Polarographic Study of the Photodecomposition of Nimodipine

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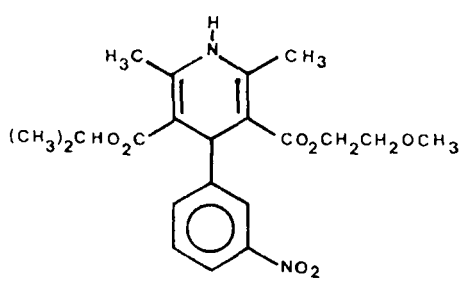
Abstract □ Nimodipine, a calcium antagonist belonging to the dihydropyridine family, produces a well-defined polarographic peak due to the four-electron reduction of the nitro group. This peak was used to track the photodecomposition of nimodipine induced by UV light and daylight. Nimodipine was modified by UV irradiation with degradation following first-order kinetics. A degradation rate constant of 0.099 min^{-1}, with a half-life of 7.78 min, for UV irradiation without a filter was obtained. Furthermore, a quantum yield of 1.32×10^{-3} molecules/quantum absorbed was measured with a chemical actinometer. The UV degradation product, which was isolated and identified, showed that irradiation of nimodipine causes oxidation of the dihydropyridine ring and transmutation of the nitro group in the nitrobenzene moiety.

Nimodipine [isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate] is a calcium-channel blocker used primarily for its cerebral vasodilatory effect. It has also been used for neurological deficits after cerebral ischemia and for migraine.[1] For these conditions, the recommended infusion rate is 1 mg/h for 2 h and then 2 mg/h, with testing to determine that severe changes in blood pressure are not produced with this administration schedule. The starting dose should be reduced to 0.5 mg/h or less for patients weighing <70 kg or with unstable blood pressure.[2]

Exposure of some drugs to light leads to photodecomposition. The drugs undergo important chemical changes, accompanied by changes in their activities or potencies and, generally, loss of therapeutic actions. Calcium antagonists of the dihydropyridine family undergo such photodecomposition processes; some members of this family are extremely light sensitive.[3-10] The chemical changes in the irradiated molecule involve the reduction of the aromatic nitro group to a nitroso group and/or the oxidation of the dihydropyridine ring to a pyridine ring. Both of these changes involve a change in the redox behavior of the molecule; consequently, electrochemical techniques play an important role in following these changes.[11]

Nimodipine belongs to the dihydropyridine family; however, no systematic studies of nimodipine photodecomposition have been reported in the literature. In this paper we report the results of a study of nimodipine photodecomposition after exposure to different light conditions. This study focused on the chemical identification of the photodegradation product, kinetic analysis of the photodegradation reaction, and quantification of the quantum yield of the photochemical process.



Nimodipine

Experimental Section

Chemicals—Nimodipine (99.8% pure drug) was obtained from Laboratorio Tecnofarma, Santiago, Chile. The solutions under study contained 30% (v/v) ethanol and were buffered with 0.02 M acetic acid and 0.02 M phosphoric acid for pHs 2–8.5 and with 0.02 M phosphoric acid and 0.02 M sodium carbonate for pHs 8.5–13. Ionic strength was kept constant at 0.3 M with KCl. All chemicals were analytical reagent grade.

Apparatus—For UV irradiation, a Black Ray lamp (model B 100-A; 125 W, 366 nm) was used. For artificial-daylight irradiation, three 200-W Phillips tungsten lamps were used.

Polarographic equipment, cells, and electrodes were similar to those previously described.[8] Cyclic voltammetric experiments were carried out on a totally automated Inelecsa assembly similar to one previously described.[12]

High-performance liquid chromatographic (HPLC) experiments were carried out on a Shimadzu liquid chromatograph (model LC-6A) equipped with a UV detector (model LC-6A). The chromatograms were analyzed with a chromatographic integrator (Chromatopac, model C-5A).

Spectrophotometric analyses were carried out in a Shimadzu UV–visible spectrophotometer (model UV-160) in standard quartz cells. A Varian Anaspect EM-360 (60-MHz) nuclear magnetic resonance (NMR) spectrometer and a Leitz Wetzlar model 3G spectrophotometer were used to obtain the NMR and IR spectra, respectively. The IR spectra were obtained in 1% potassium bromide pellets, and the NMR spectra were carried out in deuterated chloroform with tetramethylsilane as internal standard.

