# Synthesis and Reduction of some 1H-2,1,3-Benzothiadiazin-4(3H)one 2,2-Dioxides

Keith C. C. Bancroft

John Graymore Chemistry Laboratories, School of Environmental Sciences, Plymouth Polytechnic, Plymouth PLA 8AA, England

Laila H. Morcos Guindi and Arthur F. Temple

School of Chemistry, Leicester Polytechnic, Leicester LE1 9BH, England
Received June 12, 1978

Several 2,1,3-benzothiadiazin-4(3H)one 2,2-dioxides were synthesized as possible sweetening agents by reacting sulfamoyl chloride with various anthranilic acid derivatives. The isolation of 1-methyl-4-methoxy-2,1,3-benzothiadiazine 2,2-dioxide and preparation of 3,4-dihydro-2,1,3-benzothiadiazine 2,2-dioxide is also reported.

### J. Heterocyclic Chem., 15, 1521 (1978)

Cohen and Klarberg (1) reported the synthesis of a number of 2,1,3-benzothiadiazin-4(3H)one 2,2-dioxides (1a-d). As part of an investigation into potential new sweetening agents and compounds of physiological activity this synthesis has been extended, and the following compounds prepared.

Sulfamoyl chloride (4) was freshly prepared from N-carbonyl sulfamoyl chloride (3) for each experiment.

$$so_3$$
 +  $cnci$   $\rightarrow$   $o=c=nso_2ci$   $\xrightarrow{H_2O}$   $\mapsto$   $H_2nso_2ci$ 

Methyl anthranilates were reacted with sulfamoyl chloride and the crude ester (5) was dissolved in base and acidified to yield the appropriate 2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1).

Cohen and Klarberg reacted sulfamoyl chloride with methyl 4-chloroanthranilate and isolated the expected 7-chloro compound (1k, R' = R'' = H 7-Cl). We synthesized the four isomeric methyl nitroanthranilates and attempted the ring closure reaction by refluxing the nitro esters with sulfamoyl chloride in dry benzene overnight, adding the cold solution to aqueous caustic soda and the acidifying. In no case was a benzothiadiazine obtained. The product from the methyl 3-nitroanthranilate

reaction was a high melting solid which decomposed before melting. Infra-red and mass spectra of the compound indicate that it was the open chain compound, Nsulfamoyl-3-nitroanthranilic acid. When methyl 4-, 5- and 6-nitroanthranilates were reacted under the same conditions, only starting material was recovered. These results indicate that electron withdrawing nitro groups on the benzene ring inhibit the reaction of the amine with sulfamoyl chloride except in the case of methyl-3-nitroanthranilate, where the sulfamoyl chloride of the acid is obtained. In the latter case it is not clear whether the sulfamoyl ester hydrolyzes on treatment with base or that it ring closes and subsequently ring opens to yield the free acid on acidifying. The only available anthranilate substituted with an electron supplying group was methyl 5-methylanthranilate which readily underwent the ring closure reaction to yield 6-methyl-2,1,3-benzothiadiazine-4(3H)one 2,2-dioxide (1f). In similar manner methyl 3-amino-2-naphthoate yielded naphtho[2,3-d][2,1,3]thiadiazin-4-one (2).

Cohen and Klarberg had reacted 1a with dimethyl sulfate to yield 3-methyl-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1d) or 1,3-dimethyl-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1b) depending on the quantity of dimethyl sulfate used.

When 1,3-dimethyl-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1d) was made by the method of Cohen and Klarberg it had their reported melting point. However, the nmr spectrum in deuterobenzene showed not only the two N-methyl singlets at  $\tau$  6.85 and  $\tau$  7.3 but also two very much weaker singlets at  $\tau$  6.6 and  $\tau$  7.0. Investigation by tlc on silica gel using benzene as eluent showed the presence of two components, which were separated by preparative layer chromatography. The major component had an Rf of 0.27 and the minor component (ca. 10% of the mixture) had an Rf of 0.17.

