Synthesis of 2-(1-Methyl-4-piperylid-3-ene)-9,10-dihydro-4*H*-benzo[4,5]-cyclohepta[1,2-*b*]thiophen-10-one, a New Potential Antiasthmatic Analogue of Zaditene

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The title compound has been prepared in four steps from readily available starting material. The key reaction is the metallation of 10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene, which occurs exclusively at the desired 2 position.

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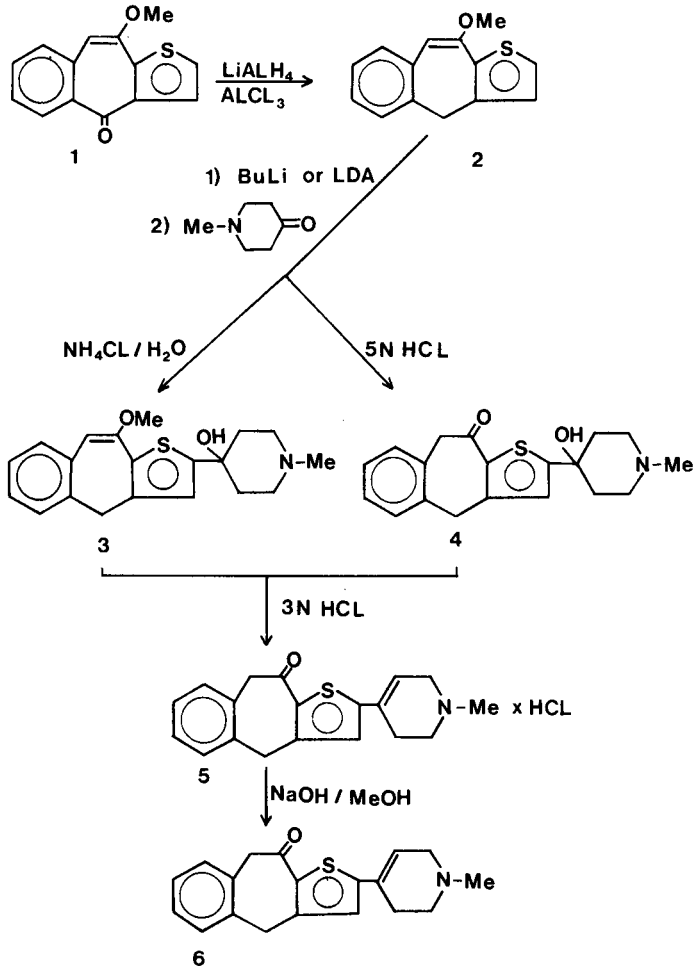
4-(1-Methyl-4-piperylidene)-9,10-dihydro-4*H*-benzo[4,5]-cyclohepta[1,2-*b*]thiophen-10-one (Zaditene) has proved to be a very effective antiasthmatic agent. It is particularly useful in those types of asthma that are associated with allergies, because it also exhibits antihistaminic activity, despite its bronchodilatory properties [1-4]. In the present work, we have prepared the analogue in which the piperidine ring is placed in the 2 rather than the 4 position and possesses an endocyclic rather than an exocyclic double bond. Introduction of other substituents at the 2 position in Zaditene has been observed to alter its pharmacological activity [5-6]. The 10-piperidyl analogue also has been prepared [7].

We considered as a starting material 9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one, which we recently prepared [8]. This material has acidic hydrogens at the 2, 4 and 9 positions. The 10-methoxy analogue, **2** (Scheme 1), has only two competing acidic positions, 2 and 4, so that the problem of metallation is simplified. We report herein the successful synthesis of the 2-piperylidene analogue of Zaditene from this material.

The desired starting material may be obtained by reduction of 10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one (**1**), which has been reported by Waldvogel *et al.* [1]. The enol ether function in **1** prevents the use of classical methods of conversion of carbonyl to methylene, such as the Clemmenson, the Wolff-Kishner, and the dithiane procedure. Use of lithium aluminum hydride/aluminum chloride [9] provided the desired reduction product. The reaction could be carried out in one step by use of 2.5 moles of lithium aluminum hydride and 2.0 moles of aluminum chloride for each mole of the ketone.