Methods—*Chromatography*—Thin-layer chromatograms were developed on aluminum plates coated with silica gel 60 F_{254} as the stationary phase and chloroform:ethyl ether (85:15) as the mobile phase.

An octadecylsilane column (Zorbax; 4.6-mm i.d. × 15 cm) and a mobile phase of 0.2 M acetic acid–sodium acetate buffer:1-propanol:ethanol (77:18:5) were used in HPLC experiments. Working conditions were as follows: flux, 1.8 mL/min; pressure, 2 kg-force/cm^2. The samples were monitored at $\lambda = 240$ nm.

Polarography—A thermostated polarographic cell with a dropping mercury electrode, silver–silver chloride (Ag/AgCl) electrode, and a platinum wire counterelectrode were used. Differential-pulse polarograms were recorded from an initial potential of −0.25 V versus the Ag/AgCl electrode at a scan rate of 5 mV/s in the negative direction. The pulse modulation was 50 mV, and the current was varied from 2.5 μA to 500 nA, as required. Drop time was fixed at 1 s. All the solutions were deoxygenated by bubbling with nitrogen before the run. Quantification was by the calibration curve method.

Irradiation Procedure—The samples were irradiated in 6-mm-i.d. Pyrex tubes that were placed in a rotatory system-type merry-go-round with a capacity of eight tubes. The quantum yields were evaluated by using the photofragmentation of valerophenone as the secondary actinometer. The sample solution and the actinometer solution in benzene were matched at an absorbance of 0.96 ($\lambda = 366$ nm) and deaerated with three freeze–vacuum cycles in a high-vacuum system before photolysis.

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Isolation of UV Photodecomposition Product—A 25-mL aliquot of a 4.8×10^{-2} M solution of nimodipine in ethanol was irradiated for 60 h. The irradiated solution was concentrated to 3 mL and chromatographed on silica column with chloroform:ethyl ether (85:15) as eluant. The chromatographically pure UV degradation product had a retardation factor value of 0.5 at the same conditions of stationary and mobile phases. Nimodipine had a retardation factor value of 0.35 under the same conditions. The solutions obtained from the column were concentrated under reduced pressure to give an oily yellow substance that was analyzed by IR and NMR spectroscopy, chromatography, and polarography.

Results and Discussion

Nimodipine produces a well-defined polarographic peak over the entire pH range.[11] This peak is pH dependent, irreversible, and linearly dependent on nimodipine concentration. The peak is due to the four-electron reduction of the nitro group. Because the nitro group is photoactive, nimodipine decomposition can be monitored by polarographic tracking of the nitro group. We also used alternative techniques, such as HPLC and UV spectrophotometry. Three irradiation light modes were used: UV light with a 366-nm filter, UV light without a filter, and artificial daylight.

When nimodipine samples were irradiated with UV light, the differential-pulse polarogram was altered as follows: (1) the peak at −540 mV versus Ag/AgCl electrode (pH 6) due to the nitro group in nimodipine vanished, and a more positive peak at −420 mV versus Ag/AgCl electrode (pH 6) appeared. (2) A new peak at −1375 mV appeared. Figure 1 shows the evolution of the polarographic nitro peak in nimodipine due to UV irradiation, and Figure 2 shows the polarogram when all the nimodipine has been photodegraded. With this polarographic evidence, we can explain qualitatively the molecular consequence of the UV irradiation of nimodipine. Several

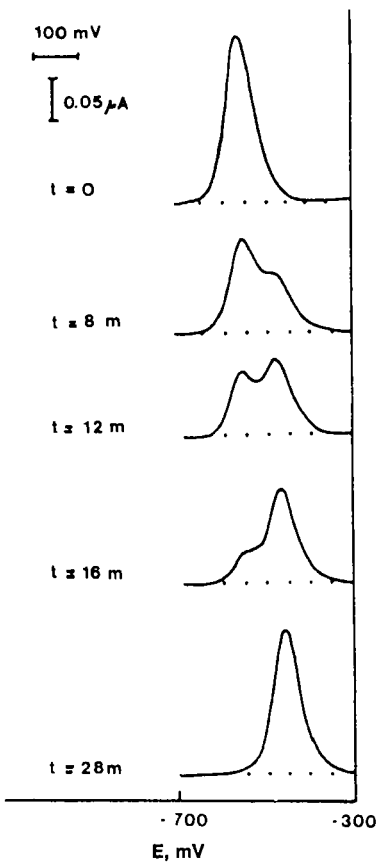


Figure 1—Differential-pulse polarograms of nimodipine solution (pH = 6) at different times after UV irradiation. E, potential.

