The Synthesis of a New Benzothiazine Derivative, Related to Oxicams, Synthesized from Natural Safrole [1]

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The synthesis of the new derivatives, 2-methyl-6,7-methylenodioxy-2*H*-1,2-benzothiazin-3-one-4-(*N*-phenyl)carboxamide 1,1-dioxide (**6a**) from natural safrole (**5**) is described. The principal feature of this route is brevity and the high overall yield, producing the new analogue in *ca.* 35% from the natural product.

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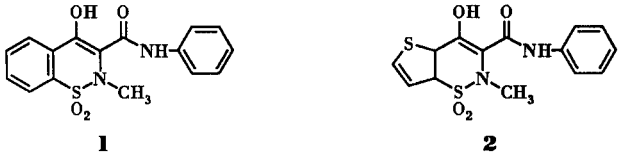
Introduction.

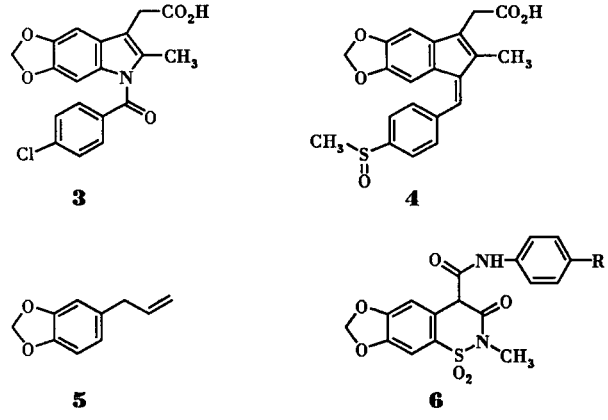
The search for more effective antiinflammatory agents has led to the discovery of potent activity for carboxamides derived from the 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide system [2,3]. In this class of enolic compounds is placed a new class of antirheumatic drugs referred to as oxicams [4], exemplified in Figure 1 by the widely used drug Piroxicam (**1**) [5,6] and the more recently introduced Tenoxicam (**2**) [7].



1 **2**

Figure 1

As part of a research program with the objective to synthesize bioactive compounds using abundant Brazilian natural products as inexpensive starting materials, we have described in previous works the synthesis of the indomethacin analogue **3** [8] and an indene isostere related to sulindac **4** [9], using safrole (**5**) as starting material (Figure 2).



3 **4** **5** **6**

Figure 2

In this paper we described the synthesis of a new member of the 3-oxo-2*H*-benzothiazine 1,1-dioxide series **6**, synthesized from natural safrole (**5**) in 35% overall yeild [10].

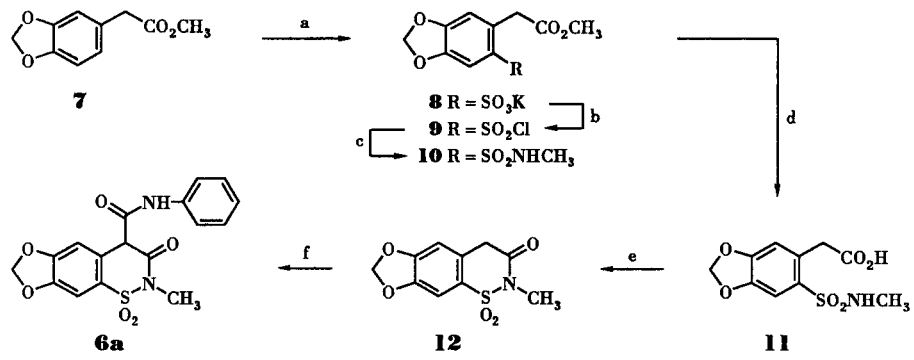
Chemistry.

