Synthesis of 3,4-Dihydro-2-methyl-3-oxo-*N*-aryl-2*H*-[1]benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxides

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A novel synthesis of the title compounds, representing a new heterocyclic ring system, is described. Chlorosulphonation of 3-methylbenzo[*b*]thiophene followed by reaction with methylamine gave sulfonamide, **4**. Lithiation of **4**, followed by quenching with carbon dioxide yielded acetic acid, **5**. Cyclodehydration of **5** to benzothienothiazine **6** followed by reaction with aryl isocyanates afforded the desired benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamides **1a-f**.

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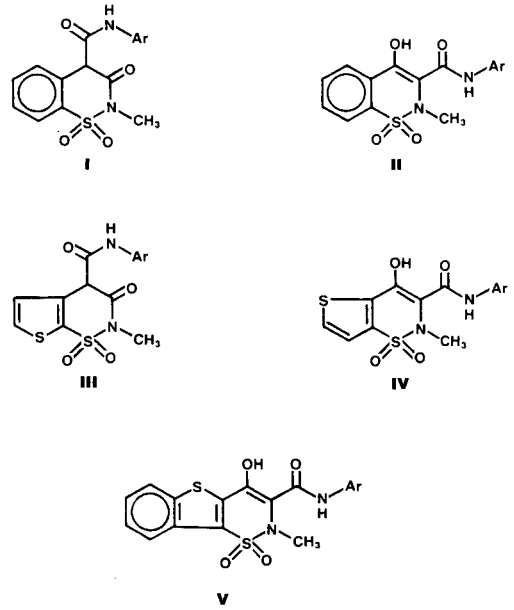
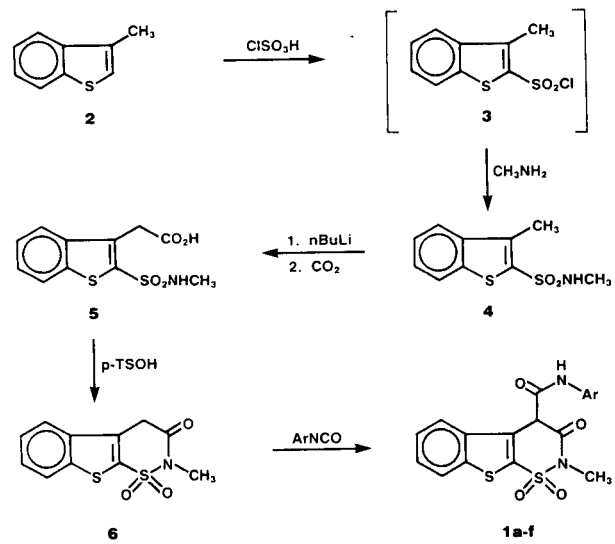
In recent years enolic carboxamides of 2-methyl-1,2-thiazine 1,1-dioxides (oxicams) have received widespread attention as nonsteroidal antiinflammatory drugs (NSAID) [1]. The first oxicams reported to possess antiinflammatory activity were 2-methyl-3-oxo-1,2-benzothiazine-4-carboxamide 1,1-dioxides (**I**) [2] and 2-methyl-4-hydroxy-1,2-benzothiazine-3-carboxanilide 1,1-dioxides (**II**) (Figure 1) [3]. Exploration of the structure activity relationships (SAR) in the oxicams included the replacement of the benzene ring in the benzothiazine with a thiophene ring giving the antiinflammatory 2-methyl-3-oxothieno-1,2-thiazine-4-carboxamide-1,1-dioxide **III** [4] and 2-methyl-4-hydroxythieno-1,2-thiazine-3-carboxanilide 1,1-dioxide **IV** [5]. Biological activity is retained upon interchange of the oxy and carboxamide functions in **III** and **IV** and in the positional isomers of the thieno sulfur. A further structural extenstion, in which a benzo ring is incorporated onto the thienothiazine nucleus, is found in 2-methyl-4-hydroxybenzothieno-1,2-thiazine-3-carboxanilide 1,1-dioxide **V**, which is claimed as an analgesic, antipyretic, antithrombotic and antiphlogistic agent [6]. Since the positional isomer of **V**, namely benzothienothiazines **1a-f**, had not been previously reported, we developed a short, efficient synthesis of 3,4-dihydro-2-methyl-3-oxo-*N*-aryl-2*H*-[1]-benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-dioxides.

A synthetic route to **1a-f** (Scheme 1) analogous to the reported synthesis of 2-methyl-3-oxo-1,2-benzothiazine-4-carboxamide 1,1-dioxide **I** was utilized [2]. Thus, chlorosulphonation of 3-methylbenzo[*b*]thiophene **2** with chlorosulfonic acid followed by reaction of the intermediate sulfonyl chloride **3** [7] with gaseous methylamine afforded **4** in 15% overall yield. Lithiation of **4** with *n*-butyllithium followed by quenching the resultant dianion with gaseous carbon dioxide gave after acidification, compound **5** in a 54% yield. Cyclodehydration of **5** in the presence of *p*-toluenesulfonic acid afforded **6** in a 76% yield. Reaction of **6** with aryl isocyanates gave the desired carboxamides **1a-f** in yields ranging from 55-68%. The results of pharmacological profiling of these compounds will be reported in due course.