Metallation could occur theoretically at either the 2 or the 4 position. Treatment of **2** with an equimolar amount of either butyllithium or lithium diisopropyldiamide (LDA) gave exclusive metallation at the desired 2 position. Either the methoxy isomer **3** or the keto product **4** could be isolated after hydrolysis, depending on work-up conditions. Both proceeded to the dehydration product **5** on treatment with 3 *N* hydrochloric acid. The hydrochloride **5** produced the free base **6** on treatment with a methanolic solution of sodium hydroxide.

Scheme I



EXPERIMENTAL

Melting points were measured on an Electrothermal Apparatus and are uncorrected. The nmr spectra were recorded at 60 MHz on a Varian

EM 360 spectrometer. Infrared spectra were recorded on a Perkin-Elmer SP 200G spectrophotometer. Diethyl ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride prior to use. The metallation reactions were carried out in flame-dried apparatuses under a positive pressure of argon. The argon gas was dried by passing it through columns filled with sulfuric acid and sodium hydroxide pellets. The molarity of the butyllithium was determined by the procedure of Turner *et al.* [10].

10-Methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**2**).

To a stirred suspension of lithium aluminum hydride (3.8 g, 0.1 mole) in diethyl ether (50 ml) cooled to 5° by an ice bath, a solution of aluminum chloride (11 g, 0.082 mole) in 100 ml of ether was added. The ice bath was removed and 10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one (**1**) [1] (10 g, 0.041 mole) in THF (100 ml) was added at such a rate as to promote gentle reflux. The solution was then heated at reflux for 30 minutes, allowed to cool, hydrolyzed with an excess of water and with aqueous ammonium chloride (10 g, 0.186 mole), and extracted with ether (5 × 50 ml). The organic extracts were dried (sodium sulfate), decolorized with charcoal overnight, filtered through Celite, and concentrated by rotary evaporation. The residue was crystallized from methanol, 8 g, 85%, mp 94-96°, Rf 0.64 (SiO_2, 9/1 chloroform/ethyl acetate); ir (potassium bromide): ν 1625 and 1250 cm^{-1} ($CH=COCH_3$); ^{1}H-nmr (deuteriochloroform): δ 7.20 (s, 4H, aromatic), 7.00 (ABq, 2H, J = 5.6 Hz, H on C2 and C3), 6.20 (s, 1H, H on C9), 3.89 (s, 3H, OCH_3), 3.69 (s, 2H, methylene).

Anal. Calcd. for $C_{14}H_{12}OS$: C, 73.65; H, 5.29. Found: C, 73.30; H, 5.10.

10-Methoxy-2-(1-methyl-4-hydroxy-4-piperidyl)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (**3**).

To a stirred solution of **2** (1.8 g, 0.0078 mole) in 10 ml of THF was added butyllithium (5.7 ml, 0.0086 mole, 1.53 *M* solution in benzene) at -20°. The reaction mixture was stirred at -10° for an hour. The temperature then was lowered to -50°, and 1-methyl-4-piperidone (0.97 g, 0.0086 mole, 1 ml) in 5 ml of THF was injected. The mixture was stirred at -50° for 1 hour, warmed to room temperature, and allowed to sit overnight. Ammonium chloride (2.5 g, 0.046 mole) in 10 ml of water was added in one portion, and the mixture was poured into 1 ℓ of water. The precipitate was filtered off, washed with water, and recrystallized from methanol, 1.9 g, 71%, mp 213-215°, Rf 0.22 (silica gel, 4/1 chloroform-methanol); ir (potassium bromide): ν 3120 (OH), 1600 and 1245 (C=C-OMe) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.20 (d, 4H, J = 4 Hz, aromatic), 6.77 (s, 1H, H on C3), 6.20 (s, 1H, H on C9), 3.89 (s, 3H, OCH_3), 3.61 (s, 2H, H on C4), 2.75-1.67 (m + s, 12H, OH, CH_2, and CH_3). The metallation also was carried out in a similar yield with lithium diisopropylamide (LDA). To a stirred solution of diisopropylamine (1.2 ml, 0.87 g, 0.0086 mole) in 10 ml of THF, was added butyllithium (5.7 ml, 0.0086 mole, 1.53 *M* solution in hexane) at -20°. Stirring was continued for 30 minutes at -50°, and **2** (1.8 g, 0.0078 mole) in 20 ml of THF was added slowly at -20°. The remainder of the procedure was the same as above.

