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Mechanistic Studies on the Photochemical Degradation of Nifedipine

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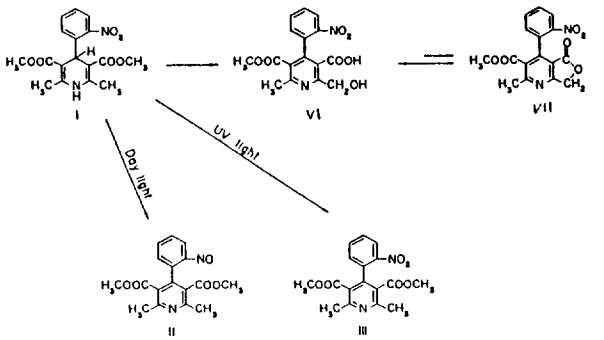
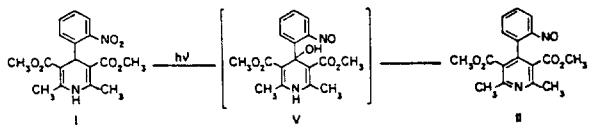
Irradiation of nifedipine in methylene chloride at 366 nm yielded 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrosophenyl)-pyridine with the quantum yield 0.37, while irradiation at 254 nm initially gave nitroso compound which in turn is photooxidized to 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrophenyl)-pyridine with the quantum efficiency of 0.014 on further irradiation in the presence of oxygen. The intramolecular hydrogen abstraction of nifedipine proceeded from the triplet excited state.

Introduction

Nifedipine(I), 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrophenyl)-dihydropyridine, is one of the most used coronary vasodilator of which the activity has been ascribed to calcium antagonism, i.e. the calcium antagonistic inhibition of excitation-contraction coupling in vascular smooth muscle.[1] Nifedipine has also been proven to be effective for the prevention of angina pectoris, particularly the variant form (Brinz-metal's angina), and also in controlling the blood pressure of hypertensive patients.[2] The metabolic studies showed that the metabolites are 4-(2'-nitrophenyl)-2-hydroxymethyl-5-methoxycarbonyl-6-methyl-pyridine-3-carboxylic acid(VI) and the corresponding lactone(VII).[1,3]

Nifedipine is light sensitive. It decomposes under 366 nm UV or visible light to give 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrosophenyl)-pyridine(II) through internal oxidation-reduction rearrangement and an oxidation product, 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrophenyl)-pyridine (III).[4,5] Product II is most likely formed via loss of water from the intermediate V. The 4-(4'-nitrophenyl)- and 4-(3'-nitrophenyl)-1,4-dihydropyridine derivatives are stable even under intense irradiation with sunlight or mercury arc lamp indicating that the chemical changes occur through an intramolecular reaction.[5,6]





The formation of V may be similar to the well-known photorearrangement of o-nitrobenzaldehyde to o-nitrosobenzoic acid.[7,8] Irradiation of nifedipine at 254 nm has been known to produce the direct dehydrogenation product.[4] However, the mechanistic details of the photoreaction of nifedipine are not firmly established even though comprehensive studies of photochemical degradation of nifedipine have been reported. Since stability of the nifedipine as a drug is at risk due to the photochemical processes, mechanistic understanding of the process is of great importance.

Results and Discussion

When solutions of nifedipine in methylene chloride and

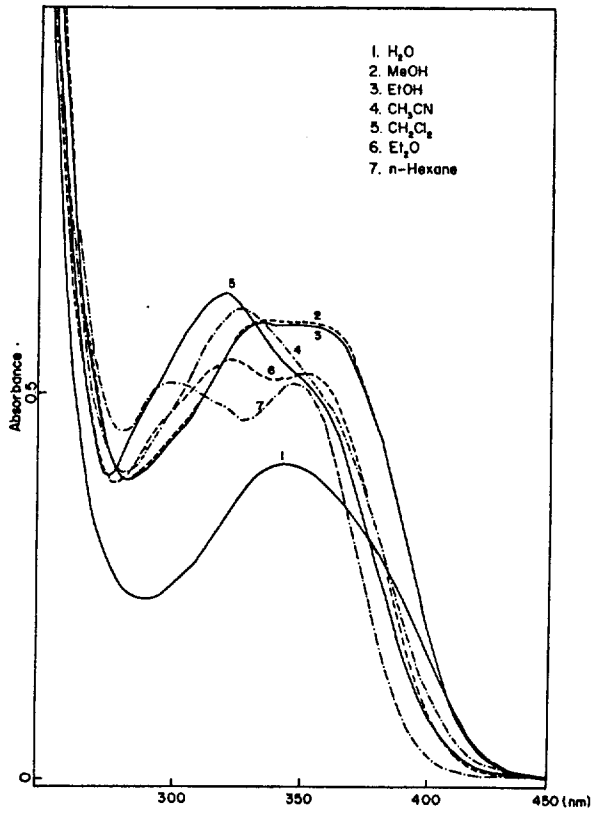


Figure 1. Solvent Effect on UV Spectra of Nifedipine.