Figure 1



Scheme 1



EXPERIMENTAL

Melting points were determined on a Thomas Hoover Melting Point Apparatus and are uncorrected. Proton nmr spectra were recorded on a Bruker-WM250 or Varian EM-390 spectrometer. Mass spectra were recorded on a Finnigan 4510 spectrometer at 70eV. Infrared spectra were recorded on a Perkin Elmer 383B spectrophotometer. Elemental analysis was recorded on a Control Equipment Corp. 240XA CHN analyzer.

N-3-Dimethylbenzo[*b*]thiophene-2-sulfonamide (**4**).

To a solution of 3-methylbenzo[*b*]thiophene (20.0 g, 135.1 mmoles), in chloroform (300 ml) was added dropwise chlorosulfonic acid (22.4 ml, 39.6 g, 337.9 mmoles) at −5°. The reaction mixture was stirred at 0° for 3 hours, then dry methylamine gas was bubbled in at 0° for 3 hours. The reaction mixture was slowly warmed to ambient temperature, then stirred overnight. The mixture was diluted with ethyl acetate, then washed with dilute hydrochloric acid and water, dried (magnesium sulfate), and concentrated *in vacuo* to give an oil. This oil was chromatographed on silica gel, eluting with ethyl acetate:methylene chloride (1:39) to give 5.0 g (15%) of **4**. Trituration using ether:hexane gave an analytically pure compound, mp 124-127°; ms: m/e 241 (m+, 21), 176 (13), 162 (24), 146 (100); ^{1}H-nmr (deuteriochloroform): δ 7.85 (m, 2H), 7.50 (m, 2H), 4.64 (m, 1H), 2.80 (d, 3H), 2.72 (s, 3H); ir (potassium bromide): 3298 cm^{-1}.

Anal. Calcd. for $C_{10}H_{11}NO_2S_2$: C, 49.77; H, 4.59; N, 5.80. Found: C, 49.66; H, 4.52; N, 5.68.

2-[(Methylamino)sulfonyl]benzo[*b*]thiophene-3-acetic Acid (**5**).

To a solution of **4** (1.0 g, 4.15 mmoles) in dry tetrahydrofuran (75 ml) was added a 2.0 *M* solution of *n*-butyllithium in hexane (4.6 ml, 9.13 mmoles) at 0°. The reaction mixture was stirred at 0° for 30 minutes, warmed to 15° for 10 minutes, then cooled to −20° and dry carbon dioxide gas was bubbled in for 2 hours. The reaction mixture was poured into water, and acidified, then extracted with ethyl acetate. The organic extract was washed with water, dried (magnesium sulfate), then concentrated *in vacuo*, and the resulting solid triturated using ether:hexane to give 633 mg (54%) of analytically pure **5**, mp 190-192°; ms: m/e 285 (m+, 7), 241 (8), 176 (13), 162 (24), 146 (100); ^{1}H-nmr (deuteriochloroform:dimethylsulfoxide-d$_6$): δ 7.96 (m, 2H), 7.56 (m, 2H), 6.93 (m, 1H), 4.33 (s, 2H), 2.76 (d, 3H); ir (potassium bromide); 3323, 2942, 1705 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_4S_2$: C, 46.30; H, 3.89; N, 4.91. Found: C, 46.28; H, 3.90; N, 4.82.

2-Methyl-2*H*-[1]benzothieno[3,2-*e*]-1,2-thieno[3,2-*e*]-1,2-thiazine-3-(4*H*)-one 1,1-Dioxide (**6**).

A solution of **5** (450 mg, 1.58 mmoles) and *p*-toluenesulfonic acid (45 mg) in xylenes (100 ml) was refluxed in a Dean-Stark trap for 6 hours. The solvent was evaporated and the resulting solid recrystalized from isopropanol to give **6** (318 mg) in a yield of 76%, mp 175-178°; ms: m/e 267 (m+, 25), 210 (8), 160 (5), 146 (100); ^{1}H-nmr (deuteriochloroform): δ 7.96 (m, 1H), 7.80 (m, 1H), 7.58 (m, 2H), 4.22 (s, 2H), 3.38 (5, 3H); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_{11}H_9NO_3S_2$: C, 49.42; H, 3.39; N, 5.24. Found: C, 49.71; H, 3.40; N, 5.20.

General Procedure for the Reaction of Benzothienothiazine **6** with Arylisocyanates.

