Isolation and Structure Elucidation of the Major Photodegradation Products of Pirmenol Hydrochloride

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Abstract \Box Column chromatography, thin-layer chromatography, highperformance liquid chromatography, nuclear magnetic resonance spectrometry, and high-resolution mass spectrometry were employed to separate and identify the photodegradation products of pirmenol hydrochloride [(±)-*cis*- α -[3-(2,6-dimethyl-1-piperidinyl)propyl]- α -phenyl-2-pyridinemethanol monohydrochloride monohydrate], a new antiarrhythmic drug. A methanol solution of pirmenol was irradiated using a low-pressure mercury lamp. The solution afforded four major degradation products, three of which were identified as 3-(*cis*-2,6-dimethylpiperidinyl)propyl 2-(2pyridyl)phenyl ketone, 2-(2-pyridyl)benzoic acid, and methyl 2-(2-pyridyl)benzoate. The degradation followed apparent-first-order reaction kinetics. In addition, the possible photodegradation pathways are discussed with reference to reaction mechanisms.

Pirmenol (1), whose structure shown in Scheme 1, is a new antiarrhythmic drug¹ synthesized at Parke-Davis Research Division, Warner-Lambert Co. Its tertiary carbon atom having a hydroxyl group and two geminal aromatic rings has allowed us the possibility of studying intramolecular photoreactions. However, contrary to our expection, it has exhibited good stability under the practical irradiation conditions by chemical and fluorescent light. Therefore an intense irradiation from a low-pressure mercury lamp was applied to cause substantial photodegradation.

In this report, we present the results of our study of the photodegradation of pirmenol (1) in methanol. The isolation and structure elucidation of major degradation products and the degradation kinetics are described. Characterization of the products by IR, NMR, and mass (MS) spectroscopy revealed structures containing a (2-pyridylphenyl)carbonyl moiety. The formation of these compounds indicates some fascinating chemistry, involving intramolecular photo-cycloaddition or -sigmatropic rearrangement in pirmenol (1).

Experimental Section

Pirmenol (1), provided by Warner-Lambert Co., Ann Arbor, MI, was allowed to degrade in 2-5 mg/mL concentrations in methanol (0.07% water) using a quartz immersion photoreactor with a 10-W low-pressure mercury lamp (main wavelength, 254 nm). The photodegradation process was followed with HPLC.

Analysis—Monitoring by HPLC was achieved on a Varian chromatographic system consisting of a model Vista 5000 pump, a model Vista UV-100 detector (254 nm), and a model Vista 401 data station. The reversed-phase HPLC column of YMC-PAK AM-312 ODS (6 \times 150 mm) (YMC, Kyoto, Japan) was used at 45 °C. A mixture of 50 mM ammonium phosphate buffer (pH 7.2), acetonitrile and acetic acid was used as the mobile phase according to the following programmed time-flow rate-mobile phase mixture ratio: 0-10 min, 1.0 mL/min, 88:10:2 (v/v) mixture; 10-15 min, 1.0 mL/min, 80.5:17.5:2 (v/v) mixture; 15-27 min, 1.0 mL/min, 73:25:2 (v/v) mixture; 27-40 min,

Table	1—Mass	Spectral	Assignment	of Major	Fragment	lons of
Photo	product 2	2	-		-	



1.2 mL/min, 58:40:2 (v/v) mixture. ¹H- and ¹³C-NMR spectra were recorded on a JEOL (Tokyo, Japan) JNM-GX400 spectrometer using tetramethylsilane as internal reference and deuteriated chloroform as solvent. Mass spectra were recorded on a Hitachi (Tokyo, Japan) M80B high-resolution, double focusing, magnetic sector mass spectrometer. IR spectra were recorded on a Perkin-Elmer 684.

Isolation—Photoproduct 2 was first isolated in a 10% yield from the reaction solution irradiated for 16 h by preparative TLC with a hexane—ethyl acetate—triethylamine (5:5:1 v/v) mixture as developing solvent, and the crude 2 was further purified by silica gel column chromatography using the same solvent mixture. The reaction solution when eluted with a different solvent mixture ratio (1000: 100:1 v/v) yielded 14% photoproduct 4 as white crystals upon evaporation of solvents. Photoproduct 3 was isolated in the separate run as an oil (yield, 20%) by preparative TLC with a chloroform methanol—strong ammoniac water (60:35:1 v/v) development solvent. However, the photoproduct marked as peak X in Figure 1 could not be isolated.

