Synthesis of 3-Disubstituted 3*H*-4,1,2-Benzothiadiazines and 3-Disubstituted 3*H*-4,1,2-Benzothiadiazine 4,4-Dioxides

A. Balbi*, M. Mazzei and E. Sottofattori

Istituto di Scienze Farmaceutiche, Università degli Studi di Genova,
Viale Benedetto XV, 3, 16132 Genova, Italy

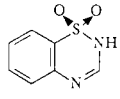
Received March 8, 1991

3*H*-4,1,2-Benzothiadiazines **8** and **9** have been prepared by cyclization of the key intermediates **6** and **7**. The diazotisation of 2-aminophenylthio and 2-aminophenylsulfone derivatives could represent a new convenient synthetic way to obtain 4,1,2-benzothiadiazines.

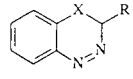
J. Heterocyclic Chem., **28**, 1633 (1991).

A very large number of analogs have been prepared since the discovery of chlorothiazide as a diuretic and hypotensive agent. Most of them are analogs of substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides **1**. Few syntheses have been directed towards the preparation of congeneres of a general structure **2** (X = S or SO_2).

The methods reported in literature lead to 4,1,2-benzothiadiazines with or without a 3-substitutent [1,2], while the 3-disubstituted 4,1,2-benzothiadiazines are unknown. Thus, 3-aryl and 3-phenylazo compounds [1] were readily obtained, and 3-acetyl and 3-ethoxycarbonyl derivatives were also obtained but with slightly more difficulty.



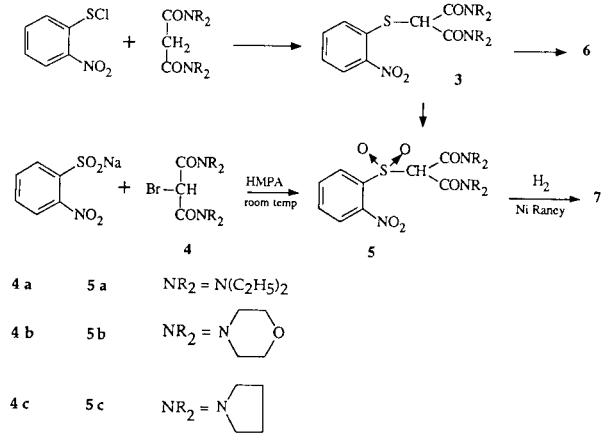
1



2

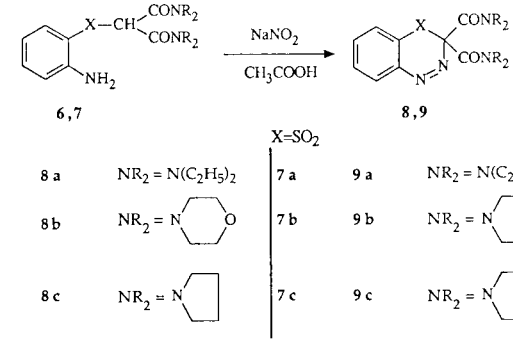
Because of the above and continuing our research programme [4,5] concerning the development of heterocyclic pharmaceuticals, we turned our attention to the synthesis of 3-dicarboxamide derivatives. The synthesis of the desired compounds **8** and **9** was accomplished by using the viable starting materials **6** and **7**. The 2-amino derivatives **6** (X = S, Y = NH_2) were prepared reducing the corresponding nitro derivatives **3** as reported by us in a previous paper [5]. The key intermediates **7** (X = SO_2, Y = NH_2) were prepared with an excellent yield through catalytic reduction of compounds **5** which were synthesized by condensing sodium 2-nitrobenzensulfinate with the 2-bromomalonamides **4** [5] in hexamethylphosphoramide (HMPA) at room temperature. Oxidation of compounds **3**, which were prepared as described in [5], also led to the key intermediate **5** but the yield was lower (see Scheme 1).

Scheme 1

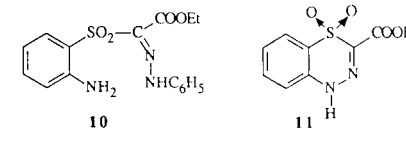


The desired compounds **8** and **9** were then prepared by diazotisation and cyclization of the 2-amino derivatives **6** [5] and **7**, as shown in Scheme 2.

Scheme 2



Up to now, attempts to form a thiadiazine ring by diazotisation and cyclization of *o*-aminophenylsulphones have failed. Only benzothiadiazine **11** was quoted as unexpectedly coming from a diazotisation of amine **10** [3]. Furthermore attempts to oxidize the compounds **8** to form the corresponding 4,4-dioxdes **9** gave only the recovery of the starting materials.



