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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 8107–8109

Photolysis of NSAIDs. Part 3: Structural elucidation of photoproducts of tolmetin in methanol

Ming-Thau Sheu,[a] Jender Wu,[b] Chih-Jui Chen,[a] Su-Hui Chao[a] and An-Bang Wu[a,*]

[a]*Graduate Institute of Pharmaceutical Sciences, College of Pharmacy, Taipei Medical University, 250 Wu Hsing Street, Taipei 110, Taiwan*
[b]*Department of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan*

Received 6 February 2004; revised 15 August 2004; accepted 23 August 2004
Available online 21 September 2004

Abstract—A sample of 10 mM tolmetin in methanol was photo-irradiated with a Hanovia 200 W high-pressure quartz Hg lamp for four days. In total, eight photoproducts were observed from the HPLC chromatogram. Three major photoproducts were separated, and their structures were elucidated by spectroscopic methods. The structures of all photoproducts were further determined by LC–ESI-MS. A reaction scheme of tolmetin was proposed.

Tolmetin (TLM), 1-methyl-5-(*p*-toluoyl)-1*H*-pyrrole-2-acetic acid sodium salt dihydrate, is a non-steroidal anti-inflammatory drug (NSAID), which is widely used as an analgesic and antirheumatic agent.[1] However, drug-induced photosensitivity or phototoxicity is always related to photoproducts.[2] Photolysis showed that 0.1 mM TLM in phosphate-buffered saline solution undergoes photodecarboxylation to *p*-toluoyl-1,2-dimethyl-5-pyrrolyl ketone in nitrogen and to *p*-toluoyl-1-methyl-2-hydroxymethyl-5-pyrrolyl ketone and 5-(*p*-toluoyl)-1-methyl-2-pyrrole carbaldehyde in air.[3]

In the present study, an amount of 10 mM TLM in methanol was irradiated with a Hanovia 200 W high-pressure mercury lamp[4] for four days. In total, eight photoproducts were observed from the HPLC[5] and LC–MS[6] chromatograms. Three major photoproducts **3**, **7**, and **8**, were separated according to the elution order by the preparative HPLC. The structures of photoproducts **3**, **7**, and **8** were identified by spectroscopic methods to be *p*-methylbenzaldehyde, 5-(*p*-toluoyl)-1-methyl-2-pyrrole carbaldehyde, and *p*-toluoyl-1,2-dimethylpyrrolyl ketone, respectively.[7] The molecular weights of the remaining five minor photoproducts were determined by LC–ESI-MS with a positive mode of polarity.

A novel α-cleavage of a ketone: Photoproduct **2** had a molecular weight of 109 g mol^{-1}, and its structure is most likely to be *N*-methyl-2-formylpyrrole. The successful identification of **2** represents an interesting finding, which indicates that a typical radical reaction of α-cleavage of a ketone[8] into two moieties occurred. TLM is a diaryl ketone with a phenyl ring on one side and a pyrrolyl group on the other. Consideration of the resonance energy of benzene versus pyrrole[9] in conjugation with the carbonyl group, which equals 36 versus 22 kcal mol^{-1}, implies the double bond character of C8′–C1′ is stronger than C8′–C5 due to the greater electron distribution of the former bond. The counterpart of the cleavage is photoproduct **3**, *p*-methylbenzaldehyde, as verified by NMR spectroscopy. Due to the apparently weaker bond strength of C8′–C5 in the parent drug, TLM, the bond fission occurs mainly along C8′–C5 to generate acyl (*m*/*z* 119) and pyrrolyl radicals (*m*/*z* 138). Next, each of the two radicals picks up a hydrogen atom from the solvent molecules and the former becomes photoproduct **3**. The latter pyrrolyl radical forms firstly an acetic acid derivative, which decarboxylates and follows by oxidation with singlet oxygen producing photoproduct **2** (MW = 109 g mol^{-1} equivalent to *m*/*z* 138 − 30 + 1; when the functional group changed from –CH_2(C=O)OH to –CHO, *m*/*z* would decrease by 30 units). Meanwhile, TLM is a weak acid, which releases protons as the catalyst. An equilibrium reaction of nucleophilic addition of methanol to the carbonyl group of **2** (*m*/*z* increases by 32 units) produces a hemiacetal **1** (MW = 141 g mol^{-1}).

