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Photodecomposition of CI-981, an HMG-CoA Reductase Inhibitor

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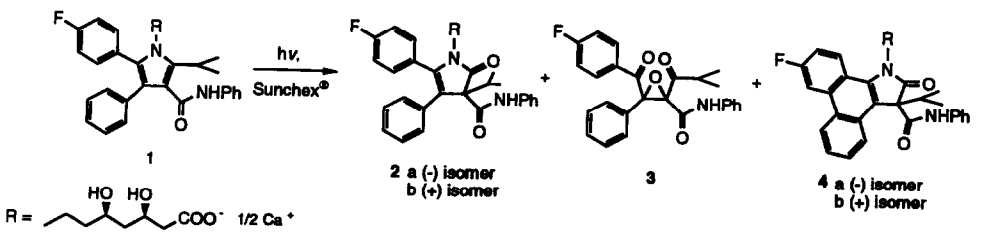
Abstract: *Upon exposure to intense simulated sunlight, CI-981 (1) readily decomposes into three major by-products. This paper reports on the products formed when 1 is decomposed in acetonitrile/water solutions under intense simulated sunlight, ultraviolet light filtered at 254 nm and visible light. Included is a discussion of the isolation of the major by-products and possible mechanisms for the photooxidative processes which lead to them.*

INTRODUCTION

Previous articles from our laboratories have documented that CI-981 [R-(R*,R*)]-2-(4-fluorophenyl)-ß,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (1) functions as an efficient inhibitor of HMG-CoA reductase.[1] Upon exposure to intense simulated sunlight, the compound in solution readily decomposes into three major by-products (Scheme 1).



Scheme 1. Photodecomposition of **1** Under Intense Simulated Sunlight

This report discusses the possible mechanisms for the formation of the photodegradation products of **1**. The lactam products (-)-5-(4-fluorophenyl)-2,3-dihydro-ß,δ-dihydroxy-3-(1-methylethyl)-2-oxo-4-phenyl-3-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (**2a**) and (+)-5-(4-fluorophenyl)-2,3-dihydro-ß,δ-dihydroxy-3-(1-methylethyl)-2-oxo-4-phenyl-3-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (**2b**) and the diketoepoxide product 3-:(4-fluorophenyl)carbonyl:-2-(2-methyl-1-oxopropyl)-N,3-diphenyl-2-oxiranecarboxamide (**3**) require visible light, a sensitizer and triplet oxygen. The photodecomposition of pyrroles to 2,5-diketo-3,4-epoxy products has been reported.[2-5] Previous articles have reported lactam formation from pyrrole photooxidation.[6-8] Migration of the 5 substituent to the 4 position, as demonstrated in the rearrangement of the isopropyl group in lactams **2** (**a** and **b**), has also been reported.[2,4,5,9,10] The formation of the phenanthrene products (-)-9-fluoro-2,3-dihydro-ß,δ-dihydroxy-3-(1-methylethyl)-2-oxo-3[(phenylamino)carbonyl]-1H-dibenz[e,g]indole-1-heptanoic acid hemicalcium salt (**4a**) and (+)-9-fluoro-2,3-dihydro-ß,δ-dihydroxy-3-(1-methylethyl)-2-oxo-3[(phenylamino)carbonyl]-1H-dibenz[e,g]indole-1-heptanoic acid hemicalcium salt (**4b**) requires the irradiation of **2** (**a** and **b**) with light from the ultraviolet region. Phenanthrene formation from the photocyclization of stilbenes has been reported.[10-14]

EXPERIMENTAL SECTION

Photodecomposition of **1**: One hundred milliliters of a 0.50 mg/mL solution of **1** in 60/40 acetonitrile/water was irradiated in an open beaker in an Atlas Sunchex® exposure instrument (Xenon arc lamp, set to 0.35 W/m^2 at 340 nm) at a distance of 100 mm from the lamp source. The solution was assayed by HPLC at 15-minute intervals. Figure 1 shows an HPLC chromatogram of the solution after 60 minutes. After 90 minutes, the peak corresponding to the starting material had completely disappeared.

