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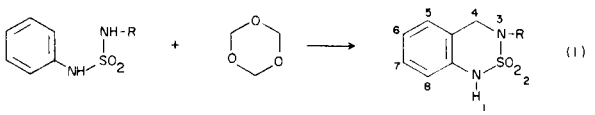
A new heterocyclic system, 3*H*-2,1,3-benzothiadiazine 2,2-dioxide has been prepared *via* oxidation of the 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides.

J. Heterocyclic Chem., 16, 1069 (1979).

Recently (1), we published a new synthetic method for the synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides by an intramolecular sulfonylamidomethylation reaction as shown in equation 1.

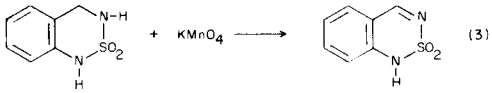


(1)

We report here the oxidation of several 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides to the corresponding 3*H*-2,1,3-benzothiadiazine 2,2-dioxides, the first derivatives of a new heterocyclic system. The following oxidizing agents were investigated: nitric acid, bromine, *N*-bromosuccinimide, and 2,3-dichloro-5,6-dicyano-1,4-

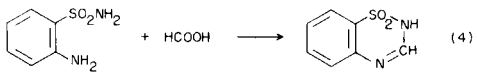
(2)

benzoquinone. Several of the possible benzothiadiazine dioxides have been reported. 1*H*-2,1,3-benzothiadiazine 2,2-dioxide has been prepared by Knollmüeller by the oxidation of the dihydro compound with potassium permanganate (2). The 4*H*-1,2,4-benzothiadiazine 1,1-dioxide system is readily prepared from the cyclization of



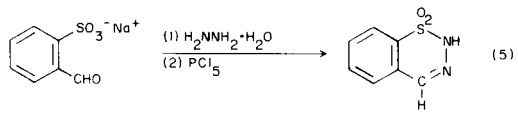
(3)

the 2-aminobenzenesulfamides with formic acid (3). The parent compound, 2*H*-1,2,3-benzothiadiazine 1,1-dioxide



(4)

has been synthesized by the two-step sequence outlined in equation 5 (4). The benzothiadiazine dioxides described

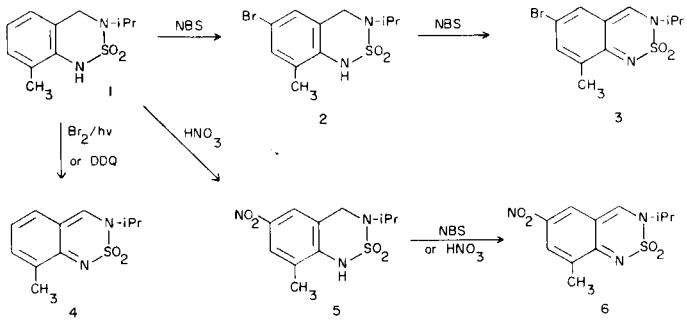


(5)

in equations 3-5 appear to be the only systems reported to date.

N-Bromosuccinimide (NBS) gave the best yields of the oxidants investigated. Either pyridine or a solution of *t*-butyl alcohol were found to be suitable solvents for the reaction. The disadvantage of this reagent is substitution. If substituents are not present in the 6 or 8 position, substitution occurs prior to oxidation as illustrated in Scheme I for 3-(1-methylethyl)-8-methyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide. With one equivalent of NBS, **1** gives the 6-bromo derivative **2** and the second equivalent oxidizes **2** to **3**, the 3*H*-2,1,3-benzothiadiazine system. Structure **3** follows from the evidence of elemental analyses and spectroscopic data. Noteworthy is the absence of a CH_2 in the nmr and the N-H in both the ir and nmr. The mass spectrum gave m/e 316. When allowed to react with concentrated nitric acid in acetic acid at room temperature, **1** was converted to the 6-nitro derivative **5**. By increasing the temperature to 60-70° low yields of **6** are obtained. However, fuming nitric acid was required to convert the 8-CF_3 derivative to 6-nitro-8-trifluoromethyldihydrobenzothiadiazene 2,2-dioxide and subsequent oxidation with NBS gave 6-nitro-8-trifluoromethyl-3*H*-2,1,3-benzothiadiazine 2,2-dioxide.