The major and minor components had 100 MHz nmr spectra in benzene-d<sub>6</sub> which were different, but which were both plausible spectra for the title compound, as

both had aromatic signals and two N-methyl signals in the ratio of 4:3:3. The mass spectra of the mixture and of each pure component appear to be almost identical. The major component was assigned structure 1b and the minor component the structure 1-methyl-4-methoxy-2,1,3-benzothiadiazin 2,2-dioxide (6) based on infra-red evidence.

The absence of strong bands above 3000 cm<sup>-1</sup> in the infra-red due to NH or OH stretching argues against the presence of non-ring-closed structures such as N,N'-dimethyl-N-sulfamoylanthranilic acid (7). The SO<sub>2</sub> group

should absorb in the regions 1320-1360 and 1150-1180 cm<sup>-1</sup> and strong bands can be seen. The minor component shows an additional strong absorption in the region 1100-1200 cm<sup>-1</sup>, which suggests the C-O stretching vibration of the ether linkage. In addition the minor component shows a band at 1610 cm<sup>-1</sup> and the major component a band at 1685 cm<sup>-1</sup>, which are reasonably assigned the C=N and C=O stretchings, respectively.

The following 3-substituted compounds have been prepared by reaction of 1a with a suitable alkyl halide or alkyl sulfate: 3-trideuteromethyl-2,1,3-benzothiadiazin-4(3H) one 2,2-dioxide (1e); 1,3-diethyl-2,1,3-benzothiadiazin-4(3H) one 2,2-dioxide (1g); 3-phenacyl-2,1,3-benzothiadiazin-4(3H) one 2,2-dioxide (1i); and 1,3-ethoxy-carbonylmethyl-2,1,3-benzothiadiazin-4(3H) one 2,2-dioxide (1j).

Since a nitro benzothiadiazine could not be prepared by ring closure of the nitroanthranilates, 1,3-dimethyl-2,1,3benzothiadiazin-4(3H)one 2,2-dioxide (1b) was nitrated with concentrated nitric acid/sulfuric acid in acetic acid solution. That 6-nitration has occurred is deduced from the fact that the 6- and 8-positions of 1,3-dimethyl-2,1,3-benzothiadiazin-4(3H) one 2,2-dioxide should be positions of highest electron density being para and ortho to the N-methyl group. Mono-nitration should thus give the 6- or 8- nitro isomer. The aromatic proton adjacent to the strongly electron withdrawing carbonyl group (position 5-) in the parent compound is assigned to the signal at lowest field in the benzene-d<sub>6</sub> nmr spectrum at  $\tau$  1.9. This doublet of a doublet has splitting of 7.5 and 1.8 Hz. On mononitration this signal moves to lower field ( $\tau$  1.23) and becomes a doublet with a splitting of 2.75 Hz. If nitration had occurred at the 7- or 8-positions, the 5proton signal would appear with large (ca. 7 Hz) ortho coupling.

Lithium aluminum hydride reduction of 1a yielded 3,4-dihydro-2,1,3-benzothiadiazine 2,2-dioxide (8).

#### **EXPERIMENTAL**

N-Carbonylsulfamoyl chloride was prepared by the method of Graf (2). Sulfamoyl chloride (3) was freshly prepared for each experiment. Tlc was carried out on plates with Merck silica gel GF .254 or PF .254 (preparative). Nmr spectra were recorded with a Varian (100 MHz) spectrometer for solutions with tetramethylsilane as internal standard. Ir spectra were measured (potassium bromide) with a Perkin-Elmer 337. Uv spectra were recorded with a Unicam SP 800 instrument, and mass spectra were measured with an A.E.I. MS 9 instrument (4). The following compounds were synthesized by the method of Cohen and Klarberg (1): 1H-2,1,3-Benzothiadiazin-4(3H)one 2,2-dioxide (1a) (4); 1-methyl-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1d) (4); and 6-methyl-1H-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1f). 1,3-Dimethyl-2,1,3-benzothiadiazin-4(3H)one 2,2-dioxide (1f).

and 1-Methyl-4-methoxy-2,1,3-benzothiadiazine 2,2-Dioxide (6).

