0.69 g), mp 145-147°, after recrystallization from the same solvent mixture; ir (chloroform): ν 3480 and 3380 (NH_2), 1640 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60 (broad s, 6H, β-CH_2), 3.50 (sl, 4H, α-CH_2), 4.28 (s, 2H, CH_2), 5.20 (broad s, 2H, NH_2, deuterium oxide exchangeable), 6.61-7.80 (m, 4H, arom H).

Anal. Calcd. for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92; S, 11.35. Found: C, 55.12; H, 6.38; N, 9.87; S, 11.26.

2-[(2-Aminophenyl)sulfonyl]-1-(4-morpholinyl)ethanone **6c3**.

Compound **6c3** was obtained in 75% yield (0.70 g), mp 114-115° after recrystallization from the same solvent mixture; ir (chloroform): ν 3485 and 3405 (NH_2), 1645 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (broad s, 8H, α and β-CH_2), 4.28 (s, 2H, CH_2), 5.42 (broad s, 2H, NH_2, deuterium oxide exchangeable), 6.70-7.80 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85; S 11.28. Found: C, 50.51; H, 5.58; N, 9.80; S 11.17.

3-(Dialkylamine)-2*H*-1,4-benzothiazine 1,1-dioxides **8**. General Procedure

Phosphorus oxychloride (15.0 mmoles, 2.3 g) was added dropwise within 15 minutes at 0° with external cooling to a solution of **6c** (3.0 mmoles) in 15 ml of 1,2-dichloroethane in a two-necked flask protected from atmospheric moisture and efficently stirred with a magnetic bar. The resulting solution was left to stir at room temperature for 20 minutes and then refluxed for 3.5 hours. After cooling, a solution of 10 g of trihydrate sodium acetate in 50 ml of water was added and the mixture was heated at 75° for 60 minutes, while stirring. The mixture was then cooled, made alkaline by the slow addition of sodium hydrogen carbonate. The organic layer was then collected and the aqueous phase exhaustively extracted with chloroform. The combined organic layers were washed with brine, dried over sodium sulfate and finally evaporated under reduced pressure to give a thick oil or a solid which, after crystallization from ethyl acetate:hexane (1:5), afforded the following compouds as white solids:

3-(Diethylamino)-2*H*-1,4-benzothiazine 1,1-Dioxide **8a1**.

The yield was 54%, mp 113-114°; ir (chloroform): ν 1560 strong cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (t, 6H, CH_3), 3.54 (q, 4H, CH_2), 3.98 (s, 2H, 2-CH_2), 7.00-8.00 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; S, 12.71. Found: C, 57.00; H, 6.35; N, 11.15; S, 12.61.

3-(1-Piperidinyl)-2*H*-1,4-benzothiazine 1,1-Dioxide **8a2**.

The yield was 51%, mp 115-16°; ir (chloroform): ν 1550 strong cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60 (broad s, 6H, β-CH_2), 3.70 (broad s, 4H, α-CH_2), 4.07 (s, 2H, 2-CH_2), 7.00-8.00 (m, 4H, arom H).

Anal. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 58.92; H, 6.21; N, 10.74; S, 12.26.

3-(4-Morpholinyl)-2*H*-1,4-benzothiazine 1,1-Dioxide **8a3**.

The yield was 38%, mp 153-154° ir (chloroform): ν 1560 strong cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.72 (s, 8H, α and β-CH_2), 3.95 (s, 2H, 2-CH_2), 7.00-8.00 (m, 4H, arom H).

Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52; S, 12.04. Found: C, 54.32; H, 5.41; N, 10.63; S, 12.24.

Diazotization. General Procedure.

In an ice bath cooled flask, a solution of 0.37 g (5.40 mmoles) of sodium nitrite in 15 ml of water was added dropwise to a stirred solution of 3.70 mmoles of **6b** or **6c** in 15 ml of glacial acetic acid. The reaction mixture was kept at 0° for 5 minutes, at room temperature for 3 hours, neutralized by a saturated sodium acetate solution, heated at 70° for 30 minutes and finally cooled at room temperature. The oil-water mixture or the solid, which separated out, gave the compounds **10** or **11** as indicated below:

Ethyl 3-(Diethylcarbamoyl)-3*H*-4,1,2-benzothiadiazine-3-carboxylate 4,4-dioxide **10b**.

The entire oil-water mixture was extracted twice with chloroform. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated. The oily residue was purified on a silica gel column [toluene:ethyl acetate (7:3)] to give **10b** as a pale yellow solid (0.35 g, 37%), mp 182-183° from toluene; ir (chloroform): ν 1735 (CO), 1650 (NCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (m, 9H, CH_3), 3.42 (m, 4H, NCH_2), 4.30 (m, 2H, CH_2), 7.00-8.30 (m, 4H, arom H).