Results and Discussion

Degradation Profile—An example HPLC is shown in Figure 1, and the time-course of the photolysis of 1 is shown in Figure 2. According to the progress of reaction, the concentration of photoproduct 2 first increases, then reaches

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Figure 1—HPLC monitoring of pirmenol (1) undergoing photodegradation in methanol. Key: (A) 0.5 h; (B) 18 h; (C) 160 h. The peaks labeled 1, 2, 3, and 4 refer to structures in Scheme 1.



Figure 2—Time course of pirmenol (1) undergoing photodegradation in methanol. Key: 1 (\odot), 2 (\bigcirc), 3 (\Box), 4 (\triangle).

a maximum, and then decreases. After a time lag of about 2 or 3 h, the concentration of photoproducts 3 and 4 increases with time. Thus, it was presumed that 1 must go through intermediate photoproduct 2 before photoproducts 3 and 4could be produced. This was evidenced by the photodegradation of 2 shown in Figure 3, where the photolysis of 2yielded 3 and 4. However, in a separate experiment, the interconversion between 3 and 4 was not observed under the same photolysis conditions. Thus, the formation of photoproduct 3 can be attributed to the reaction of 2 with the trace of water in methanol.

Degradation Rate—The degradation rate of 1 was monitored by HPLC and the plot of time—logarithm (natural) of the residual ratio of 1 is shown in Figure 4. The linear regression afforded a slope parameter of -0.03521 and an intercept parameter of 0.00265 with a relative coefficient of correlation 0.9979. This result predicts apparent-first-order kinetics with a rate constant of 3.5×10^{-2} h⁻¹.

Structure Elucidation—The high-resolution MS of photoproduct **2** established a molecular formula of $C_{22}H_{28}N_2O$ (found for M⁺, 336.2228, calcd, m/z 336.2256), which is formed when two hydrogen atoms are removed from **1**. The electron impact MS yielded the molecular ion peak at m/z 336, and three other distinct fragments as shown in Table **1**. IR absorption at 1690 cm⁻¹ is consistent with the carbonyl function in **2**. Analysis of the ¹H-NMR spectrum (Table 2) confirmed one-proton-loss from **1** in the aromatic region and identified one distinctive proton at a higher chemical shift





Figure 3—Time course of 2 undergoing photodegradation in methanol. Key: 2 (\bigcirc), 3 (\square), 4 (\triangle).



Figure 4—Plot of the natural logarithm of pirmenol (1) residual ratio as a function of time. The regression line (solid line) was calculated by the least-squares method (dotted lines indicate 95% confidence limits for the regression line).

(8.63 ppm) attributable to the proton at the α -position of the pyridine ring. The number of protons for the methyl, methylene, and methine group is preserved from 1. In a proton decoupling spectrum, the ortho disubstitution pattern on the benzene ring was confirmed. The lack of alcoholic hydrogen originally existed in 1 at 6.1 ppm is also supportive of the



Scheme 1-Proposed pathways for the photodegradation of pirmenol (1).

Table 2—NMR Spectral Assignments of Photoproduct 2

Chemical Shift (ppm)		
Site	¹³ C-NMR	¹ H-NMR
1	149.2 (d)	8.63 (1H, br d, $J_2 = 4.2$ Hz, $J_3 = 1.7$ Hz)
2	122.2 (d)	7.25 (1H, m, $J_1 = 4.9$ Hz, $J_3 = 7.6$ Hz)
3	136.8 (d)	7.78 (1H, ddd, $J_1 = 1.7$ Hz, $J_2 = 7.6$ Hz, $J_4 = 7.8$ Hz)
4	122.2 (d)	7.63 (1H, br d, $J_3 = 7.8$ Hz)
5	157.2 (s)	
6	141.8 (s)	
7	128.6 (d)	
8	127.3 (d)	7.46–7.43 (3H, m)
9	129.9 (d)	
10	128.8 (d)	7.48 (1H, d, $J_9 = 8.1$ Hz)
11	138.2 (s)	
12	206.6 (s)	
13	40.9 (t)	2.40 (2H, t, $J_{14} = 7.3$ Hz)
14	17.0 (t)	1.74 (2H, m)
15	48.9 (t)	2.71 (2H, t, $J_{14} = 8.3$ Hz)
16	55.0 (d)	2.50 (1H, m)
17	35.0 (t)	1.55 (1H, m), 1.32 (1H, m)
18	24.7 (t)	1.65 (1H, m), 1.32 (1H, m)
19	20.9 (q)	1.09 (6H, d)

structure 2. The ¹³C-NMR spectrum (Table 2) confirmed the presence of 19 carbons which, according to chemical shifts, can be broken into the following classes: one sp²-hybridized carbonyl carbon linked to an aromatic ring; eleven sp²-hybridized aromatic carbons; six sp³-hybridized methylene and methine carbons, one sp³-hybridized methyl carbon. Further, from a two-dimensional NMR experiment (not shown) designed to correlate protons with protons, and with carbons, it was possible to assemble these observations to assign the structure 2.