Dimethylsulfate (10 ml., 0.04 mole) and 1a (5 g., 0.025 mole)

Dimethylsulfate (10 ml., 0.04 mole) and 1a (5 g., 0.025 mole) were dissolved in 10% sodium bicarbonate (100 ml.) and stirred for 12 hours. The crude solid was filtered and crystallized from aqueous ethanol to give 4.3 g., m.p. 96-100° (lit. (1) for 1b, m.p. 98-100°). The nmr spectrum indicated the presence of two compounds, which were separated by preparative tlc using chloroform as eluent. The major component (ca. 90%) had Rf 0.27 and the minor component Rf 0.17.

## Major Component.

This compound was assigned structure **1b**; uv (ethanol):  $\lambda$  max ( $\epsilon$  mole<sup>-1</sup>dm<sup>-2</sup>) 219 (202 x 10<sup>3</sup>), 237 (673 x 10<sup>2</sup>) and 305 (148 x 10<sup>2</sup>) nm; nmr (benzene-d<sub>6</sub>):  $\tau$  1.85 (multiplet, 5-H), 3.1 (multiplet, 7-H), 3.3 (multiplet, 6-H), 3.6 (multiplet, 8-H), 6.85 (singlet, 1-Me) and 7.35 (singlet, 3-Me); ir:  $\nu$  max 1155 (SO<sub>2</sub>), 1360 (SO<sub>2</sub>) and 1685 cm<sup>-1</sup> (C=O).

Anal. Calcd. for  $C_9H_{10}N_2SO_3$ : C, 47.8; H, 4.45; N, 12.38. Found: C, 47.6; H, 4.67; N, 12.21.

## Minor Component.

This compound was assigned structure **6**; uv (ethanol):  $\lambda$  max ( $\epsilon$  mole  $^{-1}$  dm  $^{-2}$ ) 222 (275 x  $10^3$ ), 258 (533 x  $10^2$ ), 265 (476 x  $10^2$ ) and 333 (287 x  $10^2$ ) nm; nmr (benzene-d<sub>6</sub>):  $\tau$  2.45 (multiplet, 5-H), 3.02 (multiplet, 7-H), 3.45 (multiplet, 6-H), 3.75 (multiplet, 8-H), 6.7 (singlet, Me) and 7.1 (singlet, Me); ir:  $\nu$  max 1135 (C-O), 1170 (SO<sub>2</sub>), 1360 (SO<sub>2</sub>) and 1610 cm  $^{-1}$  (C=N).

Anal. Calcd. for  $C_9H_{10}N_2SO_3$ : C, 47.8; H, 4.45; N, 12.38. Found: C, 47.8; H, 4.51; N, 12.50.

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

Potassium carbonate (0.97 g., 7 mmoles) and 1a (1.4 g., 7 mmoles) were dissolved in water (3 ml.), methanol (3 ml.) and trideuteromethyl iodide (0.97 g., 7 mmoles) and the solution

Notes 1523

refluxed for 3 hours. The solvent was removed under reduced pressure and the crude product acidified with concentrated hydrochloric acid was filtered to yield 1.2 g. (80%) of 1e, m.p. and mixed m.p. with undeuterated sample 1a 209-210° (lit. (1) gives m.p. 201-203°).

Anal. Calcd. for  $C_8H_5D_3N_2SO_3$ : C, 44.6; H, 3.72; N, 13.02. Found: C, 44.9; H, 3.87; N, 13.15.

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

Diethyl sulfate (16.4 g., 0.1 mole) and 1a (10 g., 0.05 mole) were dissolved in 10% sodium hydroxide (200 ml.) and the solution stirred for 15 hours. The crude solid (9.5 g.), m.p. 190-200°, was purified by glc (7' x 3/8" 20% APL at 264°); molecular weight 254 (mass spectrum).