ethyl ether were exposed to 366 nm or 254 nm UV light, blue or yellow substances were obtained, respectively. The products were isolated by column chromatography and recrystallized from n-hexane.

Nifedipine is not fluorescent as nitroaromatics generally show very weak or no fluorescence.[10] Nitroso compound (II) which was first formed by irradiation at 254 nm shows fluorescence with a maxima at 445 nm in acetonitrile and at 425 nm in isopropyl alcohol, methylene chloride, and carbon tetrachloride indicating that the excited singlet state of nitroso compound (II) is stabilized by polar solvents. The UV spectrum of nifedipine shows a strong absorption band around 240 nm and a weak broad band around 350 nm. The spectra are dependent on the polarity of solvents as shown in Figure 1. The broad band with λ_{max} around 350 nm separates into two red or blue shifted bands as polarity of solvents decreases from water to n-hexane. These bands are most probably due to the mixture of π,π^* and n,π^* transitions. The quantum yield of photochemical degradation of nifedipine at 366 nm is relatively high (about 0.37). When the reaction is sensitized with xanthone (Table 1), higher quantum yield was obtained suggesting that the photoreaction at 366 nm proceeds from the triplet excited state. However, good triplet quenchers like azulene and oxygen did not affect the photoreaction at all. It is not surprising because the intramolecular hydrogen abstraction in the triplet state would be much faster than the intermolecular quenching which requires bimolecular collision. Generally, in aliphatic amines such as diethylamine or triethylamine, the intramolecular hydrogen abstraction is quenched almost completely.[10] It is probably due to formation of charge transfer complex with amines. The quantum yield of photodegradation of nifedipine

Table 1. Xanthone Sensitized Quantum Yield at 366 nm

conc. of xanthone	A/A° [a]	sens[b]
0.000	1.00	0.000
0.005	0.78	0.029
0.010	0.64	0.048
0.030	0.37	0.082
0.050	0.26	0.096

[a]Fraction of photons absorbed by nifedipine in this condition. [b]Quantum Yield by absorption of sensitizer.

Table 2. Quenching Effect on Intramolecular Hydrogen Abstraction by Diethylamine and triethylamine

conc. of amine ($\times 10^4$M)	Φ°/Φ_d[a]	Φ°/Φ_t[b]
0	1.00	1.00
5	1.89	1.63
10	1.95	1.86
30	2.31	2.29
50	2.57	2.17

[a]Quantum yield in the presence of diethylamine. [b]Quantum yield in the presence of triethylamine.

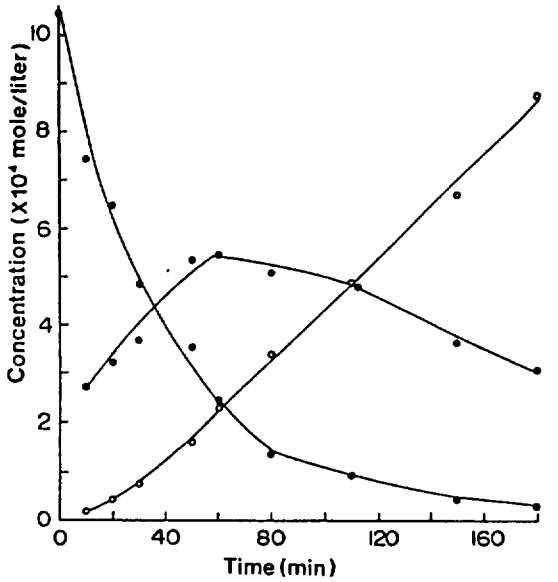


Figure 2. Photoreaction of Nifedipine at 254 nm with irradiation time: ○, Nifedipine; △, Nitroso compound (II); ●, Nitro compound (III).

at 366 nm decreased as the concentration of amines increased as shown in Table 2.