Scheme I



Direct oxidation of **1** without substitution was achieved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Although nmr analysis of the reaction mixture indicated good conversions, isolated yields were low. Limited success resulted from photobromination due to competing substitution. Substitution could be reduced by maintaining a very low bromine concentration. Work is in progress to investigate the chemistry of this new heterocyclic system.

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EXPERIMENTAL

3(1-Methylethyl)-6-bromo-8-methyl-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3-(1-Methylethyl)-8-methyl-3,4-dihydro-1*H*-2,1,3-benzothiadizine 2,2-dioxide (16.0 g., 0.066 mole) was dissolved in a solution of 75 ml. of methylene chloride and 75 ml. of *t*-butyl alcohol. *N*-Bromosuccinimide (24.8 g., 0.14 mole) was added in small portions over a 45 minute period. The reaction was allowed to stir at room temperature for 1 hour, then poured into water and extracted with methylene chloride. The organic layer was washed three times with water, dried (magnesium sulfate) and evaporated. The residue was slurried with chloroform and filtered to give 5.3 g. (25%), m.p. 200-202°; nmr (deuteriochloroform): δ 1.60 (d, 6, N-3 CH_3), 2.26 (s, 3, C-8 CH_3), 4.66 (m, 1, methine), 7.23 (d, 2, C-5 and C-7), 8.03 (s, 1, C-4). In DMSO the aromatic doublet for C-5 and C-7 is 7.53 and the C-4 proton appears at 9.00.

Anal. Calcd. for $C_{11}H_{13}BrN_2O_2S$: C, 41.50; H, 4.40; N, 8.00. Found: C, 41.40; H, 4.21; N, 9.10.

3(1-Methylethyl)-8-methyl-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

Procedure A. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

3-(1-Methylethyl-8-methyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (1 g., 0.00416 mole) was dissolved in 50 ml. of benzene and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1 g., 0.0044 mole) was added in 150 ml. of benzene. The solution was allowed to stir overnight at room temperature. It was then washed with water several times, dried (magnesium sulfate) and evaporated. The residue was slurried in ethylacetate-hexane and filtered to give 0.3 g. (30%) of product, m.p. 200-202°; nmr (DMSO): δ 1.53 (d, 6, N-3 CH_3), 2.20 (s, 3, C-8 CH_3), 4.57 (m, 1, methine), 6.60-7.68 (m, 3, C-5, C-6, C-7), 9.17 (s, 1, C-4).

Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.46; H, 5.85; N, 11.71; S, 13.4. Found: C, 55.3; H, 6.08; N, 11.75; S, 13.3.

Procedure B. Photobromination.

The oxidation may also be carried out by irradiating a carbon tetrachloride solution of the dihydro compound while adding dropwise a dilute solution of bromine in carbon tetrachloride. Poor radiation results in competitive ring bromination.

3-(1-Methylethyl)-6-bromo-8-trifluoromethyl-3*H*-2,1,3-Benzothiadiazine 2,2-Dioxide.

3(1-Methylethyl)-8-trifluoromethyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (10.4 g., 0.0354 mole) was dissolved in a solution of 50 ml. of methylene chloride, 50 ml. of *t*-butyl alcohol and 4 ml. of pyridine. *N*-Bromosuccinimide (14.5 g., 0.082 mole) was added portionwise and the reaction mixture allowed to stir overnight at room temperature. The precipitate was filtered and washed with chloroform and dried, 1.64 g., m.p. 199-200°. The filtrate was extracted with methylene chloride as described above to give an additional 2.64 g. of product, m.p. 195-198°, yield 36%; nmr (DMOS): δ 1.57 (d, 6, N-3 CH_3), 4.50 (m, 1, methine), 8.00 (d, 2, C-5 and C-7), 9.20 (s, 1, C-4).

Anal. Calcd. for $C_{11}H_{10}BrF_3N_2O_2S$: C, 35.59; H, 2.72; N, 7.55. Found: C, 35.62; H, 2.77; N, 7.59.

