9-Methylene-1,5-dithiacyclononane (6h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–1.90, 1.90–1.99 (2 m, 2 × 2 H, $SCH_2CH_2CH_2S$ and $CH_2CH_2CH_2$), 2.67–2.72 (m, 2 × 2 H, $CH_2CH_2CH_2$), 2.82–2.86, 3.11–3.15 (2 m, 2 × 2 H, $SCH_2CH_2CH_2S$), 5.14, 5.40 (2 s, 2 × 1 H, CH_2=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.0, 28.6, 29.4, 29.9, 31.3, 115.0, 144.4; MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 37), 132 ($M^{\cdot+} - C_3H_6$, 18), 113 (12), 106 ($C_3H_5S_2$, 10), 100 (C_5H_8S, 100), 99 (24), 85 (13), 67 (14).

(*Z*)-9-Methyl-1,5-dithiacyclonon-8-ene (*Z*-3h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77–1.83 (m, 2 H, $SCH_2CH_2CH_2S$), 2.09 (s, 3 H, CH_3), 2.57–2.62 (m, 2 H, =CCH_2CH_2), 2.76–2.80 (m, 2 H, =CCH_2CH_2), 2.90–3.00 (m, 4 H, $SCH_2CH_2CH_2S$), 5.70 (t, 1 H, *J* = 8 Hz, CH=C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.1, 27.5, 28.1, 30.1, 32.3, 133.9, 134.9; MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 52), 127 (16), 113 (13), 106 ($C_3H_5S_2$, 27), 100 (77), 99 (C_5H_7S, 100), 85 (47), 71 (14); IR (mixture) ($CHCl_3$) 3086, 2995, 1602, 1441 cm^{-1}; HRMS (mixture) calcd for $C_8H_{14}S_2$ 174.0537, found 174.0537.

(*E*)-9-Methyl-1,5-dithiacyclonon-8-ene (*E*-3h): ^{1}H NMR (300 MHz, $CDCl_3$) (key signals observed) δ 1.97 (d, 3 H, *J* = 1 Hz, CH_3), 2.29–2.36 (m, 2 H, =CCH_2CH_2), 6.08 (tq, 1 H, *J* = 8, 1 Hz, CH=C); MS *m/z* (relative intensity) (GCMS) 174 ($M^{\cdot+}$, 90), 127 (49), 113 (39), 106 ($C_3H_5S_2$, 67), 100 (93), 99 (C_5H_7S, 100), 85 (81), 71 (39).

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Supplementary Material Available: ^{1}H and ^{13}C spectra (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Facile Synthesis of Tepoxalin, 5-(4-Chlorophenyl)-*N*-hydroxy-1-(4-methoxyphenyl)-*N*-methyl-1*H*-pyrazole-3-propanamide

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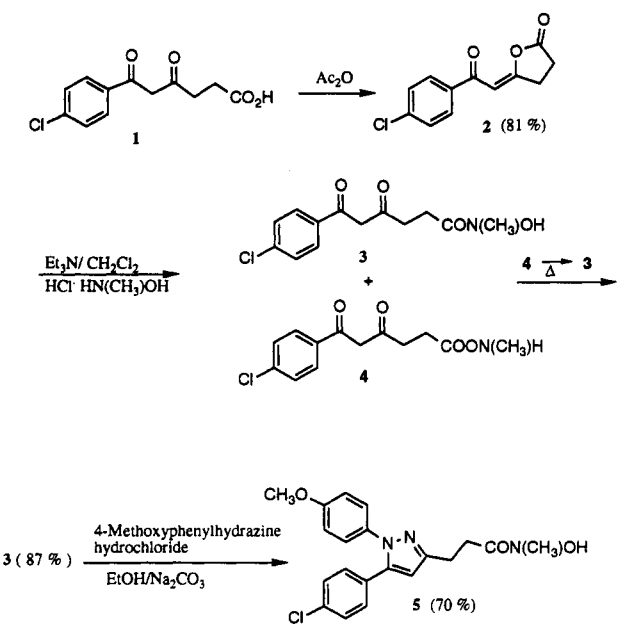
Tepoxalin (**5**)[1] is a potent inhibitor of both the cyclooxygenase and lipoxygenase pathways of the arachidonic acid cascade. We have previously described a highly efficient regioselective synthesis of this compound.[2] Due to toxicity considerations it became desirable to synthesize tepoxalin without using methylene chloride or oxalyl chloride in the last step. Herein we report a high-yield synthesis of tepoxalin which meets this objective.