Solution of nifedipine in ethyl ether was irradiated at 254 nm for varying periods of time (Figure 2) to find that the photoreaction at 254 nm proceeds in two steps. The intermediate was isolated and characterized to be the same compound as obtained from the photoreaction at 366 nm. This compound is further photooxidized to give 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrophenyl)-pyridine(III) in the presence of oxygen and photosplitted to give 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl pyridine(IV) as a minor product. These compounds were confirmed by NMR, IR, and mass spectral data.

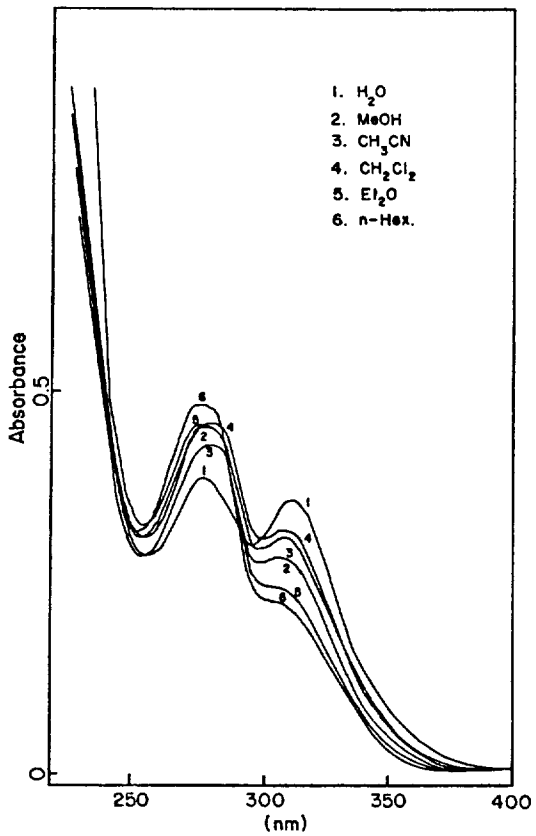


Figure 3. Solvent Effect on UV spectra of Nitroso compound (II).

Table 3. Solvent Effect on Quantum Yield at 254 nm

Solvent	$\Phi \times 10^4$	Polarity Index
MeOH	0.5	6.6
CH_3CN	6.5	6.2
EtOH	13.7	5.2
i-PrOH	24.0	4.3
THF	134	4.2
CH_2Cl_2	137	3.4
Et_2O	189	2.9
CCl_4	228	1.7
n-Hexane	94.7	0.0

The absorption band of nifedipine at 350 nm disappeared and the new absorption band appeared at 310 nm in the UV spectrum of nitroso compound(II) as shown in Fig. 3. The 310 nm band shows red-shift and increase in intensity with increase in polarity of the solvents. It has been ascribed to charge transfer from benzene to the nitroso group.[11]

The quantum yields at 254 nm irradiation of nitroso compound(II) sharply increase with the decrease in polarity of the solvents as shown in Table 4. It is probably due to the strong charge transfer character in the excited state of nitroso compound(II).

When the photooxidation of nitroso compound(II) at 254 nm is sensitized with xanthone, higher quantum yield was obtained suggesting that the reaction proceeds from the triplet excited state. But it is difficult to calculate quantitatively due to the strong quenching effect for sensitizer by oxygen.

The irradiation of nitroso compound(II) at 366 nm in the presence of oxygen and xanthone as sensitizer yielded 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrophenyl)-pyridine(III). The conversion of nitroso compound(II) at 366 nm without sensitizer is not effective because of lack of light absorption above 330 nm.

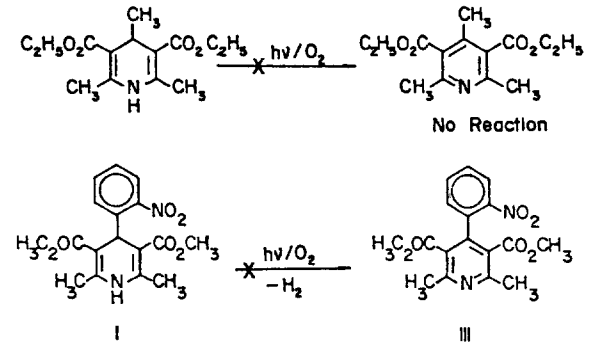


Figure 4. Photoreaction of 2,4,6-trimethyl-3,5-dicarboethoxy pyridine.

