Photochemistry and Photobiology, 2006, 82: 225–230

Photochemistry of 4-(2-Nitrophenyl)-1,4-Dihydropyridines. Evidence for Electron Transfer and Formation of an Intermediate†

Elisa Fasani*, Daniele Dondi, Andrea Ricci and Angelo Albini

Department of Organic Chemistry, University of Pavia, Italy

Received 01 June 2005; accepted 18 July 2005; published online 22 July 2005 DOI: 10.1562/2005-06-01-RA-561

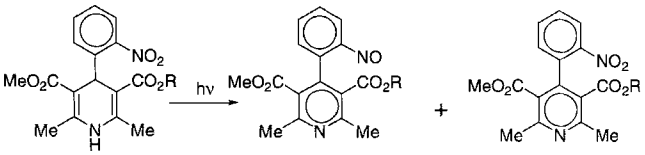
ABSTRACT

New evidence about the path followed in the photochemical reaction of 4-(2-nitrophenyl)-1,4-dihydropyridines such as the drugs nifedipine (Compound 1) and nisoldipine (Compound 2) to give the corresponding nitrosophenylpyridines has been found through determination of the steady-state photochemical parameters and a comparison of the photoreactions in solution and in matrix at 90 K. Additional support is given by comparison with the isomeric 4-(3-nitrophenyl)dihydropyridine as well as with simpler derivatives, such as the corresponding 4-methyldihydropyridine. In Compounds 1 and 2, the lowest lying singlet, localized on the dihydropyridine chromophore, is deactivated by (largely exothermic) electron transfer to the nitrobenzene moiety, as evidenced by the complete quenching of the blue fluorescence observed in analogues not containing the electron-accepting group. Intramolecular proton transfer ensues in the 2-nitrophenyl derivatives with a relatively medium-independent quantum yield of ~0.3 and leads to an aromatic zwitterion, which is detected in matrix at 90 K (photoionization of this intermediate takes place in 2-methyltetrahydrofuran secondary). The intermediate is smoothly converted into the end product upon melting the glass. The 3-nitrophenyl analog, for which such a path is not available, is less reactive by about three orders of magnitude at 366 nm, although the quantum yield arrives at ~0.01 by irradiation at 254 nm in MeOH, reasonably via the nitrophenyl localized triplet.

INTRODUCTION

Interest in the photochemistry of drugs is particularly justified when they absorb ambient light and undergo an efficient reaction, because light-induced degradation may make a serious contribution to the lability of a drug (1,2). This results in a limited shelf life, or at least in the requirement that the drug be given suitable protection during its preparation, and further makes it advisable that patients be advised that the drugs require such precautions. A paradigmatic case is that of calcium-antagonist dihydropyridines, and in particular of nifedipine, 4-(2-nitrophenyl)-1,4-dihydropyridine (Compound 1). This molecule has been largely used for several decades due to its activity as a vasodilator in heart disease and hypertension. (3,4) The conspicuous photolability of this yellow drug, both in solution and in solid state, was reported early (5) and has been repeatedly investigated (6–11).

There is no doubt about the nature of the primary photoprocess, which leads to 4-(2-nitrosophenyl)pyridine (Compound 3). This is expected because this is but one example of the large family of highly photoreactive 2-alkyl nitrobenzenes, which have long been known to undergo reduction of the nitro group and oxidation at the benzylic position (12,13). Minor products that have been detected (*e.g.* the corresponding nitro and azoxy derivatives) clearly result from further thermal reactions of Compound 3 (14,15) (Scheme 1).



1 R=CH_3
2 R=$CH_2CH(CH_3)_2$

3 R=CH_3
5 R=$CH_2CH(CH_3)_2$

4 R=CH_3

Scheme 1.

However, while many technologically important aspects (*e.g.* degradation kinetics under applicative conditions or formation of minor products in drug preparation) have been reported (16–18), basic photochemical data such as the quantum yield and its dependence on conditions and structure have not been determined (there is a single report on the quantum yield of Compound 1) (7). Likewise, mechanistic investigations have been limited to some aspects, in particular to electron paramagnetic resonance (EPR) (19,20), and no comprehensive effort has been carried out.

Therefore, we decided to explore in some detail the photoreaction in solution of Compound 1 and of one of its analogues, the methyl isobutyl ester (Compound 2), used as a drug under the name of nisoldipine (21–24).

For the sake of comparison, some photochemical properties of analogues either lacking the nitrophenyl moiety or bearing the nitro group in a different position have also been studied.

MATERIALS AND METHODS

General. Samples of dihydropyridines 1 and 2 were kindly supplied by Lusochimica, Milan, Italy. Compound 6 was of commercial origin (Aldrich,

* To whom correspondence should be addressed: Department of Organic Chemistry, University of Pavia, Via Taramelli 10, 27100 Pavia, Italy. Fax: 39 0382 987323; e-mail: elisa.fasani@unipv.it

† This paper is part of a special issue dedicated to Professor J. C. (Tito) Scaiano on the occasion of his 60th birthday.