Anal. Calcd. for $C_{15}H_{19}N_3O_5S$: C, 50.98; H, 5.42; N, 11.89; S, 9.07. Found: C, 50.68; H, 5.40; N, 11.79; S, 9.00.

N,N-Diethyl-1*H*-4,1,2-benzothiadiazin-3-carboxamide 4,4-Dioxide **11a**.

The solid which separated was collected and crystallized from ethyl acetate to give **11a** (0.53 g, 51%), mp 173-174°; ir (potassium bromide): ν 3240 (NH), 1615 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.18 (t, 6H, CH_3), 3.44 (q, 4H, CH_2), 7.32-8.07 (m, 4H, arom H), 12.90 (broad s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.94; S, 11.41. Found: C, 51.11; H, 5.30; N, 14.84; S, 11.30.

(1-Piperidinyl)-[3-(1*H*-4,1,2-benzothiadiazinyl)]methanone 4,4-Dioxide **11b**.

The solid which was collected and crystallized from ethyl acetate gave **11b** (0.59g, 54%), mp 255-256°; ir (potassium bromide): ν 3220 (NH), 1625 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.61 (broad s, 6H, β-CH_2), 3.56 (broad s, 4H, α-CH_2), 7.35-8.12 (m, 4H, arom H), 12.75 (broad s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32; S, 10.93. Found: C, 53.10; H, 5.10; N, 14.11; S, 10.85.

N,N-Dialkyl-4*H*-1,4-benzothiazine-2-carboxamide 1,1-Dioxides **9**. General Procedure.

A mixture of 3.7 mmoles of **6c** and 10 ml of ethyl orthoformate was left stirring at 130° for the amount of time indicated below for each compound. The reaction solution, on cooling at room temperature, gave a crude precipitate which was filtered and crystallized from ethyl alcohol to afford **9** as a white solid.

N,N-Diethyl-4*H*-1,4-benzothiazine-2-carboxamide 1,1-Dioxide **9a**.

The time of reaction was 48 hours, 62% yield; mp 228-230°; ir (potassium bromide): ν 3230 (NH), 1600 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.15 (t, 6H, CH_3), 3.40 (q, 4H, CH_2), 7.20-8.20 (m, 5H, arom H + H-3), 11.20 (broad s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.19; H, 5.55; N, 9.85; S 11.29.

(1-Piperidinyl)-[2-(4*H*-1,4-benzothiadiazinyl)]methanone 1,1-Dioxide **9b**.

The time of reaction was 36 hours, 45% yield; mp 253-254°; ir (potassium bromide): ν 3220 (NH), 1600 (CO) cm^{-1}; ^1H nmr (200 MHz) (DMSO-d_6): δ 1.55 (m, 6H, β-CH_2), 3.55 (m, 4H, α-CH_2), 7.55 (s, 1H, H-3), 7.30-7.90 (m, 4H, arom H), 11.20 (broad s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.12; H, 5.42; N, 9.13; S, 10.63.

(4-Morpholinyl)-[2-(4*H*-1,4-benzothiadiazinyl)]methanone 1,1-Dioxide **9c**.

The time of reaction was 48 hours, 72% yield; mp 252-253°; ir (potassium bromide): ν 3225 (NH), 1605 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.60 (m, 8H, α- and β-CH_2), 7.20-8.15 (m, 5H, arom H + H-3), 11.30 (broad s, 1H, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 52.91; H, 4.49; N, 9.29; S 10.48.

(1-Piperidinyl)-[2-(4-methyl-4*H*-1,4-benzothiadiazinyl)]methanone 1,1-Dioxide **12**.

To a stirred suspension of 3.40 mmoles (1.0 g) of **9b** in 10 ml of chlorobenzene at room temperature, 2 ml of 40% sodium hydroxide and 1.0 g of benzyltriethylammonium bromide were added, followed by the immediate addition of 1.36 mmoles of methyl iodide. The mixture was kept stirring at room temperature for 22 hours, quenched with water and extracted three times with chloroform. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The solid residue was crystallyzed from ethyl acetate:cyclohexane (1:1) to give 0.74 g (71%) of **12**, as pale yellow crystals, mp 168-170°; ir (chloroform): ν 1630 (CO) cm^{-1}; ^1H nmr (deuteriochloroform) (200 MHz): δ 1.65 (m, 6H, β-CH_2), 3.65 (s, 3H, CH_3), 3.70 (m, 4H, α-CH_2), 7.33 (s, 1H, H-3), 7.10-8.15 (m, 4H, arom H).

Anal. Calcd. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; S, 10.46. Found: C, 58.62; H, 5.70; N, 9.01; S 10.23.

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