An obvious synthetic approach to the new derivative **6** suggests the methylenedioxy phenylacetic acid derivative **7** as an intermediate. This compound could be easily prepared from natural product **5** by using a previously described procedure [11], involving ozonolysis of the terminal double bond followed by an oxidative workup. The corresponding methyl ester **7** was isolated in 80% yield. Treatment of **7** with sulfuric acid and acetic anhydride in ethyl acetate followed by the addition of ethanolic potassium acetate solution [12] furnished, as the only product, in 90% yield, the potassium salt of the corresponding sulfonic acid **8**. This crystalline derivative was next treated with thionyl chloride and a catalytic amount of DMF [13] to furnish the sulfonyl chloride intermediate **9**, as shown by pmr analysis. In fact, the two aromatic protons signals occurring at δ 6.65 and δ 7.30 ppm as a doublet indicated a typical *para*-hydrogen aromatic pattern. Treatment of **9** with a aqueous methylamine solution [14] afforded the *N*-methylsulfonamide derivative **10** in 90% yield. This compound was subsequently hydrolyzed to furnish the sulfonamide acid **11** which was cyclized by reflux under acidic conditions [2] affording the desired benzothiazin-3-one 1,1-dioxide system **12** [15].

Finally, the synthesis of the new carboxamide derivatives **6a-b** was completed by C-4 regioespecific functionalization upon treatement of **12** with the appropriated aryl isocyanate in DMF in the presence of triethylamine [4], to furnish the desired 4-carboxamide **6a** in *ca.* 70-75% yield. The same procedure furnished the *p*-chlorophenyl-4-carboxamide derivative **6b** (Scheme 1).

Analysis of the infrared spectra indicates that these compounds exist as the keto (non-enolized) form, although they give a deep purple color with ferric chloride suggesting an equilibrium. Furthermore, the pmr spectra of these

Scheme 1



a) 1- H_2SO_4, Ac_2O, AcOEt, 0°, 2- KOAc, EtOH, rt (90%); b) $SOCl_2$/DMF (cat), 60° (81%); c) 40% aq $NHCH_3$, $CHCl_3$, 0° (90%); d) KOH, MeOH/H_2O, reflux (98%); e) TsOH, $PhCH_3$, reflux (94%); f) 1-Et_3N, DMF, rt, 2-PhNCO, rt (73%).

derivatives indicates a contribution by the enolic form (δ 8.48 ppm for **6a** and δ 10.3 ppm for **6b**).

The antiinflammatory profile of these compounds will be described in due course. Meanwhile, preliminary results obtained in carrageenan induced rat paw edema [16] with **6a** and **6b** at 33mg/Kg p.o. showed that **6b** was *ca.* three fold more active than **6a** and showed comparable activity to that observed to piroxicam (**1**), suggesting that the antiinflammatory profile in this series seems to be dependent on the presence of electron-withdrawing substituents in the 4'-position (positive σ_p Hammett values), indicating that the enhancement of enolic proton acidity could be an important physical-chemical factor to the antiinflammatory activity.

EXPERIMENTAL

Proton magnetic resonance (pmr), unless otherwise stated, was determined in deuteriochloroform containing *ca.* 1% tetramethylsilane as an internal standard with a Varian EM 360 spectrometer at 60 MHz. Infrared (ir) spectra were obtained with a Perkin-Elmer 1600 spectrophotometer by using potassium bromide plates. Ultraviolet (uv) spectra were determined in dimethyl sulfoxide solution on a Varian UV-VIS 634-S spectrophotometer. The mass spectra were obtained by chemical ionization (ammonia/isobutane) with a Nermag/Sidar V 3.1 spectrometer.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm x 6.0 cm aluminium sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior to use and stored over 3-4A molecular sieves. The usual workup means that the organic extracts prior to concentration, under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous magnesium or sodium sulfate and filtered.

Potassium 6-Methylenecarbomethoxy-3,4-methylenedioxybenzenesulfonate (**8**) [12].