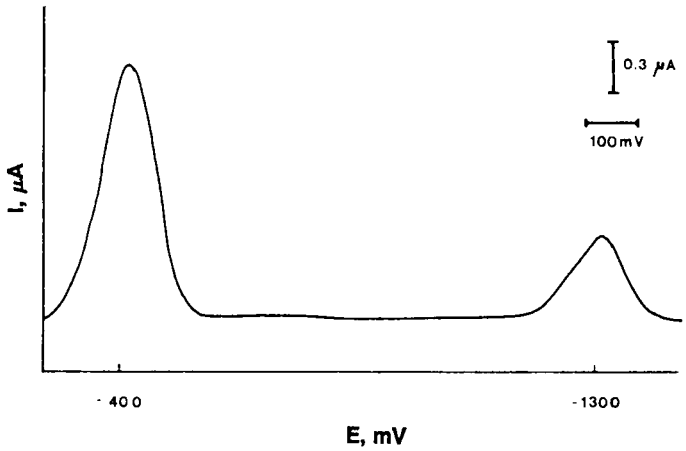


Figure 2—Differential-pulse polarogram of UV photodecomposition product of nimodipine. E, potential; I, current.

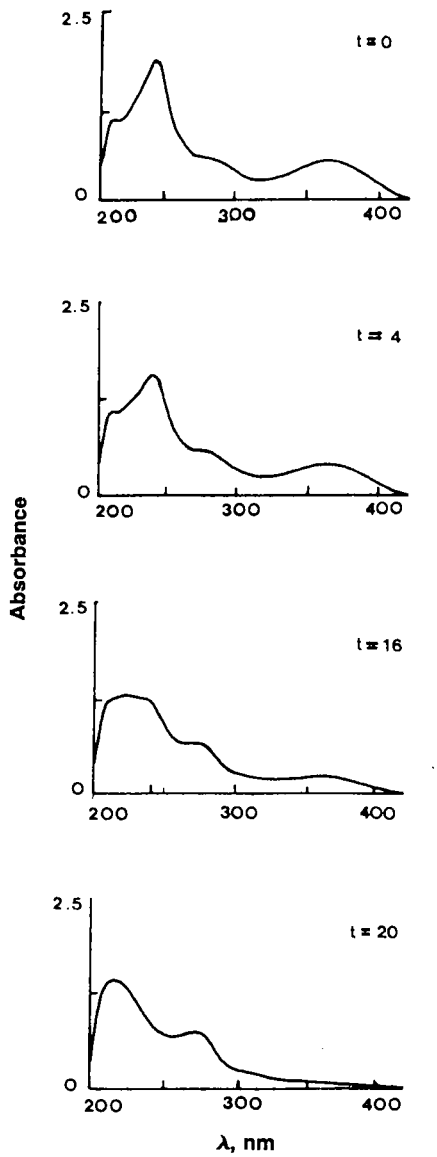


Figure 3—Evolution of nimodipine solution UV spectra with time of UV light irradiation.

previous studies of related molecules[8–10] indicate that the oxidation of the dihydropyridine ring to the pyridine ring is

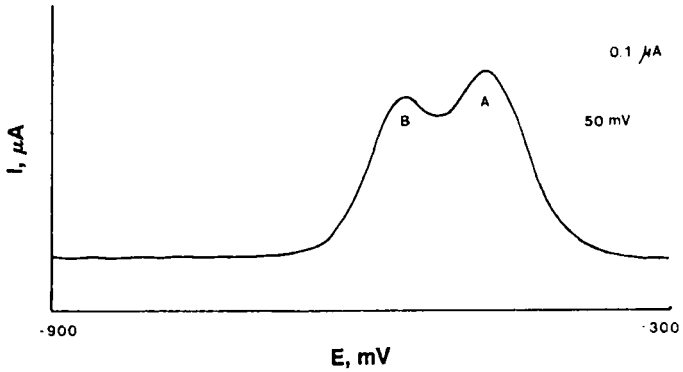


Figure 4—Overlapped peaks for the nitro group in a partially UV-irradiated nimodipine solution: (**A**) UV derivative; (**B**) nimodipine. E, potential; I, current.