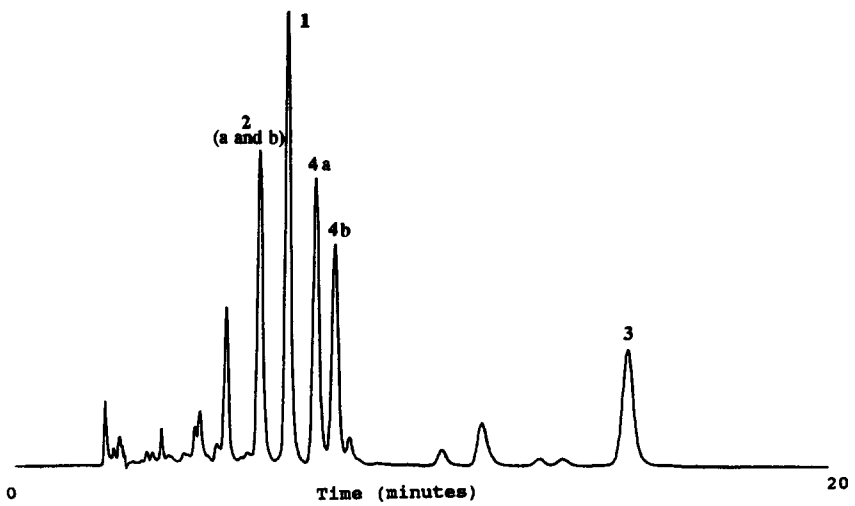


FIGURE 1. HPLC chromatogram of a 0.50 mg/mL solution of **1** in 60/40 acetonitrile/water after 60 minutes of exposure to intense simulated sunlight. Analytical HPLC conditions are described in the Experimental Section.

The analytical HPLC system used to monitor photodecomposition reactions included an Alltech Econosphere® 5 μ C18 column (150 mm x 4.6 mm I.D.), 57:23:20 0.05 M citric acid (pH 4.0 with NH_4OH):CH_3CN:THF, 2.0 mL/minute, 254 nm detection.

Wavelength-specific photodecomposition experiments were also carried out on similar solutions of **1** in 60/40 acetonitrile/water. The solutions were irradiated in an open beaker for 3 hours at a distance of 100 mm from the following lamp sources: 254 nm (Spectroline® Model CX-20), 365 nm (Spectroline® Model CX-20), and visible (100 W, 120 V, tungsten spotlight). The same experiments were repeated with 0.50 μg/mL methylene blue added as a sensitizer. Table 1 summarizes the formation of the major by-products expressed as a normalized percentage of the total HPLC area of known products under the reaction conditions described above.

TABLE 1. Formation of By-Products of **1**

hυ Source	Sensitizer	% Area Normalization (HPLC)			
		1	**2 (a + b)**	**3**	**4 (a + b)**
Sunchex®	-	0	44	8	48
254 nm	-	79	7	1	14
254 nm	Methylene Blue	79	8	1	12
365 nm	-	0	20	16	64
365 nm	Methylene Blue	0	21	15	64
Visible (W)	-	100	0	0	0
Visible (W)	Methylene Blue	0	69	31	0

Preparative Chromatography: Isolation of the individual by-products outlined in Scheme 1 required both reverse-phase and normal-phase preparative chromatography. The conditions for reverse-phase chromatography were:

Column: Rainin Dynamax® 8 μ C18, 300 mm x 41.4 mm I.D.
Mobile Phase: 50:30:20 0.05 M citric acid (pH 4.0 with NH_4OH):CH_3CN:THF
Flow Rate: 25 mL/minute

The conditions for normal-phase chromatography were:

Column: Rainin Dynamax 8 μ silica gel, 300 mm x 41.4 mm I.D.
Mobile Phase: 60:36:4 hexane:$CHCl_3$:MeOH
Flow Rate: 25 mL/minute

The preparative chromatographic fractions were combined based on their purity by HPLC. Rotational data conducted on isolated compounds **2 (a,b)** and **4 (a,b)** was used to designate each isomer at (+) or (-).