To a solution of 2 g (10.3 mmoles) of ester derivative **7** and 2.9 ml (30.7 mmoles) of acetic anhydride in 15.3 ml of ethyl acetate was added, dropwise, a solution of 0.6 ml (11.2 mmoles) of concentrated sulfuric acid in 4.1 ml of ethyl acetate at 0°. The reaction mixture was stirred at room temperature over 3 hours, after which a solution of 1.1 g (11.2 mmoles) of potassium acetate in 95% ethanol was added and the mixture was stirred additionally for 30 minutes at room temperature. The potassium salt **8** (2.89 g, 90%) was isolated by filtration as a white solid, mp 179°; ir: ν CO 1737, ν SO_2 1146 and 1058 cm^{-1}.

6-Methylenecarbomethoxy-3,4-methylenedioxybenzenesulfonyl Chloride (**9**) [13].

A solution of 0.635 ml (8.74 mmoles) of thionyl chloride and 0.01 ml of dry dimethylformamide was added to 0.5 g (1.6 mmoles) of potassium salt derivative **8**. The reaction mixture, maintained under a nitrogen atmosphere, was stirred at 60° for 3.5 hours and then poured into an ice water mixture and extracted with methylene chloride (3 x 20 ml). The organic extracts was dried and evaporated to give 0.38 g (81%) of **9** as a yellow solid, mp 105°; ir: ν CO 1732, ν SO_2 1372 and 1169 cm^{-1}; pmr: δ 3.60 (s, 3, OCH_3), 3.90 (s, 2, $ArCH_2CO$), 5.95 (s, 2, OCH_2O), 6.55 (s, 1, Ar), 7.3 (s, 1, Ar); ms: (m/z) 310 (M+18, 100%), 293 (MH+, 12%), 257 (12%), 171 (60%), 135 (38%), 110 (41%).

2-(*N*-Methylsulfamoyl)-4,5-methylenedioxyphenylacetic Acid Methyl Ester (**10**) [14].

To a solution of 1 g (3.42 mmoles) of sulfonyl chloride **9** in 10 ml of chloroform was added 1 ml (11.6 mmoles) of an 40% aqueous solution of methylamine. The reaction mixture was stirred for 3 hours at 0° and then 10 ml of chloroform was added. The organic layer was separated and washed with a solution of dilute hydrochloric acid (10 ml), water (10 ml). After the usual workup the resulting solid was chromatographed on a silica gel column to give 0.89 g (90%) of the *N*-methylsulfonamide **10** as a yellow solid, mp 131°; ir: ν NH 3269, ν CO 1711 cm^{-1}; pmr: δ 2.45 (d, 3, $NHCH_3$), 3.55 (s, 3, OCH_3), 3.9 (s, 2, $ArCH_2CO$), 5.05 (br, s, 1, NH), 5.85 (s, 2, OCH_2O), 6.55 (s, 1, Ar), 7.20 (s, 1, Ar); ms: (m/z) 305 (M+18, 17%), 288 (MH+, 100%), 256 (16%), 134 (7%).

Anal. Calcd. for $C_{11}H_{13}NO_6S$: C, 46.01; H, 4.52; N, 4.87. Found: C, 45.98; H, 4.56; N, 4.78.

2-(*N*-Methylsulfamoyl)-4,5-methylenedioxyphenylacetic Acid (**11**) [17].

The methyl ester **10** (0.8 g, 2.78 mmoles) was refluxed in 80 ml of aqueous methanolic solution (1:1) containing 1.6 g (28.5 mmoles) of potassium hydroxide for 4 hours. Neutralization with hydrochloric acid followed by the usual workup afforded 0.75 g (98%) of **11**, mp 173°; ir: ν NH 3283, ν OH 2923, ν CO 1699 cm^{-1}; pmr: (dymethyl sulfoxide-d_6): δ 2.3 (d, 3, $NHCH_3$), 3.75 (s, 2, $ArCH_2CO$), 5.95 (s, 2, OCH_2O), 6.8 (s, 1, Ar), 7.05 (br s, 2, Ar and SO_2NH).