Our method seems to be general when the key intermediate is a malonic derivative: the coupling of a diazonium salt at the active CH group of **6** or **7** replaces a hydrogen

in a formal substitution to furnish **8** or **9**. Thus, even when X = SO_2, the mechanism of the process involved the replacing of a single active hydrogen atom instead of eliminating a functional carboxamide group (according to the Japp-Klingemann reaction).

We are now testing others malonic derivatives so as to prove that this method is a general one.

The structures of the new compounds were determined on the basis of their elemental microanalyses and spectral data which are in agreement with their proposed structures. Detailed nmr and ir spectra are given in the experimental.

For example, in the ^1H nmr spectra, the singlet at δ = 5.82 characteristic of CH of **7** (δ = 6.28 of **5**) disappears in the corresponding cyclic compounds **9**. On the other hand in the ir spectra NH_2 bands at 3420 and 3330 cm^{-1} (average values) of **6** and **7** disappear in the corresponding derivatives **8** and **9** proving that the cyclization concerned the amino group itself.

Compounds **7, 8, 9** will be submitted to general pharmacological screening and the results will be given in a separate paper.

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) spectrometer 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 precoated plates and the spots were located in uv light or by iodine vapor. Elemental analyses were performed in the Microanalysis Laboratory of our Institute on a Carlo Erba 1106 Elemental Analyzer.

N,N,N',N'-Tetrasubstituted 2-[(2-Nitrophenyl)sulfonyl]malonamides **5**.

A solution of 1.05 g (5 mmoles) of sodium *o*-nitrobenzensulfinate, prepared as indicated in [6], and 5 mmoles of 2-bromomalonamide **4** [4] in 5 ml of HMPT was left stirring at room temperature 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 white solid.

2-[(2-Nitrophenyl)sulfonyl]-*N,N,N',N'*-tetraethylmalonamide (**5a**).

According to the general method from **4a** after stirring for 6 hours and 20 minutes after that the reaction mixture was poured onto crushed ice, the precipitate was collected and crystallized from ethyl acetate:cyclohexane (1:1) to give **5a** (0.88 g, 44%), mp 110-111°; ir (chloroform): ν 1650 (CO), 1540, 1360, 1155 cm^{-1}; ^1H nmr deuteriochloroform): δ 1.19 (q, 12H, CH_3), 3.40 (m, 8H, CH_2), 6.28 (s, 1H, CH), 7.77 (m, 3H, H-4,5,6), 8.50 (m, 1H, H-3).

Anal. Calcd. for $C_{17}H_{25}N_3O_6S$: C, 51.12; H, 6.31; N, 10.52; S, 8.03. Found: C, 50.96; H, 6.19; N, 10.57; S, 7.99.

Preparation of **5a** by Oxidation of **3a**.

One ml (10 mmoles) of 30% hydrogen peroxide was added to a stirred solution of **3a** [5] (0.5 g, 1.36 mmoles) in acetone (20 ml) and glacial acetic acid (0.5 ml). The mixture was heated under reflux for 12 hours, cooled and kept at room temperature for 1 week. The crystallized solid was collected and recrystallized to give **5a** (0.05 g, 10%), identical (mp, infrared) to the previous sample.

2-{[(2-Nitrophenyl)sulfonyl]malonyl}dimorpholine (**5b**).

According to the general method from **4b** after stirring for 3 days, the product that had separated after 1 hour of standing at room temperature was filtered and crystallized from ethyl acetate to give **5b** (1.2 g, 56%), mp 180-181°; ir (potassium bromide): ν 1635 (CO), 1535 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.68 (m, 16H, α and β CH_2), 6.27 (s, 1H, CH), 7.86 (m, 3H, H-4,5,6), 8.50 (m, 1H, H-3).

Anal. Calcd. for $C_{17}H_{21}N_3O_8S$: C, 47.77; H, 4.95; N, 9.83; S, 7.50. Found: C, 47.87; H, 4.98; N, 9.83; S, 7.65.

2-{[(2-Nitrophenyl)sulfonyl]malonyl}dipyrrolidine (**5c**).

According to the general method from **4c** after stirring for 20 hours and left standing for 24 hours at room temperature, the product that had separated gave **5c** (1.49 g, 75%), mp 164-165° from ethyl acetate; ir (chloroform): ν 1660 (CO), 1545 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.97 (m, 8H, β-CH_2), 3.52 (m, 8H, α-CH_2), 6.10 (s, 1H, CH), 7.88 (m, 3H, H-4,5,6), 8.60 (m, 1H, H-3).

Anal. Calcd. for $C_{17}H_{21}N_3O_6S$: C, 51.64; H, 5.35; N, 10.63; S, 8.11. Found: C, 51.88; H, 5.44; N, 10.75; S, 7.90.