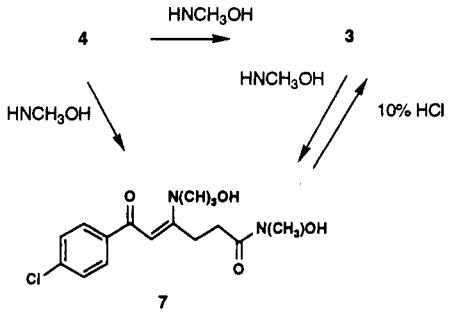
Results and Discussion

The synthesis of tepoxalin is outlined in Scheme I. The starting 6-(4-chlorophenyl)-4,6-dioxohexanoic acid (**1**) was previously synthesized in our laboratories.[2,3] When **1** was treated with acetic anhydride at 100 °C the enol lactone **2** was produced in 81% yield.[4] Compound **2** was added

Scheme I



Scheme II



to *N*-methylhydroxylamine hydrochloride in methylene chloride containing triethylamine, initially forming a mixture of the N- and O-acetylated *N*-methylhydroxylamines. Stirring at room temperature with excess *N*-methylhydroxylamine converts the O-acylated compound **4** to the N-acylated compound **3** in 87% yield.

During the course of performing this reaction we noticed that a portion of **3** was isolated from the aqueous acid portion of our workup. We surmised that some intermediate to **3** was being extracted into the acid phase and hydrolyzed in the aqueous phase to **3**. We felt that the extracted compound was likely to be **7**. By direct chromatography of the concentrated reaction mixture we were able to isolate a small quantity of a compound whose spectral properties (notably the UV absorbance at 322 nm) were consistent with **7**.[5] Furthermore this compound could be converted to **3** by dissolving it in 10% HCl (Scheme II). We can envision a number of mechanisms by which **4** can be converted to **3**. Scheme III outlines a mechanism where **4** closes to an internal vinylogous amide **6**. The six-membered ring can then be opened by excess *N*-methylhydroxylamine to afford **7** which is then hydrolyzed to **3** during acidic workup. In an attempt to isolate **6**, we dissolved **4** in methylene chloride and allowed it to stand at room temperature overnight. With no additional *N*-methylhydroxylamine present we found 70% of **4** had been converted to **3**. An alternative mechanism is shown in Scheme IV where **4** is converted to **3** through the in-

(1) (a) Wachter, M.; Ferro, M. U.S. Patent 4,826,868, 1989. (b) Robinson, C. *Drugs Future* **1990**, *15* (9), 202 and references therein.
(2) Murray, W.; Wachter, M., Barton, D., Forrero-Kelly, Y. *Synthesis* **1991**, 18.
(3) Murray, W.; Wachter, M. *J. Org. Chem.* **1990**, *55*, 3424.
(4) Hori, K.; Takaishi, N., *Bull. Chem. Soc. Jpn.* **1988**, *61* (5), 1791.
(5) Ostercamp, D. *J. Org. Chem.* **1965**, *30* (4), 1169 and references therein.

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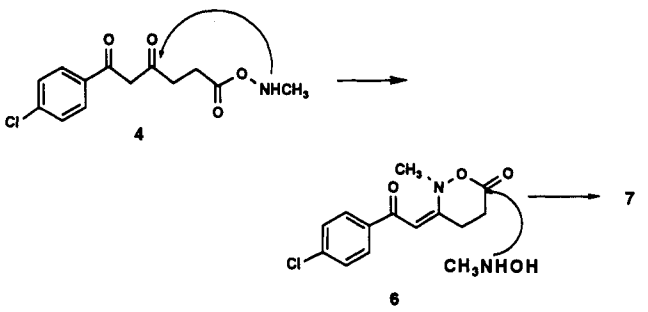
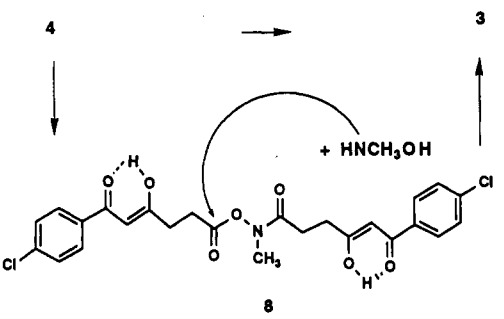
Scheme III



Scheme IV



termediate mixed methylhydroxamic anhydride 8. Compound 8 is then attacked by the liberated *N*-methylhydroxylamine from the initial step of this mechanism.

