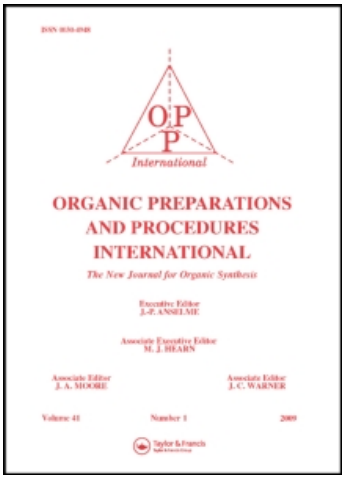

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THE SYNTHESIS OF SOME NEW 1,2-BENZOTHIAZINES

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THE SYNTHESIS OF SOME NEW 1,2-BENZOTHIAZINES

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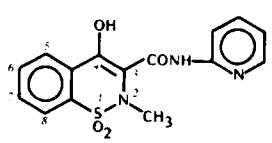
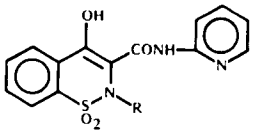
Dedicated to Professor C.G. Overberger on the Occasion of his 60th Birthday

In connection with our studies of the acidic anti-inflammatory agent piroxicam,[1-4] it was necessary to prepare a number of related 1,2-benzothiazines in order to determine the structural features critical to biological activity such as the inhibition of prostaglandin biosynthesis.[5]

Structural modifications were made at the 2-position and included replacement of CH_3 by H, CH_2CH_3 and $CH_2Ch_2CH_3$ (1a-c). Compounds of type 1 were generally prepared by combination of the appropriate benzothiazine-3-carboxylic ester with 2-aminopyridine. Replacement of the enolic H by CH_3 to give compound 2 was accomplished by the use of CH_3I in basic solution.

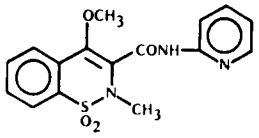


Piroxicam



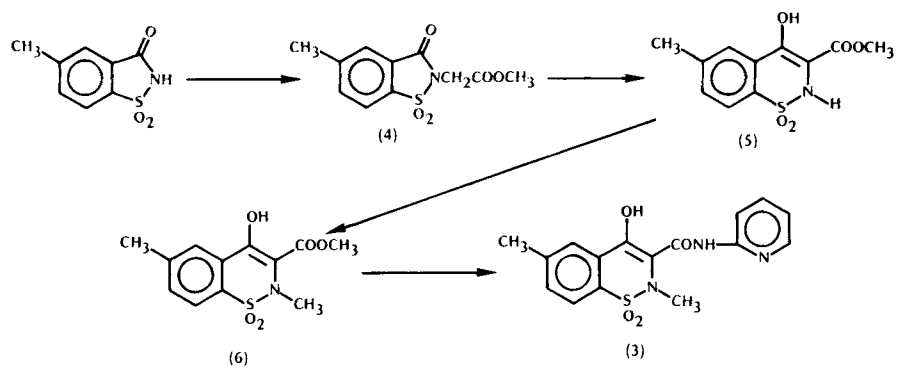
(1)

a) R = H
b) R = CH_2CH_3
c) R = $CH_2CH_2CH_3$



(2)

Finally, a multistep synthetic sequence was employed to prepare a 6-CH_3 derivative (3) of piroxicam.



All of these new 1,2-benzothiazines were examined in biological systems and the results of which are reported elsewhere.[5]

EXPERIMENTAL

Mps were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. A Varian A-60 spectrometer (TMS standard) was used to measure nmr spectra and mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E. IR spectra were determined as KBr pellets.

Methyl ester of 2-Ethyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide. A solution of 15.3 g (0.060 mole) of the methyl ester of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide[6] and 22 g (0.14 mole) of ethyl iodide in 50 ml of H_2O, 60 ml of 1N NaOH and 150 ml EtOH was allowed to stand at room temperature for 18 hrs. The resulting precipitate was filtered to yield 6.0 g (35%) of product, mp 97-99°. This compound is soluble in $NaHCO_3$ and produces a dark red color with $FeCl_3$ solution, evidence that N-alkylation, rather than O-alkylation, had taken place.

Anal. Calcd. for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.62; N, 4.95.
Found: C, 50.74; H, 4.55; N, 4.64.

2-Ethyl-4-hydroxy-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (1b). A solution of the above ester (5.0 g, 0.0177 mole) and 1.9 g (0.0203 mole) of 2-aminopyridine in 200 ml of m-xylene was refluxed for 24 hrs in a Soxhlet apparatus containing 4A molecular sieves. Removal of all solvent and recrystallization of the residue from MeOH yielded 3.79 g (61%) of 1b, mp 145-147°. Mass spectrum: m/e 345 (calc. 345), 281. IR: 6.13, 7.63, 8.45 μ.

Anal. Calcd. $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17.
Found: C, 55.82; H, 4.52; N, 12.16.

Methyl ester of 4-Hydroxy-2-(n-propyl)-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide. Using the same procedure described above for the 2-ethyl analog, a 0.060 mole scale reaction was conducted using 1-iodopropane. The oil which separated was crystallized by cooling and scratching. The resulting solid was filtered to give 3.8 g (21%) of product, mp 125-127°.

Anal. Calcd. for $C_{13}H_{15}NO_5S$ $0.5H_2O$: C, 51.02; H, 5.22; N, 4.58.
Found: C, 51.06; H, 5.09; N, 4.58.