2-Methyl-6,7-methylenedioxy-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (**12**) [2].

A solution of **11** (0.5 g, 1.83 mmoles) and *p*-toluenesulfonic acid (0.05 g, 0.29 mmoles) in 100 ml of dry toluene was refluxed using a Dean-Stark trap for 6 hours. The solvent was next evaporated and resulting solid recrystallized from ethanol:water to give **12** (0.437 g, 94%), mp 129-130°; ir: ν CO 1713 cm^{-1}; pmr: d 3.15 (s, 3, NCH_3), 3.8 (s, 2, $ArCH_2CO$), 5.85 (s, 2, OCH_2O), 6.55 (s, 1, Ar), 7.1 (s, 1, Ar); uv (DMSO): 261 nm (ϵ, 9000), 298 nm (ϵ, 9600); ms: (m/z) 273 (M + 18, 82%), 256 (MH+, 100%), 134 (20%).

Anal. Calcd. for $C_{10}H_9NO_5S$: C, 47.07; H, 3.52; N, 5.48. Found: C, 47.17; H, 3.56; N, 5.53.

General Procedure for the Reaction of Methylenedioxybenzothiazinone **12** with Aryl Isocyanates [2,3].

To a solution of **12** (0.3 g, 1.17 mmoles) in 12.6 ml of dry dimethylformamide was added 0.18 ml (1.29 mmoles) of dry triethylamine at room temperature. The reaction mixture, maintained under a nitrogen atmosphere, was stirred for 5 minutes, then aryl isocyanate (1.29 mmoles) was added. The reaction mixture was stirred for 5 hours, then poured into an ice-water mixture acidified with 6*N* hydrochloric acid (5 ml). The resulting precipitate was filtered out, washed with water (10 ml) and air dried. Recrystallization from an appropriate solvent gave an analytically pure compound.

3,4-Dyhydro-2-methyl-6,7-methylenedioxy-3-oxobenzothiazine-4-(*N*-phenyl)carboxamide 1,1-Dioxide (**6a**).

This compound was obtained in 73% yield as needles (benzene:hexane), mp 218°; ir: ν NH 3317, ν CO 1681 cm^{-1}; pmr (pyridine-d_5): δ 3.25 (s, 3, NCH_3), 5.8 (s, 2, OCH_2O), 7.00-7.85 (m, 8, Ar and NH), 8.48 (1, s, OH); uv (DMSO): 312 nm (ϵ, 6400), 263 nm (ϵ, 5300); ms: (m/z) 392 (M + 18, 14%), 375 (MH+, 100%), 255 (18%), 94 (42%).

Anal. Calcd. for $C_{17}H_{14}N_2O_6S$: C, 54.56; H, 3.74; N, 7.48. Found: C, 54.73; H, 3.72; N, 7.57.

3,4-Dihydro-2-methyl-6,7-methylenedioxy-3-oxo-2*H*-1,2-benzothiazine-4-(*N*-*p*-chlorophenyl)carboxamide 1,1-Dioxide (**6b**).

This compound was obtained in 88% yield as needles (2-propanol:water), mp 225-226°; ir: ν NH 3318, ν CO 1714 and 1665 cm^{-1}; pmr (dimethyl sulfoxide-d_6): δ 3.1 (s, 3, NCH_3), 5.15 (s, 1, NH), 6.05 (s, 2, OCH_2O), 6.90-7.50 (m, 6, Ar), 10.3 (s, 1, OH); uv (DMSO): 318 nm (ϵ, 6050), 262 nm (ϵ, 5800); ms: (m/z) 426 (M + 18, 8%), 409 (MH+, 23%), 256 (24%), 128 (100%).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_6S$: C, 49.96; H, 3.18; N, 6.85. Found: C, 49.78; H, 3.39; N, 6.93.

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