3(1-Methylethyl)-6-nitro-8-methyl-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3(1-Methylethyl)-6-nitro-8-methyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (14.4 g., 0.05 mole) was dissolved in 72 ml. of pyridine at 5°. *N*-bromosuccinimide (13.5 g., 0.076 mole) was added portionwise maintaining the temperature below 10°. After the addition was complete, the solution was allowed to warm to room temperature, poured onto water and extracted with methylene chloride. The extract was washed with water and dilute hydrochloric acid until neutral, dried (magnesium sulfate) and evaporated to give 7.8 g. (55%) of product. Recrystallization from methylene chloride-benzene gave the pure product, m.p. 188-191°; nmr (deuteriochloroform): δ 1.58 (d, 6, N-3 CH_3), 2.3 (s, 3, C-8 CH_3), 4.67 (m, 1, methine), 7.93 (d, 2, C-5 and C-7), 8.20 (s, 1, C-4).

Anal. Calcd. for $C_{11}H_{13}N_3O_4S$: C, 46.63; H, 4.62; N, 14.82. Found: C, 46.71; H, 4.59; N, 14.37.

3(1-Methylethyl)-6-nitro-8-fluoro-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3-(1-methylethyl)-8-fluoro-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (10 g., 0.0369 mole) was dissolved in 70 ml. of glacial acetic acid and 10 ml. of concentrated (70%) nitric acid was added dropwise at room temperature. After stirring for 1 hour at room temperature, the reaction mixture was poured into water and the product was isolated by extraction with methylene chloride. After drying (magnesium sulfate) and evaporation, 8.4 g. of crude product was obtained. The nmr spectrum was consistent for the dihydro nitro derivative. The latter was dissolved in 30 ml. of pyridine and *N*-bromosuccinimide (5.1 g., 0.029 mole) added at room temperature. Reaction temperature increased to 35°. After the reaction cooled to room temperature the product was isolated by extraction with methylene chloride. After washing, drying (magnesium sulfate), evaporation and recrystallization from chloroform-hexane, 1.8 g. (22%) product was obtained, m.p. 210-213°; nmr (DMSO): δ 1.56 (d, 6, N-3 CH_3), 4.57 (m, 1, methine), 7.85-8.45 (m, 2, C-5 and C-7), 9.33 (s, 1, C-4).

Anal. Calcd. for $C_{10}H_{10}FN_3O_4S$: C, 41.81; H, 3.64; N, 14.49. Found: C, 41.81; H, 3.51; N, 14.63.

3-(1-Methylethyl)-6-nitro-8-chloro-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3(1-Methylethyl)-6-nitro-8-chloro-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (11 g., 0.036 mole) was dissolved in 100 ml. pyridine and *N*-bromosuccimide (9.6 g., 0.054 mole) added portionwise at ice bath temperature. The solution was allowed to warm to room temperature and stirred for 3 hours. The product was isolated by extraction with methylene chloride, dried (magnesium sulfate) and evaporated. Recrystallization from methylene chloride-benzene gave 7.35 g. (67%) of product, m.p. 220-222°; nmr (DMSO): δ 1.53 (d, 6, N-3 CH_3), 4.57 (m, 1, methine), 8.43 (d, 2, C-5 and C-7), 9.36 (s, 1, C-4).

Anal. Calcd. for $C_{10}H_{10}ClN_3O_4S$: C, 39.28; H, 3.96; N, 13.74. Found: C, 39.20; H, 4.01; N, 13.82.

3-(1-Methylethyl)-6-nitro-8-bromo-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3-(1-Methylethyl)-8-bromo-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (10 g., 0.033 mole) was dissolved in 75 ml. of glacial acetic acid and cooled to 10° in an ice bath; 5 ml. of fuming nitric acid were then added dropwise. The temperature increased to 40°. After cooling to room temperature, the product was isolated by extraction with methylene chloride, dried (magnesium sulfate) and evaporated. The nmr was consistent for the dihydro nitro derivative. The nitro derivative (6.25 g., 0.018 mole) was dissolved in 50 ml. of pyridine at ice bath temperature and *N*-bromosuccinimide (5 g., 0.027 mole) added portionwise. After the addition was complete the reaction mixture was allowed

to warm to room temperature, poured into water and extracted with methylene chloride. After washing, drying (magnesium sulfate), evaporation, and recrystallization from chloroform-hexane, 4.15 g. (28%) of product was obtained, m.p. 230-234°; nmr (DMOS): δ 1.57 (d, 6, N-3 CH_3), 4.57 (m, 1, methine), 8.53 (d, 2, C-5 and C-7), 9.43 (s, 1, C-4).