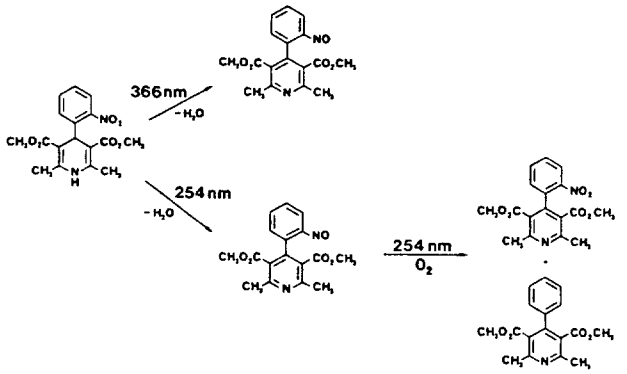


Figure 5. The Scheme of Photoreaction of Nifedipine.

When 2,4,6-trimethyl-3,5-dicarboethoxypyridine is irradiated with 366 nm or 254 nm light, no chemical reaction was observed indicating that direct dehydrogenation of nifedipine at 254 nm does not occur (Figure 4). The results show that irradiation of nifedipine at 254 nm initially gives nitroso compound which is further photooxidized to nitro compound in the presence of oxygen as shown in Figure 5.

Conclusions

Nifedipine decomposes at 254 nm as well as at 366 nm or visible light to give 2,6-dimethyl-3,5-dicarbomethoxy-4-(2'-nitrosophenyl) pyridine(II). At 254 nm, however, nitroso compound(II) is further photooxidized to give nitro compound(III) in the presence of oxygen. The photooxidation quantum yields of nitroso compound strongly increase with decrease in polarity of the solvents probably due to the charge transfer character in the excited state of nitroso compound.

Experimental Section

Materials. Nifedipine was obtained from Sigma Chemical Company and used without further purification. 2,6-Dimethyl pyridine (Aldrich Chem. Co.) was used for internal standard of quantitative analyses of 254 nm photoreaction. Kiesel Gel GF_{254} (Merck) and Kiesel Gel 60 (70-230 mesh)

(Merck) were used for silica gel thin layer chromatography and column chromatography, respectively. n-Hexane (Tedia Chem. Inc.) and ethyl ether (Merck) were used for high performance liquid chromatography. Azulene (Aldrich) was purified by vacuum sublimation. Diethylamine and triethylamine (Aldrich) were used for quenching experiments. Xanthone (Aldrich) were recrystallized from cyclohexane.

Spectroscopic measurements. Ultraviolet-visible spectra were recorded on a Cary 17 spectrophotometer. Infrared spectra were measured on a Perkin Elmer 267 spectrophotometer using potassium bromide pellet. ^{1}H-NMR spectra were obtained on a Varian FT-80A NMR spectrometer at 79.542 MHz or a Varian T-60A NMR spectrometer in chloroform-d. Mass spectra were obtained on a Hewlet Packard 5985A GC/MS system using electron impact (EI) method. Florescence and phosporescence spectra were recorded on an Aminco Bowman spectroflurometer with Aminco-XY recorder. High performance liquid chromatogram was obtained on a Waters Associates Model 244 equipped with Model 600A solvent delivery system and Model 440 absorbance detector (254 nm).

Quantum yield measurements. Samples for quantum yield determination at 366 nm were degassed and sealed in Pyrex ampoules. Usually, 3 m*l* of sample solution (5×10^{-4} M) in methylene chloride was pippeted into the ampoules, degassed through three to five cycles of freeze-pump-thaw method with cooling in liquid nitrogen and sealed. The sealed samples were irradiated with Hanovia 450 W medium pressure mercury arc lamp (Type 697A36) in a merry-go-round apparatus. Mercury emission line of 366.0 was isolated by Corning glass filters # 0-52 and # 7-37.

Diethylether Sample solutions were oxygenated for 3 mins by bubbling oxygen gas and were irradiated with low pressure mercury arc lamp TNN 15/32. Ferrioxalate actinometry was used to monitor the intensity of the exciting light. Quantitative analyses were carried out by HPLC techniques under following conditions. Nitroso compound(II): internal standard; 2,6-dimethylpyridine, column; Zorbox SIL(4 mm × 15 cm), eluent; n-hexane:ethyl ether = 2:1 v/v, flow rate; 2.0 m*l*/min, detector; UV 254 nm, Nitro compound: 2,6-dimethylpyridine or 4-dimethylamino benzaldehyde, column; Zorbox SIL(4 mm × 15 cm) or μ-Bondapak C-18 (3.9 mm × 30 cm), eluent; water-methanol-tetrahydrofuran(300:300:1, v/v) flow rate; 2.0 m*l*/min or 1.2 m*l*/min, detector; UV 254 nm.