Abbreviations: DHP, dihydropyridine; EPR, electron paramagnetic resonance; MP, 3-methylpentane; MTHF, 2-methyltetrahydrofuran.

Steinheim, Germany) and Compound 7 was prepared by a conventional procedure (25). A sample of nitrophenylpyridine 4 for comparison with the photoproducts was prepared according to a published procedure (26).

Photochemistry. Small-scale experiments were carried out on 2 mL samples of 5×10^{-4} *M* solutions of the dihydropyridines in MeCN or MeOH in spectrophotometric cuvettes after argon flushing when appropriate. These were irradiated by means of 15 W low-pressure mercury arcs (254 nm) or 15 W phosphor-coated lamps (center of emission, 366 nm; midheight width, 35 nm) and the course of the reaction was monitored by HPLC by using a C-18 reverse-phase RP-18 endcapped 5 μm column and eluting with a methanol–water 7:3 mixture, λ_{an} 238 nm. Retention times were t_R 9.8 min (Compound 1), t_R 9.5 min (Compound 2), t_R 8.7 min (Compound 3), t_R 11.0 min (Compound 4) and t_R 8.5 min (Compound 5).

Preparative experiments were carried out on 300 mL portions of 5×10 M^{-3} solutions of the dihydropyridines (Compounds 1 and 2) in an immersion well apparatus after argon flushing. These were internally irradiated by means of a 125 W medium-pressure mercury arc through Pyrex until an ~80% conversion was reached (HPLC). Evaporation of the solvent and chromatography afforded the photoproducts are reported in Table 1; these were characterized by examination of their properties, in particular HPLC and NMR. In the case of nitroso Derivative 3, these were identical to those reported in the literature (9,11) and nitro Derivative 4 was identical to an authentic sample prepared as above. Only mass spectroscopy data and chromatographic data were available for Compound 5, which is characterized in more detail below.

2-Methylpropyl methyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (Compound 5), greenish solid, mp 102–105°C ^{1}H NMR ($CDCl_3$) δ0.55 [d, 6H, $CH(CH_3)_2$], 1.5 [m, 1H, $CH(CH_3)_2$] 2.6 and 2.7 (2 s, 3 + ^{3}H, ring CH_3), 3.4 (s, ^{3}H, OCH_3), 3.65 (m, 2H, OCH_2CH), 6.5 (d, 1H, 6′-H), 7.4 (t, 1H, 5′-H), 7.5 (d, 1H, 3′-H), 7.7 (t, 1H, 4′-H); IR (KBr) ν1730, 1558, 1490 cm^{-1}.

Photophysical measurements. The quantum yield of the reaction was measured in spectrophotometric cuvettes (1 cm optical path) by means of a high-pressure mercury arc collimated and filtered by means of an interference filter (366 nm). The chemical conversion was determined by HPLC as above and the light flux was measured by ferrioxalate actinometry.

The luminescence was measured either at room temperature or at 77 K by means of a Perkin-Elmer (Beaconsfield, UK) LS55 fluorimeter. Quantum yields of emission were measured taking quinine sulfate (at room temperature, $\Phi_f = 0.55$ in 1 *N* H_2SO_4) or carbazole (in glass, $\Phi_p = 0.24$) (27) as a standard.

Photolysis in matrix. A 1×10^{-4} *M* solution of Compound 1 in EtOH, 2-methyltetrahydrofuran (MTHF), or 3-methylpentane (MP) (2 mL) in a 1-cm optical path quartz cell with a quartz-to-glass graded seal was degassed by means of four freeze-pump-thaw cycles and sealed. The cell was inserted into an Oxford (Oxford, UK) DN 1704 liquid nitrogen cryostat fitted with a calibrated ITC4 temperature controller and placed in a UV-visible Kontron (Milan, Italy) Uvikon spectrophotometer. The cell was illuminated by means of a focused, high-pressure mercury arc (Osram 150 W) through an interference filter as described above for some minutes. The beam reached the cell through a side opening perpendicular to the analyzing beam. UV-visible spectra were periodically registered as indicated in the figures and the solution after melting was analyzed by HPLC as indicated above.

Table 1. Quantum yield of reaction in the photolysis of dihydropyridines 1, 2 and 7 in argon and air equilibrated solutions

Compound	Conditions	Φ_r(Ar)	Φ_r(Air)
1	MeOH, 254	0.23	0.28
	MeOH, 366	0.35	0.35
	MeCN, 254	0.24	0.28
	MeCN, 366	0.27	0.33
2	MeOH, 254	0.25	0.37
	MeOH, 366	0.35	0.41
	MeCN, 254	0.23	0.36
	MeCN, 366	0.30	0.40
7	MeOH, 254	0.013	0.013
	MeOH, 366	0.004	0.004
	MeCN, 254	0.003	0.003
	MeCN, 366	0.0006	0.0005

RESULTS

4-Phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid esters such as Drugs 1 and 2 are soluble in most organic solvents (poorly in alkanes) but not in water. The absorption spectrum of nifedipine (Fig. 1) exhibits a long-wavelength band with a shape depending on the solvent and maximum in the region 320–360 nm ($\varepsilon \sim 7 \times 10_3$) that tails beyond 400 nm, as well as more intensive bands at 235 and 280 nm (ε 2.5 to 2.7 $\times 10^4$ M^{-1} cm^{-1}). The spectrum of nisoldipine is almost identical.