2-[(2-Aminophenyl)sulfonyl]-*N,N,N',N'*-tetraethymalonamide (**7a**).

In a Parr apparatus, 0.1 g of 5% palladium on charcoal were added to a solution of 1.4 g (3.5 mmoles) of **5a** in 50 ml of THF 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 pure white solid result was **7a** (1.12 g, 87%), mp 159-160° from ethyl acetate; ir (potassium bromide): ν 3420, 3340, 1650, 1630 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.02 (m, 12H, CH_3), 3.32 (m, 8H, CH_2), 6.15 (s, 1H, CH), 6.80 (m, 1H, H-3), 7.10-7.80 (m, 3H, aromatic H), 8.70 (d, 2H, NH_2, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{27}N_3O_4S$: C, 55.26; H, 7.37; N, 11.37; S, 8.68. Found: C, 55.01; H, 7.29; N, 11.28; S, 8.48.

2-{[(2-Aminophenyl)sulfonyl]malonyl}dimorpholine (**7b**).

Using the above procedure 1.50 g (3.5 mmoles) of **5b** were hydrogenated until gas uptake ceased. The reaction mixture was heated because some solid was formed during the hydrogenation, the catalyst was filtered and washed twice with boiling ethanol. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give **7b** (0.63 g, 46%), a crude but pure oily residue, which was crystallized from ethanol as a white solid, mp 187-188° from ethyl acetate; ir (potassium bromide): ν 3370, 3265, 1660, 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.50 (m, 16H, α and β-CH_2), 6.40 (s, 1H, CH), 6.88 (m, 1H, H-3), 7.13-7.80 (m, 3H, aromatic H), 8.88 (s, 2H, NH_2, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{23}N_3O_6S$: C, 51.37; H, 5.83; N, 10.57; S, 8.07. Found: C, 51.09; H, 5.60; N, 10.28; S, 7.98.

2-{[(2-Aminophenyl)sulfonyl]malonyl}dipyrrolidine (**7c**).

In a similar manner to that described for the preparation of **7a**, from **5c** (1.38 g, 3.5 mmoles) we finally obtained **7c** (0.59 g, 46%) as a white solid melting at 210-212° after recrystallization from ethanol; ir (potassium bromide): ν 3480, 3380, 1650, 1620 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.78 (m, 8H, β-CH_2), 3.37 (m, 8H, α-CH_2), 5.88 (s, 1H, CH), 6.90 (m, 1H, H-3), 7.15-7.80 (m, 3H, aromatic H), 8.92 (d, 2H, NH_2, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{23}N_3O_4S$: C, 55.87; H, 6.34; N, 11.50; S, 8.77. Found: C, 55.58; H, 6.24; N, 11.22; S, 8.46.

N,N-Dialkyl-3*H*-4,1,2-benzothiadiazin-3,3-dicarboxamides **8**.

General Procedure.

In an ice bath-cooled flask, a solution of 0.18 g (2.6 mmoles) of sodium nitrite in 10 ml of water was added dropwise to a stirred solution of 1.7 mmoles of compound **6** in 8 ml of glacial acetic acid. The reaction mixture was kept overnight at room temperature, neutralized by a saturated sodium acetate solution, heated at 70° for 1 hour and then cooled at room temperature. The solid which separated out was collected by filtration, washed with water and dried. The yellow solid thus obtained was **8**, and almost pure.

N,N-Diethyl-3*H*-4,1,2-benzothiadiazin-3,3-dicarboxamide (**8a**).

According to the general procedure from 0.47 g of **6a** [5], **8a** (0.34 g, 57%) was finally obtained, mp 109-111° from ethyl acetate:cyclohexane; ir (chloroform): ν 1635 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10 (m, 12H, CH_3), 3.10-3.95 (m, 8H, CH_2), 7.35 (m, 3H, aromatic H), 8.0 (m, 1H, aromatic H).

Anal. Calcd. for $C_{17}H_{24}N_4O_2S$: C, 58.60; H, 6.94; N, 16.08; S, 9.20. Found: C, 58.58; H, 6.98; N, 16.16; S, 8.99.

1-[(3*H*-4,1,2-Benzothiadiazin-3-yl)dicarbonyl]morpholine (**8b**).

According to the general procedure, **8b** (0.30 g, 47%) was finally obtained from 0.79 g of **6b**, mp 154-155° from ethyl acetate:cyclohexane; ir (chloroform): ν 1638 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.70 (m, 16H, α and β-CH_2), 7.35 (m, 3H, aromatic H), 8.0 (sb, 1H, aromatic H).

Anal. Calcd. for $C_{17}H_{20}N_4O_4S$: C, 54.24; H, 5.36; N, 14.88; S, 8.52. Found: C, 54.25; H, 5.41; N, 14.97; S, 8.40.