Keywords: Tolmetin; Photoproducts; LC–ESI-MS.
* Corresponding author. Tel.: +886 2 27361661x6121/27366518; fax: +886 2 27366518; e-mail: anbangwu@tmu.edu.tw

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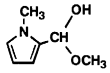
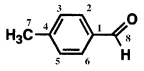
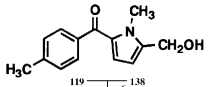
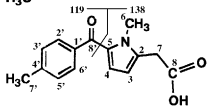
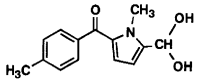
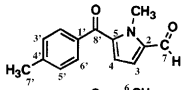
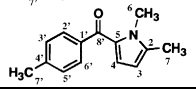
doi:10.1016/j.tetlet.2004.08.177

Decarboxylation and oxidation: By decarboxylation of TLM and *N*-methyl-2-pyrrolyl acetic acid (*m*/*z* decreases by 44 units) initially forms methylene radical intermediates. The following reactions split into two ways. First, the former intermediate intercepts a hydrogen atom from methanol to form compound **8** (MW = 213 g mol^{-1}). Second, the two intermediates proceed via similar reaction pathways by oxidation with the singlet oxygen to generate the oxidized forms of an alcohol **4** (MW = 229 g mol^{-1}), two aldehydes **3** (MW = 120 g mol^{-1}), and **7** (MW = 227 g mol^{-1}), respectively.[3] Photoproduct **5** is simply a hydrated form of **7** (MW = 245 g mol^{-1}; *m*/*z* increases by 18 units indicating that 1 mol of H_2O is added to **7**), just like its parent drug (TLM) with a dihydrate structure. Photoproduct **6** forms neither a negative nor positive charged species, thus its molecular weight could not be determined. In all, seven of the eight photoproducts with their chemical

Table 1. Structure elucidation based on LC–MS of TLM and photoproducts

Compound	Retention time (min)	Quasimolecular ion and fragment (*m*/*z*)	Difference in *m*/*z*[a]	Chemical structure[b]
1	2.41	$[MH]^+$: 142 Fragmentation: 110	−116 (−118 − 30 + 32)	
2	2.51	$[MH]^+$: 110 Fragmentation: 82, 99	−148 (−118 − 30)	
3	6.04	$[MH]^+$: 119 Fragmentation: N.D.[c]	−139 (−109 − 30)	
4	9.99	$[MH]^+$: 230 Fragmentation: 212, 119	−28	
TLM	10.77	$[MH]^+$: 258 Fragmentation: 119	—	
5	12.29	$[MH]^+$: 246 Fragmentation: 228, 214, 119	−12 (−30 + 18)	
6	15.49	—	—	—
7	24.20	$[MH]^+$: 228 Fragmentation: 214, 119	−30	
8	41.21	$[MH]^+$: 214 Fragmentation: 119	−44	

[a] $[MH]^+$ in *m*/*z* units. The difference in MW by subtracting the molecular ion of TLM from compound **1**–**8**.

[b] IUPAC names: TLM, 1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrole-2-acetic acid; **1**, a hemiacetal of **2**; **2**, *N*-methyl-2-formylpyrrole; **3**, *p*-methylbenzaldehyde; **4**, *p*-toluoyl-1-methyl-2-hydroxymethyl-5-pyrrolyl ketone; **5**, hydrate of **7**; **7**, 5-(*p*-toluoyl)-1-methyl-2-pyrrole carbaldehyde; **8**, *p*-toluoyl-1,2-dimethyl-5-pyrrolyl ketone. The structures of photoproduct **3**, **7**, and **8** confirmed by spectroscopic methods.

[c] N.D., no data.

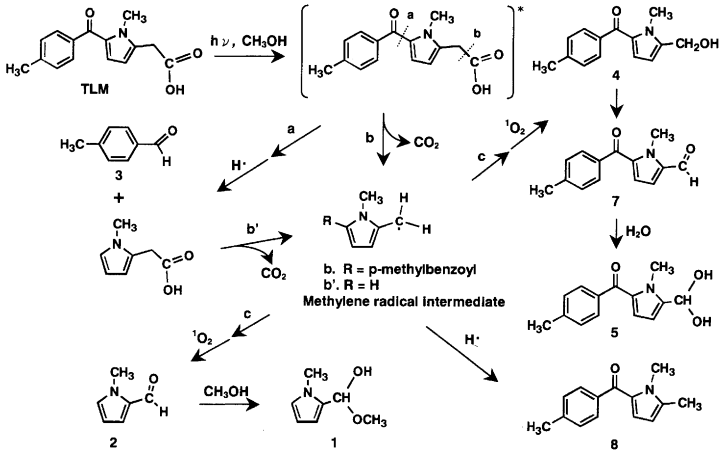


Figure 1. A proposed photodegradation reaction scheme of TLM: (a) α-cleavage of a ketone; (b) decarboxylation; (c) oxidation with singlet oxygen.

structures were further checked by LC–ESI-MS[10] and listed in Table 1. A proposed reaction scheme of photolysis of TLM in methanol is shown in Figure 1.