Anal. Calcd. for $C_{20}H_{23}SO_2N$: C, 70.34; H, 6.78; N, 4.10. Found: C, 70.16; H, 6.90; N, 4.06.

2-(1-Methyl-4-hydroxy-4-piperidyl)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one (**4**).

This material was obtained directly from the above metallation step with butyllithium, except that work-up was carried out with hydrochloric acid (10 ml, 5*N*) instead of with ammonium chloride. The acid solution was stirred for 2 hours and added to 1 ℓ of water. The solution was neutralized with 10% sodium carbonate. The precipitate was filtered off and crystallized from methanol, 0.95 g, 37%, mp 185-187°, Rf 0.22 (silica, 4/1 chloroform/methanol); ir (potassium bromide): ν 3090 (OH), 1650 (C=O) cm^{-1}; ^{1}H-nmr(deuteriochloroform): δ 7.20 (d, 4H, J = 4 Hz, aromatic), 6.90 (s, 1H, H on C3), 4.12 (s, 2H, H on C9), 4.05 (s, 2H, H on C4), 2.85-1.70 (s + m, 12H, OH, CH_2, and CH_3).

Anal. Calcd. for $C_{19}H_{20}NO_2S$: C, 69.69; H, 6.46; N, 4.27. Found: C, 69.68; H, 6.67; N, 4.23.

2-(1-Methyl-4-piperylid-3-ene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10-one Hydrochloride (**5**).

The adduct **4** (0.6 g, 1.83 mmoles) in 8 ml of 3 *N* hydrochloric acid was heated for 1 hour under reflux. A precipitate began to fall out after 0.45 hour. The flask was cooled to 5°, and the precipitate was filtered off, washed with a small amount of ice water, treated with charcoal, and recrystallized from methanol. The product was filtered off and washed with petroleum ether: 0.2 g, 32%, mp (methanol) 258-261° dec; ir (potassium bromide): ν 2500 ($^+NR_4$), 1640 (C=O) cm^{-1}. The hydrochloride also was obtained from the adduct **3** (1.1 g, 3.22 mmoles), which was dissolved in 15 ml of 3 *N* hydrochloric acid, heated to reflux for 1.5 hours, and cooled to 5°. The precipitate was filtered off, washed with a small amount of ice water, treated with charcoal, and crystallized from hot methanol, 1 g, 90%, mp (methanol) 258-261° dec.

Anal. Calcd. for $C_{19}H_{20}ClNOS$: C, 65.97; H, 5.82; N, 4.04. Found: C, 65.73; H, 6.01; N, 3.93.

1-(1-Methyl-4-piperylid-3-ene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta-[1,2-*b*]thiophen-10-one (**6**).

The hydrochloride **5** (0.6 g, 1.7 mmoles) was added to a solution of sodium hydroxide (0.14 g, 3.5 mmoles) in 20 ml of methanol. After a few minutes, a white precipitate fell out. The mixture was cooled in an ice bath, and the solid was collected and washed with small amounts of methanol and petroleum ether, 0.3 g, 56%, mp (methanol) 178-180°, Rf 0.48 (silica, 4/1 chloroform/methanol); ir (potassium bromide): ν 1640 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.20 (s, 4H, aromatic), 6.89 (s, 1H, H on C3), 6.20 (t, 1H, J = 4 Hz, H on C3'), 4.10 (s, 2H, H on C9), 4.01 (s, 2H, H on C4), 3.03 (br d, 2H, J = 4 Hz, H on C2'), 2.62 (br s, 4H, H on C5' and C6'), 2.33 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{19}NOS$: C, 73.75; H, 6.19; N, 4.53. Found: C, 73.56; H, 6.24; N, 4.45.

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