The electron-impact MS of photoproduct **3** showed an intense peak at m/z 199, which corresponded to a molecular ion of $C_{12}H_9NO_2$ composition. The other two major fragment ions at m/z 182 and 154 were attributed to possible two-step degradation of the carboxylic acid function, first the loss of the hydroxyl group followed by the loss of the remaining carbonyl group. Further, from its high-resolution MS showing the 2-phenylpyridine fragment ($C_{11}H_8N$, 154.0693) (found for m/z, 154.0675), a logical structure can then be generated for photoproduct **3**. The structure is also compatible with broad IR absorptions at $3500-2200 \text{ cm}^{-1}$ (not shown) attributable to a carboxylic acid and the ¹³C-NMR spectrum (Table 3) showing a carbonyl carbon at 171.1 ppm.

Firstly, photoproduct 4 could be derived from 3 through methylation with diazomethane. Secondly, its electron-impact MS established a molecular ion of structure 4 at m/z 213 ($C_{13}H_{11}NO_2$ composition). In addition to the IR indicating a

Table 3—NMR Spectral Assignments of Photoproduct 3

	Chemical Shift (ppm)				
Site	¹³ C-NMR	¹ H-NMR			
1	146.8 (d)	8.52 (1H, br d, $J_2 = 2.9$ Hz)			
2	122.9 (d)	7.30 (1H, m)			
3	138.5 (d)	7.83 (1H, t, $J_2 = 7.3$ Hz, $J_4 = 7.3$ Hz)			
4	124.5 (d)	7.61 (1H, d, $J_3 = 7.8$ Hz)			
5	158.1 (s)				
6	137.3 (s)				
7	130.6 (d)				
8	129.2 (d)	7.56–7.44 (3H, m)			
9	131.0 (d)				
10	132.3 (d)	8.02 (1H, d, $J_9 = 7.8$ Hz)			
11	134.0 (s)				
12	171.1 (s)				

Table 4—NMR Spectral Assignments of Photoproduct 4

	Chemical Shift (ppm)				
Site	¹³ C-NMR	¹ H-NMR			
1	149.0 (d)	8.64 (1H, br d, $J_2 = 4.3$ Hz)			
2	122.0 (d)	7.25 (1H, m, $J_3 = 7.3$ Hz)			
3	136.1 (d)	7.75 (1H, ddd, $J_2 = 7.3$ Hz, $J_4 = 7.9$ Hz)			
4	122.6 (d)	7.46 (1H, m, $J_3 = 7.9$ Hz)			
5	158.5 (s)				
6	149.0 (s)				
7	129.7 (d)	7.56–7.55 (1H, m)			
8	129.2 (d)	7.56–7.55 (1H, m)			
9	129.7 (d)	7.46 (1H. m)			
10	128.2 (d)	7.82 (1H, d, $J_9 = 7.9$ Hz)			
11	131.5 (s)				
12	168.2 (s)				
13	51.9 (a)	3.68 (3H. s)			

carboxylate absorption (not shown) at 1740 cm⁻¹, the ¹H- and ¹³C-NMR spectra (Table 4) also indicate the structure shown for photoproduct **4**.

Under the conditions reported here, the pathway which accounts for the photodegradation of 1 is proposed in Scheme 1.

Reaction Mechanism—Two possible mechanisms which explain the formation of 2 from 1 are proposed in Scheme 2. The initial photoreaction probably begins with cross bondings through a $[\pi 2_a + \pi 2_a]$ cycloaddition (route a) involving, respectively, two π -electrons on the benzene and the pyridine ring. The once-formed twisted pentagonal ring (a) opens followed by sequential rearrangements to b.

Another possibility is the [1,3] sigmatropic shift of the 2-pyridyl radical (route b). The enol intermediate **b** from



Scheme 2-Proposed mechanisms for the formation of 2 from pirmenol (1).

either route now loses two hydrogens while rearranging to the more stable keto form 2.

Conclusions

We have established that pirmenol (1) can be degraded in methanol when irradiated intensely with a low-pressure mercury lamp. The time-dependent photodegradation followed apparent first-order reaction kinetics and yielded 2-4and one unidentified product. Photoproduct 2 also acted as an intermediate which further decomposed into **3** and **4**. The interconversions between **3** and **4** were not observed. As the mechanisms operating in the initial step of the photodegradation of **1**, a $[\pi 2_a + \pi 2_a]$ cycloaddition and a [1,3] sigmatropic rearrangement are proposed to account for the formation of **2**.

References and Notes

1. Just, H. Am. J. Cardiol. 1987, 59, 1H-57H.