Anal. Calcd. for  $C_{11}H_{14}N_{2}SO_{3}$ : C, 51.9; H, 5.55; N, 11.02. Found: C, 52.1; H, 5.32; N, 11.13.

6-Nitro-1,3-dimethyl-2,1,3-benzothiadiazin-4(3H) one 2,2-Dioxide (1h).

Crude compound 1b was nitrated by the method of Vogel (5). Crystallization of the product yielded pale yellow needles, m.p.  $89-90^{\circ}$ ; nmr (benzene-d<sub>6</sub>):  $\tau$  1.23 (doublet, 5-H), 2.35 (multiplet, 7-H), 4.05 (doublet, 8-H), 6.96 (singlet, methyl) and 7.41 (singlet, methyl).

Anal. Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>5</sub>S: C, 39.85; H, 3.34; N, 15.49. Found: C, 39.83; H, 3.5; N, 15.11.

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

A saturated solution of 1a (6 g., 0.03 mole) in 10% sodium carbonate and a solution of phenacyl bromide (6 g., 0.03 mole) in ethanol were refluxed for 6 hours. The ethanol was removed and the acidified product extracted with ether. From the etherial layer was obtained a thick oily material which was washed with petroleum ether (b.p. 40-60°) and crystallized first from chloroform and then ethanol (7.5 g., 80%), m.p. 188-190°.

Anal. Calcd. for  $C_{15}H_{12}N_2O_4S$ : C, 57.0; H, 3.8; N, 8.9; S, 10.0. Found: C, 57.01; H, 3.80; N, 8.75; S, 10.08.

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

To a solution of 1a (3 g., 0.015 mole) in ethanol and aqueous

sodium hydroxide (0.6 g., 0.015 mole) was refluxed for 20 hours. Ethanol was removed from the mixture which was acidified with hydrochloric acid, and ether extracted. The oil obtained from the ether extract was purified by glc (7' x 3/8" 5% SE30 at 270°). Insufficient was purified for analysis but the ir spectrum showed the presence of a new carbonyl carbon and the loss of the N-H bond; molecular weight 370 (mass spectrum). Naphtho[2,3-d][1,2,6]thiadiazin-4-one 2,2-Dioxide (2)(4).

The method of Cohen and Klarberg (1) was used except that the reaction mixture was refluxed for 7 hours before the addition of sodium hydroxide. The white crystalline product had m.p. 238-240°.

Anal. Calcd. for  $C_{11}H_8N_2O_3S$ : C, 53.22; H, 3.25; N, 11.28. Found: C, 53.3; H, 3.4; N, 11.15.

3,4-Dihydro-2,1,3-benzothiadiazine 2,2-Dioxide (8) (4).

Compound 1a was refluxed in dry ether with excess lithium aluminum hydride for 15 hours. The crude compound crystallized from methanol had m.p. 186-189°. Ir showed loss of a carbonyl; molecular weight 184 (mass spectrum).

Anal. Calcd. for  $C_7H_8N_2O_2S$ : C, 45.64; H, 4.38; N, 15.21. Found: C, 45.71; H, 4.5; N, 15.06.

Acknowledgement.

We wish to thank Dr. T. Carter of the Physico-chemical Measurement Unit, Harwell, Berks, England for discussion of the infra-red data.

#### REFERENCES AND NOTES

- (1) E. Cohen and B. Klarberg, J. Am. Chem. Soc., 84, 1994 (1962).
  - (2) R. Graf, Angew. Chem., Int. Ed. Engl., 7, 172 (1968).
  - (3) R. Graf, Org. Synth., 46, 23 (1966).
- (4) K. C. C. Bancroft, L. H. Morcos Guindi, A. F. Temple and B. J. Millard, Org. Mass Spectrom., 6, 1313 (1972).
- (5) A. I. Vogel, "Textbook of Practical Organic Chemistry", 3rd Ed., Longmans Publishers, 1967.