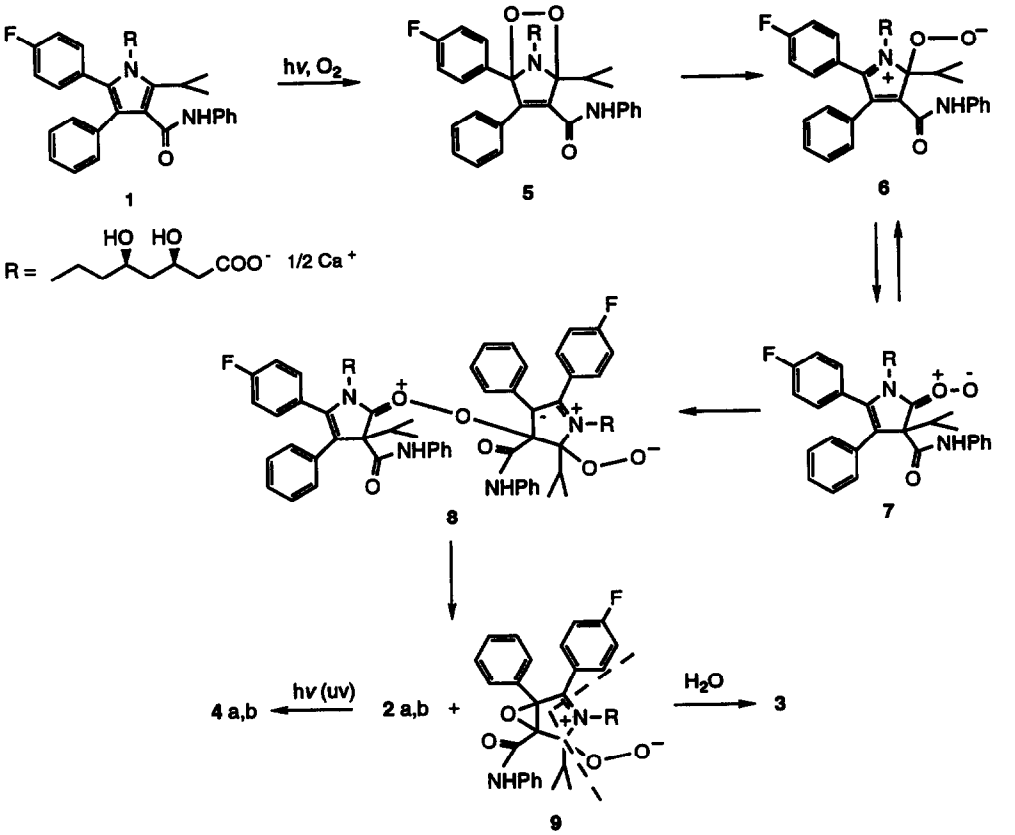
Isolation of 3: Ten grams of **1** was dissolved in 4.5 L of 70/30 acetonitrile/water and irradiated in open beakers for 25 hours under intense simulated sunlight in an Atlas Sunchex® exposure instrument. The acetonitrile was evaporated off in vacuo forming 8.8 g of a water insoluble oil. This oil was dissolved in 25 mL of acetonitrile and sonicated for 10 minutes. The crude **3** which precipitated out of solution was recrystallized from 3 mL of 2/1 hexane/chloroform. Crystalline **3** (100 mg) was recovered. The FAB mass spectrum of **3** has a molecular ion peak at m/z 432 (M+1). Signals at 189.9 ppm and 206.6 ppm in the ^{13}C-NMR of **3** in $CDCl_3$ correspond to the two ketone carbons. Chemical shifts at 74.2 and 70.8 ppm are assigned to the quaternary carbons bearing the epoxide oxygen.

Isolation of 2a and 2b: The mother liquor from the first precipitation of **3** described above was preparatively chromatographed under reverse-phase conditions. The fraction corresponding to purified **2** (**a** plus **b**) was concentrated to aqueous and extracted with chloroform. Separation of the individual (-) and (+) isomers (**2a** and **2b**, respectively) required lactonization of the mixture with HCl at 60°C, normal-phase chromatography to separate the resulting lactones and base hydrolysis of the individual isomers at 65°C with 1.0 M sodium hydroxide. The FAB mass spectrum of **2a** (Na^+ salt) has molecular ions at m/z 597 (M+1) and at m/z 619 $(M+Na)^+$. The FAB mass spectrum of **2b** is identical to that of **2a**. A signal at 177.2 ppm in the ^{13}C-NMR spectrum of **2a** in d-DMSO corresponds to the newly-formed lactam carbonyl. In a two-dimensional ^{13}C-^{13}C INADEQUATE[15] experiment, a quaternary carbon signal at 68.5 ppm demonstrates connectivity to the lactam carbonyl, the benzamide carbonyl, the methine carbon in the isopropyl moiety and an unsaturated alicyclic carbon bearing a phenyl group.