Compound 3 was then combined with 4-methoxyphenylhydrazine hydrochloride in ethanol containing sodium carbonate to afford 5 in 70% yield.[6]

This synthesis provides a straightforward process for synthesizing tepoxalin. Compound 2 also represents an interesting intermediate for the synthesis of a number of interesting heterocyclic propanamides and propanoates.

Experimental Section[7]

5-[1-(4-Chlorophenyl)-1-oxoethanylidene]-3,4-dihydrofuran-2-one (2). Compound 1 (2.54 g, 0.01 mol) was suspended in acetic anhydride (40 mL). The mixture was heated to reflux and held there for 20 min. At this point all solid was dissolved and the solution began to darken. The acetic anhydride was removed in vacuo, and the brown residue was crystallized from methylene chloride/hexane to afford 1.92 g (81%) of tan needles, mp 150–151 °C. TLC hexane/40% EtOAc showed a single spot. ^{1}H NMR (DMSO-d_6): 2.8 (t, 2 H, J = 8 Hz), 3.5 (t, 2 H, J = 8 Hz), 6.9 (s, 1 H), 7.4 (d, 2 H, J = 8 Hz), 8.0 (d, 2 H, J = 8 Hz). MS (DCI): m/z 237 (M + H). IR (KBr, cm^{-1}): 1827, 1686, 1596. Anal. Calcd for $C_{12}H_9ClO_3$: C, 60.90; H, 3.84. Found: C, 60.66; H, 3.79.

6-(4-Chlorophenyl)-4,6-dioxo-*N*-hydroxy-*N*-methylhexanamide (3). Compound 2 (2.36 g, 0.01 mol) was dissolved in CH_2Cl_2 (40 mL) and added dropwise to a mixture of *N*-methylhydroxylamine hydrochloride (1.28 g, 0.015 mol) and Et_3N (1.5 g, 0.015 mol) in CH_2Cl_2 (80 mL) at 0 °C. After the addition was complete the mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 16 h, 50 mL of 10% HCl was added, and the layers were separated. The CH_2Cl_2 layer was washed once each with 50-mL portions of 10% HCl and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to a yellow solid, which was crystallized from CH_2Cl_2/hexane to afford 1.96 g, (69%) of 3 as a yellow solid: mp 135–137 °C.[8] The acid washes deposited crystals which were filtered-dried and crystallized from CH_2Cl_2 to afford additional 3 (0.51 g, 18%). ^{1}H NMR (DMSO-d_6): 2.7 (s, 4 H), 3.1 (s, 3 H), 6.5 (s, 1 H), 7.4 (d, 2 H, J = 8 Hz), 7.8 (d, 2 H, J = 8 Hz), 9.5 (br s, 1 H), 15.7 (br s, 1 H). MS (DCI): m/z 284 (M + H). IR (KBr, cm^{-1}): 3161, 1608, 1592. Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.03; H, 4.98; N, 4.94. Found: C, 55.06; H, 5.21; N, 4.82.

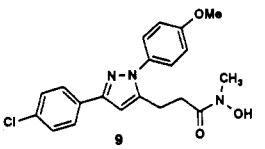
5-(4-Chlorophenyl)-*N*-hydroxy-1-(4-methoxyphenyl)-*N*-methyl-1*H*-pyrazole-3-propanamide (5).[9] Compound 3 (1.42 g, 5 mmol), 4-methoxyphenylhydrazine hydrochloride (0.96 g, 5.5 mmol), and Na_2CO_3 (0.71 g, 6.7 mmol) were combined and stirred in EtOH (100 mL) at reflux for 3 h. The cooled mixture was concentrated in vacuo and partitioned between water (50 mL) and ether (100 mL). The ether layer was washed with 5% HCl, 2% $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated to a tan solid which was chromatographed on silica gel using hexane/40% EtOAc/2% MeOH as the mobile phase. The residue was crystallized from EtOAc/hexane to afford 1.35 g (70%) of a white solid, mp 124–126 °C. ^{1}H NMR ($CDCl_3$): 2.9 (t, 2 H, J = 6 Hz), 3.2 (m, 5 H), 3.8 (s, 3 H), 6.3 (s, 1 H), 6.85 (d, 2 H), 7.2 (m, 4 H), 7.3 (d, 2 H, J = 8 Hz) 10.7 (br s, 1 H). MS (DCI): m/z 386 (M + H). IR (KBr, cm^{-1}): 3150, 1660. Anal. Calcd for $C_{20}H_{20}ClN_3O_3$: C, 62.26; H, 5.22; N, 10.89. Found: C, 62.44; H, 5.20; N, 10.99.