Preparation of 2,6-dimethyl-3,5-dicarbomethoxy-4-(2′-nitrosophenyl)-pyridine(II). Solutions of nifedipine (1×10^{-2} M) in methylene chloride or ethyl acetate were exposed to RUL-3500A lamps in a Rayonet preparative reactor RPR 208 for one hour. The product was monitored by TLC (cyclohexane:ethylacetate = 2:3 as eluent, Rf = 0.42) and separated by column chromatography(n-hexane:acetone = 3:1 as eluent) and purified by recrystallization from n-haxane (total yield of 60 %). ^{1}H-NMR($CDCl_3$); 2.6(s, $-CH_3$), 3.4(s, $-CH_3$), 6.5-7.6(m, phenyl H), Mass; M^+ 328, M^+-CO_2CH_3 269, IR(KBr); 1730 cm^{-1}(CO), 1550(NO), UV; 280, 310 nm.

Preparation of 2,6-dimethyl-3,5-dicarbomethoxy-4-(2′-nitrophenyl)-pyridine(III). Solutions of nifedipine(5×10^{-3} M) in ether was oxygenated by bubbling oxygen for 30 min and irradiated with RUL-2537A lamps in a Rayonet reactor RPR 100 for 4 hr. The product was monitored by TLC (n-hex ne:acetone = 3:1 Rf = 0.38) and separated by prep-TLC (n-hexane:acetone = 2:1) and extracted with ether and purified by column chromatography (eluent; n-hexane:acetone = 3:1). The solvents were evaporated to give pale yellow substance. NMR($CDCl_3$); 2.5(s, CH_3), 3.4(s, OCH_3), 7.1-8.1(m, phenyl H), IR(KBr); 1680(CO), 1350(NO_2), 1530 (NO_2), Mass; M^+ 344, M^+-OCH_3 313, M^+-NO_2 298.

Oxidation of nifedipine. To a solution of nifedipine (1.03×10^{-3} M) in ethanol was added sodium nitrate (10 m*l*, 10 mmol) and 10% hydrochloric acid (3.5 m*l*) over 5 hr while maintaining vigorous mechanical stirring at 35 °C. The dilute aqueous solution of sodium hydroxide was added to the solution until pH 7 was obtained. The product was extracted from ethyl ether. NMR($CDCl_3$); 2.5(s, CH_3), 3.4(s, OCH_3), 7.1-8.1(m, phenyl H), IR(KBr); 1680(CO), 1350(NO_2), 1530 (NO_2), Mass; M^+ 344, M^+-OCH_3 313, M^+-NO_2 298.

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References

1. Piergiorgio Pietta, Angelo Rava, and Pierantonio Biondi, *J. Chromatogr.*, **210,** 516 (1981).
2. J. Prous, P. Blancafort, J. Castaner, M. N. Serradell and N. Mealy, *Drugs of the Future,* **4,** 7 (1981).
3. H. Medenwald, K. Schlossmann and C. Wunsche, *Arzenium-Forsch.*, **22,** 242 (1972).
4. R. Testa, E. Dolfini, C. Reschiotto, C. Secchi and P. A. Biondi, *Il Farmaco, Ed. Prat.*, **34,** 463 (1979).
5. J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77,** 447 (1955).
6. A. P. Pillips, *J. Am. Chem. Soc.*, **73,** 2248 (1951).
7. G. Ciamician and P. Silber, *Ber.*, **34,** 2040 (1901).
8. H. A. Morrison, The Chemistry of the Nitro and Nitroso Groups, part 1, 185 (1969).
9. K. Gorlitzer and D. Buβ, *Arch. Pharm.*, **314,** 938 (1981).
10. D. Döpp, Topics in Current Chemistry, **55,** 51 (1975).
11. C. N. R. Rao and K. R. Bhaskar, The Chemistry of Nitro and Nitroso Groups, Part 1, 148 (1969).
12. K. Gorlitzer and D. Buβ, *Arch. Pharm.*, **314,** 938 (1981).