Anal. Calcd. for $C_{10}H_{10}BrN_3O_4S$: C, 34.49; H, 2.90; N, 12.07. Found: C, 34.70; H, 3.01; N, 12.25.

3(1-Methylethyl)6-nitro-8-trifluoromethyl-3*H*-2,1,3-benzothiadiazine 2,2-Dioxide.

3(1-Methylethyl)-8-trifluoromethyl-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide (16.2 g., 0.055 mole) was dissolved in 50 ml. of glacial acetic acid and cooled to 7°. Fuming nitric acid was added and the temperature increased rapidly to 60°. After cooling to room temperature the product was isolated by extraction with methylene chloride, dried (magnesium sulfate) was isolated by extraction with methylene chloride, dried (magnesium sulfate) and evaporated to give 14.90 g. of a viscous red syrup. The nmr was consistent with that for the dihydro nitro derivative. The 14.90 g. (0.044 mole) of syrup were dissolved in 100 ml. of pyridine, cooled to ice bath temperature, and *N*-bromosuccinimide (11.7 g., 0.044 mole) was added. The temperature increased 5°. The solution was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was poured onto methylene chloride and the organic phase washed with water and dilute hydrochloric acid until neutral, dried (magnesium sulfate), evaporated. The residue was slurried with chloroform and filtered to give 4.25 g. (28%), m.p. 219-221°; nmr (DMSO): δ 1.56 (d, 6, N-3 CH_3), 4.57 (s, 1, methine), 8.5 (d, 2, C-5 and C-7), 9.43 (s, 1, C-4).

Anal. Calcd. for $C_{11}H_{10}F_3N_3O_4S$: C, 34.49; H, 2.90; N, 12.07. Found: C, 34.70; H, 3.01; N, 12.25.

Ethyl 8-(1-Methylethyl)-8-bromo-3*H*-2,1,3-benzothiadiazine-6-carboxylate 2,2-Dioxide.

3(1-methylethyl)-3,4-dihydro-1*H*-2,1,3-benzothiadiazine-6-carboxylic Acid 2,2-dioxide, ethyl ester (2.98 g., 0.01 mole) was dissolved in 20 ml. of methylene chloride, 20 ml. of *t*-butyl alcohol and 3 ml. of pyridine. The solution was cooled in an ice bath to 4° and *N*-bromosuccimide (1.80 g., 0.01 mole) was added; cooling bath was removed. The solution was stirred, allowed to warm to room temperature, poured into methylene chloride and washed with water until neutral. After drying (magnesium sulfate) and evaporation, the residue (3.9 g.), was analyzed by nmr. The spectrum was consistent for ethyl 3-(1-methylethyl)-8-bromo-3,4-anhydro-1*H*-2,1,3-benzothiadiazinecarboxylate 2,2-dioxide. The crude dihydro derivative (1.9 g.) was allowed to react with *N*-bromosuccinimide (1 g., 0.0056 mole) for 3 hours at room temperature in 10 ml. of methylene chloride, 10 ml. of *tert*-butyl alcohol and 1.5 ml. of pyridine as described above to give 1.3 g. (69%) of a yellow solid, m.p. 129-131°; nmr (DMSO): δ 1.37 (t, 3, CH_3 ester), 1.60 (d, 6, N-3 CH_3), 4.27 (q, 2, CH_2 ester), 4.63 (m, 1, methane), 8.27 (d, 2, C-5 and C-7), 9.47 (s, 1, C-4).

Anal. Calcd. for $C_{13}H_{15}BrN_2O_4S$: C, 41.61; H, 4.03; N, 7.47. Found: C, 41.34; H, 4.00; N, 7.42.

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