***O*-(*N*-Methylamino)-6-(4-chlorophenyl)-4,6-dioxohexanoate (4) and 6-(4-Chlorophenyl)-4-(*N*-hydroxy-*N*-methylamino)-6-oxo-*N*-hydroxy-*N*-methyl-4-hexenamide (7).** Compound 2 (2.36 g, 0.01 mol) was dissolved in CH_2Cl_2 (40 mL) and added at once to a mixture of *N*-methylhydroxylamine hydrochloride (0.85 g, 0.01 mol) and Et_3N (1.0 g, 0.01 mol) in CH_2Cl_2 (80 mL) at room temperature. The mixture was stirred at room temperature for 0.5 h, 50 mL of 10% HCl was added, and the layers were separated. The CH_2Cl_2 layer was washed once each with 50-mL portions of 10% HCl and brine, dried over Na_2SO_4, filtered, and converted in vacuo to a brown residue, which was chromatographed on silica gel using CH_2Cl_2/1% MeOH as eluent. The less polar fraction was isolated as a tan oil which crystallized on standing to afford 0.47 g (16%) of 4. Attempts to recrystallize the compound led to varying degrees of conversion to 3. Attempts to melt this compound led to broad melting point ranges with varying degrees of conversion to 3. ^{1}H NMR ($CDCl_3$): 2.7 (t, 2 H, J = 6 Hz), 2.8 (m, 5 H), 6.15 (s, 1 H), 7.35 (d, 2 H, J = 8 Hz), 7.75 (d, 2 H, J = 8 Hz), 15.4 (br s, 1 H). MS (DCI): m/z 284 (M + H). IR (KBr, cm^{-1}): 1742, 1594. Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.03; H, 4.98; N, 4.94. Found: C, 55.06; H, 5.21; N, 4.82. The second fraction isolated yielded 3. The third and most polar fraction was isolated as a tan residue 85 mg (3%) of 7. ^{1}H NMR ($CDCl_3$): 2.5–2.8 (m, 5 H), 3.1–3.4 (m, 5 H), 5.6 (s, 1 H) (NC=C*H*CO), 7.35 (d, 2 H, J = 8 Hz), 7.75 (d, 2 H, J = 8 Hz). MS (DCI) m/z 313 (M + H). UV (EtOH) λ_{max} 322 nm (log A 4.133). Anal. Calcd for $C_{14}H_{17}N_2O_4Cl$: C, 53.77; H, 5.48; N, 8.96. Found: C, 53.41; H, 5.87; N, 8.59.

6-(4-Chlorophenyl)-4,6-dioxo-*N*-hydroxy-*N*-methylhexanamide (3) from 4 or 7. Compound 4 (0.283 g, 0.001 mol) was dissolved in CH_2Cl_2 and allowed to stand for 16 h. TLC and NMR of the mixture showed 60% conversion to 3. Compound 7 (31 mg, 0.31 mmol) was dissolved in 1 mL of 10% HCl, and after 1 h the mixture was pipetted into 10 mL of CH_2Cl_2. The CH_2Cl_2 was separated, dried over sodium sulfate, filtered, and concentrated to a tan residue (21 mg, 74%), found to be identical to 3 by NMR and MS.

Registry No. 1, 111881-78-8; 2, 142791-63-7; 3, 142791-64-8; 4, 144192-63-2; 5, 103475-41-8; 7, 144192-64-3; 4-methoxyphenylhydrazine hydrochloride, 19501-58-7.

(6) The ^{1}H NMR of the crude reaction mixture shows a 7:1 mixture (86% yield) of 1,5:1,3-pyrazole isomers. Chromatography affords 10% of 3-[3-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-pyrazolyl]-*N*-hydroxy-*N*-methylpropanamide (9) as well as tepoxalin.



(7) For general experimental procedures, see ref 2.

(8) About 10% of the keto form was observed in DMSO-d_6. The characteristic keto methylene resonance is observed in the proton NMR at δ 4.3 ppm as described in ref 3.

(9) The name in ref 2 appeared as 3-[5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-pyrazolyl]-*N*-hydroxy-*N*-methylpropanamide.