4-Hydroxy-2-(n-propyl)-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (1c). Using the procedure described above for the 2-ethyl analog 1b, 0.94 mmole of ester was converted to amide. Removal of all solvent and trituration with hot EtOH yielded, after filtration, 0.13 g (38%) of 1c, mp 174-176°. Mass spectrum: m/e 359 (calc. 359), 295, 201. IR: 6.0, 7.38, 8.40 μ.

Anal. Calcd. for $C_{17}H_{17}N_3O_4S$: C, 56.81; H, 4.77; N, 11.69.
Found: C, 56.79; H, 4.94; N, 11.55.

4-Hydroxy-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (1a). A solution of 5.0 g (0.0196 mole) of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid, methyl ester 1,1-dioxide[6] and 2.12 g (0.023 mole) of 2-aminopyridine in 200 ml of m-xylene was refluxed for 26 hrs in a Soxhlet apparatus containing 4A molecular sieves. The reaction was cooled, a solid filtered, and triturated with hot MeOH to give 1.56 g (25%) of 1a, mp 224° dec.[7] Mass spectrum: m/e 317 (calc. 317), 253. IR: 3.16, 3.26, 6.05, 7.55, 8.50 μ.

Anal. Calcd. for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24.
Found: C, 52.86; H, 3.67; N, 12.89.

4-Methoxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (2).[8] A mixture of 16.5 g (0.050 mole) of 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide, 13.8 g (0.100 mole) of anhydrous potassium carbonate and 42.2 g (0.300 mole) of methyl iodide in 300 ml of acetone was refluxed for 23 hrs. After removal of all solvent, the residue was slurried with 100 ml water and the resulting yellow solids filtered. Trituration with acetone and recrystallization from hot DMSO-MeOH yielded 10.0 g (59%) of 2, mp 264° dec. Mass spectrum: m/e 345 (calc. 345), 281. This solid produced no color with $FeCl_3$ reagent indicating the absence of an enolic function.

Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17.
Found: C, 55.46; H, 4.47; N, 12.12.

Methyl ester of 5-Methyl-3-oxo-1,2-benzoisothiazoline-2-acetic acid 1,1-dioxide (4). To 200 g (1.0 mole) of 5-methyl-3-oxo-1,2-benzoisothiazoline 1,1-dioxide[9] in 450 ml of DMF was added 54.6 g (1.0 mole) of $NaOCH_3$. To the resulting red solution was added 32.8 g (3.0 mole) of methyl

chloroacetate in 100 ml of DMF. The reaction mixture was heated for 3 hrs at 90°, cooled and then poured into 2500 ml of ice-water. Filtration gave a solid which was thoroughly washed with water to yield, after recrystallization from 1400 ml of MeOH, 198 g (73%) of 4, mp 113-115°.

Anal. Calcd. for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20.
Found: C, 49.06; H, 4.16; N, 5.22.

Methyl ester of 4-Hydroxy-6-methyl-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (5). To a solution of 9.0 g (0.033 mole) of ester 4 in 15 ml of dry DMSO at room temperature was added, over a 5 minute period, a slurry of 4.5 g (0.083 mole) of $NaOCH_3$ in 15 ml of DMSO. The red solution was stirred for 15 minutes and then poured into 200 ml of a mixture of ice and 3N HCl. After 20 minutes at 0°, a white solid formed which was filtered to yield 4.7 g (52%) of 5. After recrystallization from isopropanol, 5 had mp 156-159°. This compound is soluble in $NaHCO_3$ and produces a dark red-brown color with $FeCl_3$ solution. NMR (D_6-DMSO): δ 11.43 (OH), 9.90 (NH), 7.88 (m, 3), 3.9 (s, 3, OCH_3), 2.46 (s, 3, CH_3). IR: 3.03, 6.01, 6.35, 7.55, 8.80 μ.

Anal. Calcd. for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20.
Found: C, 49.37; H, 4.22; H, 5.24.

Methyl ester of 2,6-Dimethyl-4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (6). A solution of 2.4 g (0.0089 mole) of 5, 8.9 ml of 1N NaOH, 6 ml of H_2O, 10 ml of CH_3I and 35 ml of EtOH was allowed to stand at room temperature for 18 hrs. Cooling the reaction produced 0.94 g (37%) of 6, mp 186-187°. IR: 6.02, 6.4, 7.50, 8.32 μ.

Anal. Calcd. for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.62; N, 4.95.
Found: C, 50.47; H, 4.66; N, 4.68.

2,6-Dimethyl-4-hydroxy-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide (3). A solution of 3.1 g (0.011 mole) of 6 and 1.1 g (0.012 mole) of 2-aminopyridine in 250 ml of dry m-xylene was refluxed under a N_2 atmosphere while xylene was slowly distilled over an 18 hr period. Xylene was replaced periodically. Finally, the reaction volume was reduced to approximately 75 ml and cooled to yield 2.3 g (61%) of 3, mp 216-219° dec. This compound is soluble in $NaHCO_3$ solution and produces a dark brown color with $FeCl_3$ solution. IR: 3.0, 6.07, 6.53, 7.48, 8.40 μ.

Anal. Calcd. for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17.
Found: C, 55.81; H, 4.41; N, 11.92.

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8. This experiment was conducted by Dr. P. Hammen of these laboratories.
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