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4. Irradiation conditions: A Hanovia 200 W high-pressure quartz mercury lamp (Union, NJ) was used as a light source. The light intensity of the monochromatic radiation was measured at 310 nm to be 0.65 mW/cm^2.
5. HPLC apparatus and separation conditions: An Alcott 760 HPLC pump system (Norcross, GA) equipped with a Jasco 875-UV detector (Tokyo, Japan) set at 254 nm, and a preparative YMC-Pack Pro C18 of 250 × 20 mm id column (Tokyo, Japan) was used with a mobile phase of CH_3CN–CH_3OH–1% HOAc (4:63:33, v/v/v). The flow rate was 10 mL/min, and the injection volume was 200 μL.
6. LC–MS instrument and conditions: An HP series 1100LC/MSD (Palo Alto, CA) instrument consisted of an Inertsil 5 ODS-80A column (150 × 2.1 mm id) and a mobile phase of CH_3OH–0.1% HOAc (55:45, v/v). The UV detector was set at 254 nm, the flow rate at 0.3 mL/min, and the injection volume at 10 μL. The MS conditions were optimized as follows: API electron spray interface, positive mode polarity, a drying gas flow of 10 L/min, a nebulizer gas pressure of 60 psi, a drying gas temperature of 350 °C, a fragmentor voltage of 100 V, a capillary voltage of 3500 V, and a scan range of *m/z* 0–600, at 1.15 s/scan.
7. Characterization the photoproducts: NMR: The ^{1}H and ^{13}C NMR spectra were taken on a Brüker, ACE-500 FT-NMR (500 MHz) (Ettlingen, Germany). 2D NMR of heteronuclear multiple quantum coherence (HMQC) for determining ^1J (C, H) correlation, and heteronuclear multiple bond connectivity (HMBC) for showing ^2J (C, H) and ^3J (C, H) long-range coupling relations were used.

   p-Methylbenzaldehyde (**3**): ^{1}H NMR (in CD_3OD): δ in ppm relative to TMS, 9.89 (s, 1H, C8′O=C–H), 7.88–7.90 (m, 2H, C2′ and C6′), 7.25–7.27 (m, 2H, C3′ and C5′), 2.39 (s, 3H, *p*-CH_3). ^{13}C NMR (in CD_3OD): 191.7 (C8′), 144.9 (C4′), 130.8 (C2′ and C6′), 130.1 (C3′ and C5′), 129.4 (C1′), 21.6 (C7′). EI-MS (70 eV): *m/z* (rel int. %) 136 (47), 119 (45), 91 (100). IR: 1681 (strong, C=O), 1612.3 (medium, C=C). UV, λ_{max} in nm (absorbance): 203 (1.543), 236 (1.335).

   5-(*p*-Toluoyl)-1-methyl-2-pyrrole carbaldehyde (**7**): ^{1}H NMR (in CD_3OD): δ 9.79 (s, 1H, C7, O=C–H), 7.73–7.74 (m, 2H, C2′ and C6′), 7.33–7.34 (m, 2H, C3′ and C5′), 7.03 (d, 1H, J = 4.2 Hz, C2=C3–H), 6.67 (d, 1H, J = 4.3 Hz, C5=C4–H), 2.41 (s, 3H, C7′, *p*-CH_3). ^{13}C NMR (in CD_3OD): 189.0 (C8′), 183.6 (C7), 145.2 (C4′), 138.1(C2), 137.3 (C1′), 130.9 (C2′ and C6′), 130.4 (C5), 130.2 (C3′ and C5′), 122.4 (C3), 120.6 (C4), 35.0 (C6), 21.6 (C7′). EI-MS (70 eV): *m/z* (rel int. %): 227 (66), 212 (83), 119 (37), 91 (100). IR (KBr) in cm^{-1}: 1682.1 (strong, H–C=O) and 1635.4 (strong, RR′C=O), 1607.4 (weak, C=C). UV, λ_{max} in nm (absorbance): 202 (0.398), 317 (0.608).

   p-Toluoyl-1,2-dimethylpyrrolyl ketone (**8**): ^{1}H NMR (in CD_3OD): δ 7.59–7.61 (m, 2H, C2′ and C6′), 7.26–7.28 (m, 2H, C3′ and C5′), 6.61 (d, 1H, J = 4.0 Hz, C4, C=C–H), 5.98 (d, 1H, J = 3.9 Hz, C3, C=C–H), 2.41 (s, 3H, C7′, *p*-CH_3), 2.31 (s, 3H, C7, C=C–CH_3). ^{13}C NMR (in CD_3OD): 187.4 (C8′), 143.2 (C4′), 142.0 (C2), 138.9 (C1′), 131.6 (C5), 130.3 (C3′ and C5′), 129.7 (C2′ and C6′), 125.1 (C4), 109.7 (C3), 33.2 (C6), 21.5 (C7′), 12.5 (C7). EI-MS (70 eV): *m/z* (rel int. %): 212 (100), 198 (40), 122 (33), 91 (24). IR (KBr) in cm^{-1}: 3103, 2947, 2919, and 2857 (weak, C–H stretching), 1614.0 (strong, C=O), 1569.1 (weak, C=C). UV, λ_{max} in nm (absorbance): 205 (1.267), 254 (0.850), 316 (1.751).
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