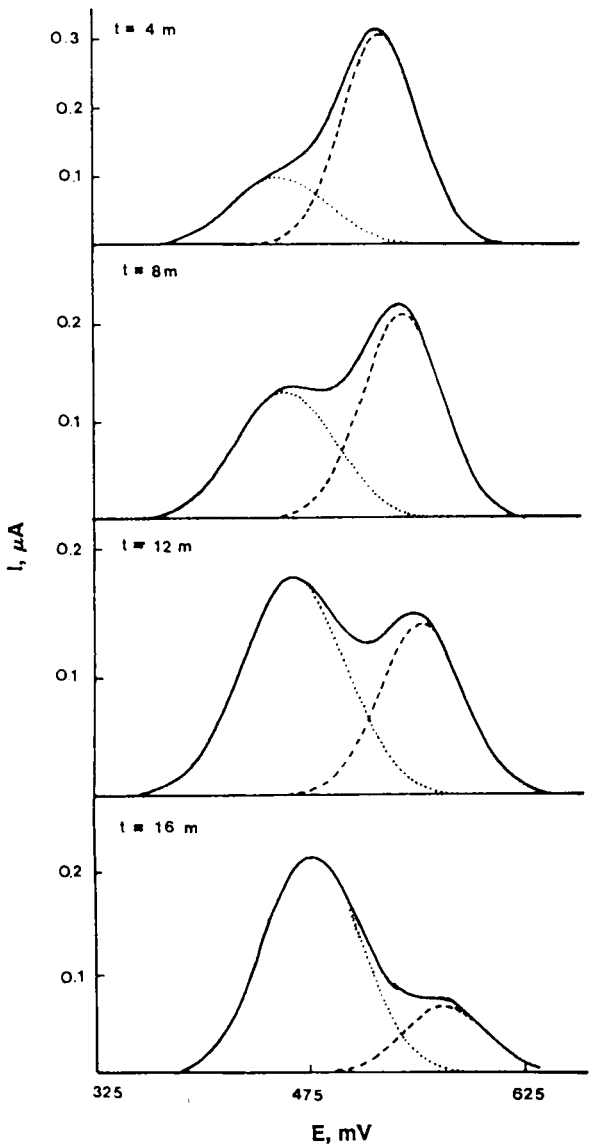


Figure 5—Deconvoluted polarograms at different irradiation times. E, potential; I, current.

the more important fate for the excited dihydropyridine compounds. In nimodipine, a similar behavior is compatible with the experimental findings. The peak at −1375 mV is due to the two-electron reduction of the C=N group in the

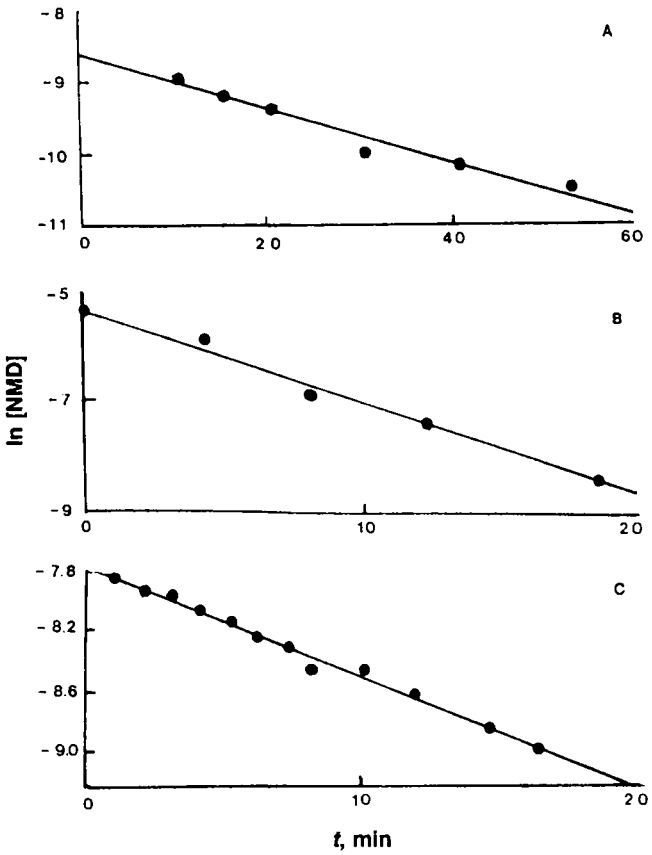


Figure 6—First-order kinetics plots for nimodipine photodegradation with (**A**) UV irradiation without filter, (**B**) UV irradiation with 366-nm filter, and (**C**) artificial daylight irradiation. [NMD], concentration of nimodipine.