Isolation of 4a and 4b: The reverse-phase column described in the isolation of **2a** and **2b** also separated the individual (-) and (+) isomers **4a** and **4b**. Each isomer was lactonized with HCl at 60°C and further purified by preparative normal phase chromatography. Base hydrolysis of the individual isomers with 1.0 M sodium hydroxide at 65°C formed the sodium salts of **4a** and **4b**. The FAB mass spectra of both **4a** and **4b** (Na^+ salts) have molecular ion peaks at m/z 595 (M+1) and m/z 617 $(M+Na)^+$. ^{1}H and ^{13}C-NMR spectra are consistent with the assigned phenanthrene structure.

RESULTS AND DISCUSSION

In 1960, Wasserman and Liberles reported a 4,4-disubstituted lactam product from the irradiation of 2,3,4,5-tetraphenylpyrrole with a 150-watt flood light in the presence of methylene blue.[2] The same article reports the formation of a tetraphenyl diketoepoxy photooxidation product of the starting pyrrole. Rio, et al.[16] have suggested that these products arise through a hydroperoxide intermediate, which in turn is derived from an endoperoxide formed at the 2,5 position in the pyrrole ring. Scheme 2 shows a possible mechanism in the oxidative rearrangements leading to **2** (**a**,**b**) and **3**. Intermediate **5**, an endoperoxide formed at the 2,5 position in **1**, further reacts to the peroxy bridged dimer **8**, which is derived from **6** and **7** in equilibrium. From **8**, **2** (**a**,**b**) and **9** are formed, and **9** continues on to the diketoepoxide **3** in the presence of H_2O. Photocyclization of **2a** and **2b** in the presence of ultraviolet radiation produces **4a** and **4b**, respectively.



Scheme 2. Photodecomposition of **1**

Upon exposure to ultraviolet light for 3 hours at 254 nm, **1** is photodegraded to lactams **2a** and **2b** and further to phenanthrenes **4a** and **4b** at a relatively slow rate when compared to exposure to 365 nm (Table 1). The reaction rate is not affected by the presence of methylene blue at 254 nm. Complete photodecomposition of **1** to by-products **2** (**a**, **b**), **3**, and **4** (**a**, **b**) occurs rapidly at 365 nm regardless of the presence of methylene blue. Only under visible light are the energy transfer properties of methylene blue required for the rapid photooxidation of **1**. The starting material is completely converted under the visible tungsten spotlight in the presence of methylene blue; in stark contrast, no reaction occurs under visible light in the absence of photosensitizer. The photodecomposition of **1** under simulated sunlight proceeds rapidly in solution without a sensitizer added. There is, however, increasing amounts of phenanthrenes **4** (**a** and **b**) generated from **2** (**a** and **b**). These products are capable of acting as sensitizers allowing energy transfer in order to form triplet oxygen at lower wavelengths (e.g., 254 and 365 nm). The "low visible" wavelengths in the 365 nm range of the broad-spectrum simulated sunlight are most responsible for the rapid photooxidation which converts **1** to **2a** and **2b**.

The analysis of the stability of pharmaceuticals such as **1** require simulated sunlight sources which, unlike most flood lamps, do not filter out ultraviolet light. In the photodecomposition of **1** in solution, the presence of oxygen, low wavelength visible light and phenanthrenes **4a** and **4b** acting as sensitizers are necessary for the formation of lactams **2a** and **2b**. Also, the formation of lactams **2** (**a** and **b**) and the presence of ultraviolet light are necessary preconditions for the photocyclization reaction leading to **4** (**a** and **b**). The apparent interdependence of **2** and **4** in the accelerated photodecomposition of **1** suggests that the presence of a trace amount of either product in the starting solution is necessary for the process to begin.

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