To a solution of **6** (500 mg, 1.87 mmoles) in dry dimethylformamide (20 ml) was added dry triethylamine (0.29 ml, 210 mg, 2.06 mmoles) at ambient temperature. The reaction mixture was stirred for 5 minutes, then arylisocyanate (2.06 mmoles) was added. The reaction mixture was stirred for 5 hours, poured into ice water and acidified. The resulting precipitate was filtered, washed with water, and air dried. Recrystallization from an appropriate solvent, indicated below, gave an analytically pure compound.

3,4-Dihydro-2-methyl-1,3-oxo-*N*-phenyl-2*H*-[1]benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1a**).

This compound was obtained in 66% yield as white needles (ethanol: methylene chloride) mp 233-236°; ms: m/e 267 (54), 162 (10), 146 (100), 119 (86); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 11.20 (s, 1H), 8.30-7.12 (m, 9H), 5.74 (s, 1H), 3.30 (s, 3H); ir (potassium bromide): ν NH 3294, ν CO 1693, 1658 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}N_2O_4S_2$: C, 55.95; H, 3.65; N, 7.25. Found: C, 55.86; H, 3.54; N, 7.18.

N-(4-Fluorophenyl)-3,4-dihydro-2-methyl-1,3-oxo-2*H*-[1]benzothieno-[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1b**).

This compound was obtained in 65% yield as white needles (2-propanol:methylene chloride) mp 250-253°; ms: m/e 404 (m+, 2), 267 (100), 146 (56), 137 (38); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 11.30 (s, 1H), 8.34-7.22 (m, 8H), 5.72 (s, 1H), 3.32 (s, 3H); ir (potassium bromide): ν NH 3300, ν CO 1696, 1657 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}FN_2O_4S_2$: C, 53.46; H, 3.24; N, 6.93. Found: C, 53.31; H, 3.30; N, 6.63.

N-(4-Bromophenyl)-3,4-dihydro-2-methyl-1,3-oxo-2*H*-[1]benzothieno[-3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1c**).

This compound was obtained in 68% yield as white needles (2-propanol:methylene chloride) mp 245-247°; ms: m/e 267 (76), 197 (40), 171 (34), 162 (22), 146 (100); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 11.40 (s, 1H), 8.34-7.64 (m, 8H), 5.72 (s, 1H), 3.32 (s, 3H); ir (potassium bromide): ν NH 3241, ν CO 1697, 1652 cm^{-1}.

Anal. Calcd. for $C_{18}H_{13}BrN_2O_4S_2$: C, 46.46; H, 2.82; N, 6.02. Found: C, 46.37; H, 2.64; N, 5.86.

N-(3-Trifluoromethylphenyl)-3,4-dihydro-2-methyl-1,3-oxo-2*H*-[1]benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1d**).

This compound was obtained in 65% yield as white needles (2-propanol:methylene chloride) mp 240-243°; ms: m/e 267 (21), 187 (69), 168 (18), 159 (23), 146 (100); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 11.62 (s, 1H), 8.34-7.54 (m, 8H), 5.76 (s, 1H), 3.32 (s, 3H); ir (potassium bromide): ν NH 3257, ν CO 1698, 1655 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}F_3N_2O_4$: C, 50.22; H, 2.88; N, 6.16. Found: C, 50.06; H, 2.82; N, 6.12.

N-(2-Methyl-4-nitrophenyl)-3,4-dihydro-2-methyl-1,3-oxo-2*H*-[1]benzothieno[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1e**).

This compound was obtained in 55% yield as white needles (methanol: acetone) mp 265-268°; ms: m/e 267 (23), 176 (61), 146 (100); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 10.78 (s, 1H), 8.32-7.72 (m, 7H), 6.06 (s, 1H), 3.02 (s, 3H), 2.42 (s, 3H); ir (potassium bromide): ν NH 3377, ν CO 1718, 1681 cm^{-1}.

Anal. Calcd. for $C_{19}H_{15}N_3O_6S_2$: C, 15.23; H, 3.39; N, 9.43. Found: C, 51.01; H, 3.33; N, 9.23.

N-(2,4-Difluorophenyl)-3,4-dihydro-2-methyl-1,3-oxo-2*H*-[1]benzothieno-[3,2-*e*]-1,2-thiazine-4-carboxamide 1,1-Dioxide (**1f**).

This compound was obtained in 66% yield as white needles (2-propanol:methylene chloride) mp 255-258°; ms: m/e 267 (61), 203 (14), 174 (14), 160 (13), 155 (69), 146 (100); ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 11.02 (s, 1H), 8.32-7.08 (m, 7H), 5.98 (s, 1H), 3.32 (s, 3H); ir (potassium bromide): ν NH 3365, ν CO 1712, 1681 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}F_2N_2O_4S_2$: C, 51.18; H, 2.86; N, 6.63. Found: C, 51.42; H, 2.93; N, 6.89.

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