pyridine ring. Moreover, the shift of the polarographic peak associated with the aromatic nitro group to more positive potentials (from −540 to −420 mV) can be explained by the coplanarity of the nitro group in the aromatic ring and the pyridine ring in the UV photodecomposition product. This coplanarity permits an extended conjugation and a higher electron delocalization, which decreases the electron density over the nitro group and makes the reduction process easier.[13] Also, the UV degradation process was followed by UV spectrophotometry. In Figure 3, the evolution of the UV spectra of a nimodipine solution with the irradiation time is shown (the absorption band at 357 nm disappears totally, and a new band at 270 nm appears). This shift can be explained by the influence of the different substituents of the nitrobenzene moiety in nimodipine (dihydropyridine ring) on the UV photodecomposition product (pyridine ring).

The photodegradation process was also followed by HPLC with UV detection. The retention times for nimodipine and the UV photodecomposition product are 16.43 ± 0.33 and 12.13 ± 0.40 min, respectively. These retention times are sufficiently different to obtain an independent quantitative determination of both nimodipine and the UV photodecomposition product. The lower retention time for the UV photodecomposition product compared with that for nimodipine is compatible with the more polar character of the photodecomposition product.

To obtain quantitative results, we used both HPLC and polarographic methods. The reproducibility of both methods was checked by using 10 successive 10^{-4} M solutions of nimodipine; the coefficients of variation were 2.4 and 0.8% for HPLC and polarography, respectively. From the polarographic calibration curve, a detection limit of 2.16×10^{-8} M,

Table I—Kinetic Parameters for Degradation of Nimodipine[a] in Methanol

Irradiation Condition	$t_{1/2}$, min	k, min^{-1}[b]
UV with 366-nm filter	27.49	0.037
UV without filter	7.78	0.099
Artificial daylight	613.8	0.0013

[a] Concentration, 4×10^{-4} M. [b] Degradation constant.

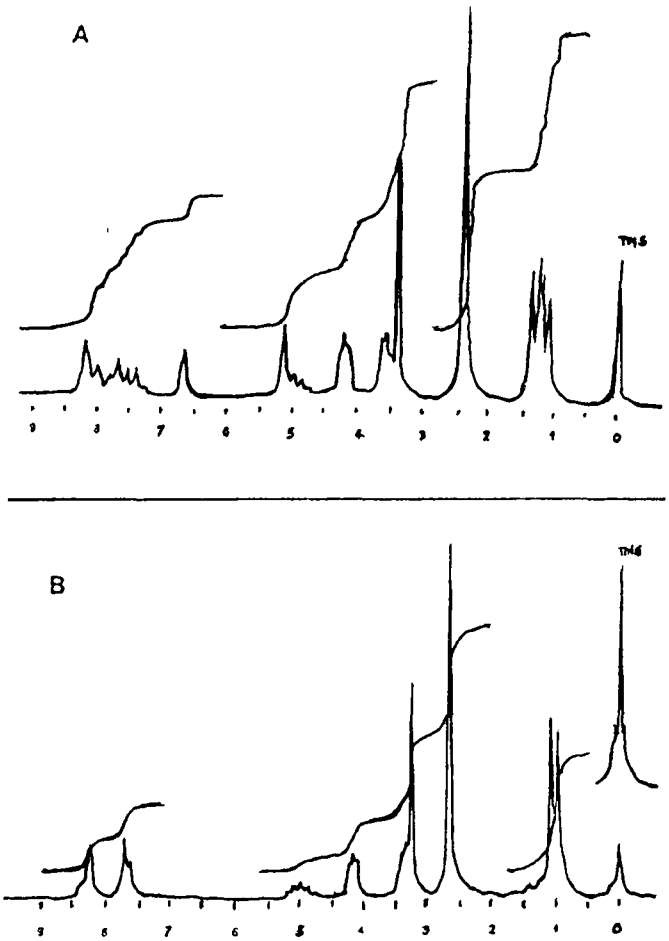
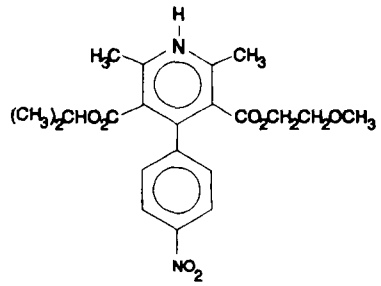


Figure 7—NMR Spectra for (**A**) nimodipine and (**B**) the UV photodecomposition product.