1-[(3*H*-4,1,2-Benzothiadiazin-3-yl)dicarbonyl]pyrrolidine (**8c**).

According to the general procedure **8c** (0.25 g, 43%) was finally obtained from 0.74 g of **6c**, mp 111-113° from isopropyl ether:benzene; ir (chloroform): ν 1635 (CO); ^1H nmr (deuteriochloroform); δ 1.88 (m, 8H, β-CH_2), 3.25-3.95 (m, 8H, α-CH_2), 7.35 (m, 3H, aromatic H), 8.0 (m, 1H, aromatic H).

Anal. Calcd. for $C_{17}H_{20}N_4O_2S$: C, 59.28; H, 5.85; N, 16.27; S, 9.31. Found: C, 59.06; H, 5.90; N, 16.13; S, 9.11.

N,N-Diethyl-3*H*-4,1,2-benzothiadiazin-3,3-dicarboxamide 4,4-Dioxide (**9a**).

In an ice bath-cooled flask, a solution of 0.18 g (2.6 mmoles) of sodium nitrite in 10 ml of water was added dropwise to a stirred solution of 2.52 mmoles (0.93 g) of amine **7a** in 2 ml of hydrochloric acid. After being left overnight at room temperature, a solution of 0.53 g (3.9 mmoles) of sodium acetate trihydrate was added to the reaction mixture, heated at 70° for 1 hour and then cooled at room temperature. The yellow solid which separated was recrystallized from cyclohexane to yield 0.18 g (19%) of **9a**, mp 130-131°; ir (potassium bromide): ν 1635 (CO), 1330, 1162 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.90-1.48 (m, 12H, CH_3), 3.15-3.90 (m, 8H, CH_2), 7.50-8.35 (m, 4H, aromatic H).

Anal. Calcd. for $C_{17}H_{24}N_4O_4S$: C, 53.67; H, 6.36; N, 14.73; S, 8.43. Found: C, 53.39; H, 6.36; N, 14.76; S, 8.22.

1-[(3*H*-4,1,2-Benzothiadiazin-3-yl)dicarbonyl]morpholine 4,4-Dioxide (**9b**).

Using the above procedure, **9b** was obtained from **7b** (2.52 mmoles, 1.0 g), as a yellow solid melting at 180-181° after recrystallization from cyclohexane:ethyl acetate (0.43 g, 42%); ir (potassium bromide): ν 1648 (CO), 1340, 1118 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.70 (m, 16H, α and β-CH_2), 7.52-8.40 (m, 4H, aromatic H).

Anal. Calcd. for $C_{17}H_{20}N_4O_6S$: C, 49.99; H, 4.94; N, 13.72; S, 7.85. Found: C, 49.76; H, 4.91; N, 13.55; S, 7.70.

1-[(3*H*-4,1,2-Benzothiadiazin-3-yl)dicarbonyl]pyrrolidine 4,4-Dioxide (**9c**).

Using a similar procedure to that described in **9a**, **9c** as a yellow solid (0.39 g, 41%) was finally obtained from **7c** (2.52 mmoles, 0.92 g) dissolved in 8 ml of glacial acetic acid instead of hydrochloric acid, mp 182-183° from cyclohexane:ethyl acetate; ir (potassium bromide): ν 1640 strong, broad (CO), 1338, 1165 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.90 (m, 8H, β-CH_2), 3.30-4.00 (m, 8H, α-CH_2), 7.52-8.35 (m, 4H, aromatic H).

Anal. Calcd. for $C_{17}H_{20}N_4O_4S$: C, 54.24; H, 5.36; N, 14.88; S, 8.52. Found: C, 54.00; H, 5.42; N, 14.61; S, 8.40.

REFERENCES AND NOTES

[1] D. J. Vukov, M. S. Gibson, W. E. Lee and M. F. Richardson, *J. Chem. Soc., Perkin Trans. 1*, 192 (1972) and earlier papers.

[2] L. Garanti, A. Scandroglio and G. Zecchi, *J. Heterocyclic Chem.*, **13**, 1339 (1976).

[3] D. E. Ames, S. Chandrasekhar and K. I. Hansen, *J. Chem. Soc., Perkin Trans. 1*, 539 (1978).

[4] A. Balbi, R. Ferreccio, M. Mazzei, A. Ermili and G. Roma, *Farmaco, Ed. Sci.*, **41**, 942 (1986).

[5] A. Balbi, R. Ferreccio, M. Di Braccio, M. Mazzei and G. Roma, *Farmaco, Ed. Sci.*, **42** 955 (1987).

[6] S. Coffey, *J. Chem. Soc. Trans.*, 3215 (1926).