UV Decomposition Product

with a calibration sensitivity of 2054.6 $mA \cdot M^{-1}$, was obtained. However, the limit of quantification of the HPLC assay from 1-mL solutions was 1×10^{-9} M (generally, concentrations of 0.5×10^{-9} M could be detected).

Because the polarographic peaks of the nitro group in both nimodipine and the UV photodecomposition product overlap appreciably (Figure 4), we applied a deconvolution program to obtain more reliable peak current values. In Figure 5, several deconvoluted polarograms, corresponding to different irradiation times, are shown. The results for the kinetic studies at the three irradiation conditions obtained with both HPLC and polarographic techniques match closely. Typical first-order plots are shown in Figure 6. From these results, we calculated the photodegradation constant and the half-life ($t_{1/2}$) for nimodipine solution at three irradiation conditions (Table I). From these results, we conclude that UV photostability of nimodipine is higher when 366-nm UV light is used for irradiation and that the drug is markedly more stable to irradiation with artificial daylight than with UV irradiation. Furthermore, a quantum yield (Φ) of 1.32×10^{-3} molecules/quantum absorbed was measured with a chemical actinometer. This result indicates that the nimodipine photostability is greater than that of nifedipine,[7] a closely related drug.

The UV, NMR, and IR spectral data for the photodecomposition product (Table II) indicate principally the loss of IR absorption bands corresponding to N–H and C=C in nimodipine. The NMR spectra show the loss of two protons in the dihydropyridine ring as a consequence of UV irradiation. Both spectroscopic results indicate oxidation of the dihydropyridine ring in the UV photodecomposition product. The most striking feature of the structure of the photodecomposition product is the position of the nitro group (*para* substitution in the product versus *ortho* substitution in nimodipine). We reached this conclusion after comparing the NMR spectra

Table II—Spectroscopic Data for Nimodipine and the UV Photodecomposition Product

Method and Property Measured	Nimodipine	UV Photodecomposition Product
UV: absorption maximum, nm	218, 238, 357	215, 270
NMR: chemical shift, ppm	1.0–1.5, **6H**, [H–C(CH_3)$_2$–]	0.9–1.2 **6H**, [H–C(CH_3)$_2$–]
	2.5, **6H**, (C–CH_3)	2.6–2.7, **6H**, (C–CH_3)
	3.5–4.0, **3H**, (O–CH_3)	3.2–3.3, **3H**, (O–CH_3)
	3.5–4.0, **2H**, (–COO–CH_2–)	3.2–3.5, **2H**, (–COO–CH_2–)
	4.0–4.5, **2H**, (–CH_2–O–CH_3)	4.1–4.3, **2H**, (–CH_2–O–CH_3)
	4.9–5.4, **1H**, [*H*–C(CH_3)$_2$–]	4.8–5.2, **1H**, [*H*–C(CH_3)$_2$–]
	5.2, **1H**, (C-*H*)	—[a]
	6.8, **1H**, (N-*H*)	—
	7.3–8.4, **4H**, (aromatic *H*)	7.5–8.5, **4H**, (aromatic *H*)
IR: wavenumber, cm^{-1}	3330, (N–H)	—
	1630–1650, (C=C)	—
	1700, (C=O)	1720, (C=O)
	1510, (C–NO_2)	1530, (C–NO_2)
	1020, (O–CH_3)	1060, (O–CH_3)

[a] Not observed.

(Figure 7) of nimodipine and the corresponding UV photodecomposition product. The signals due to the aromatic protons are markedly different. The signal in nimodipine, a multiplet, is replaced in the UV photodecomposition product by a double doublet. These results imply that the UV photodecomposition product has two pairs of equivalent protons, corresponding to *para* substitution by the nitro group in the photodecomposition product (see structure).

We conclude that UV light induces both oxidation of the dihydropyridine ring and transmutation of the nitro group in the original nimodipine molecule. Furthermore, our results and those of previous works related to nitrendipine and nicardipine[9,10] emphasize that bulkier substituents in the dihydropyridine ring produce more stable drugs.

References and Notes

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Acknowledgments

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