Irradiation of Compound 1 on a preparative scale in acetonitrile (5×10^{-4} *M*) gave a single product (80% yield), which was isolated and had identical properties to the previously identified 2-nitrosophenylpyridine (Compound 3) (10,11). Only a trace (≤2%) of the corresponding 2-nitrophenylpyridine (Compound 4) was obtained and identified by comparison with an authentic sample. Under these conditions nisoldipine gave a single isolated product (95% yield) identified as the nitrosophenylpyridine (Compound 5) on the basis of the spectroscopic properties.

The reaction of the two dihydropyridine was then tested on 5×10^{-4} *M* solutions. The solvents chosen were acetonitrile and methanol, both under air-equilibrated conditions and after argon flushing and irradiations were carried out either at 254 or at 360 nm. In all cases, the nitroso derivatives, Compounds 3 and 5, respectively, were the only products detected (80–90%) by HPLC monitoring (see Materials and Methods) up to extensive (>50%) conversion. The spectrum evolution during the irradiation is shown in Fig. 2 for Compound 1. As is apparent from the inset, the spectrum was finally transformed into that of the nitroso Derivative 3.

Under the same conditions, the quantum yield of conversion was measured (in this case, however, the decomposition was limited to 20%). The results are reported in Table 1 and are distributed

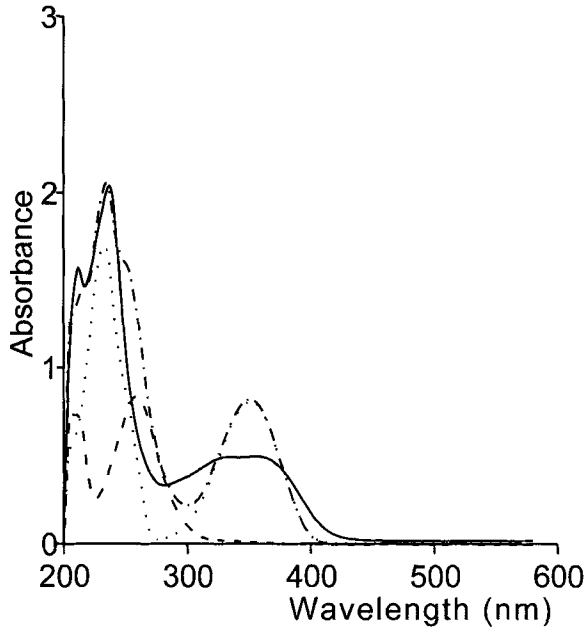


Figure 1. Absorption spectrum of 1×10^{-4} *M* ethanol solutions of (- - -) dihydropyridine 6; (– – – –) nitrobenzene; (-•-•-) sum of the above spectra; (———) nifedipine 1.

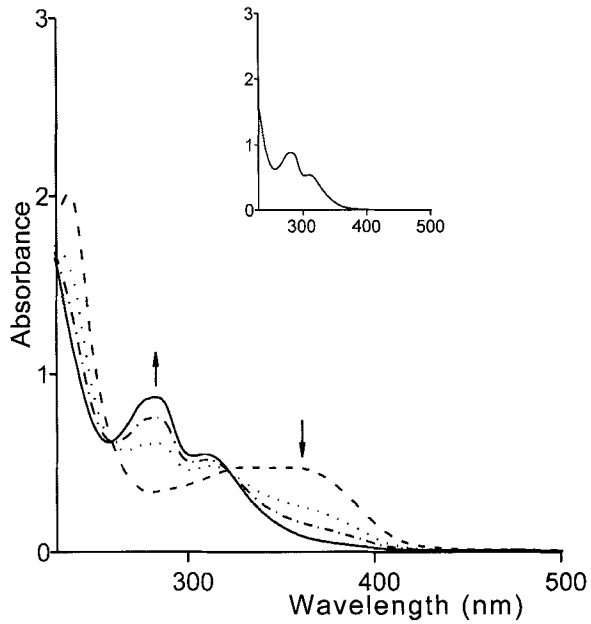


Figure 2. Time evolution of a 1×10^{-4} *M* solution of nifedipine (Compound 1) in ethanol upon irradiation at 366 nm: (– – – –) 0, (- - -) 30, (-•-•-) 60 and (———) 105 s. Inset: 1×10^{-4} *M* solution of nitroso Derivative 3 in ethanol.

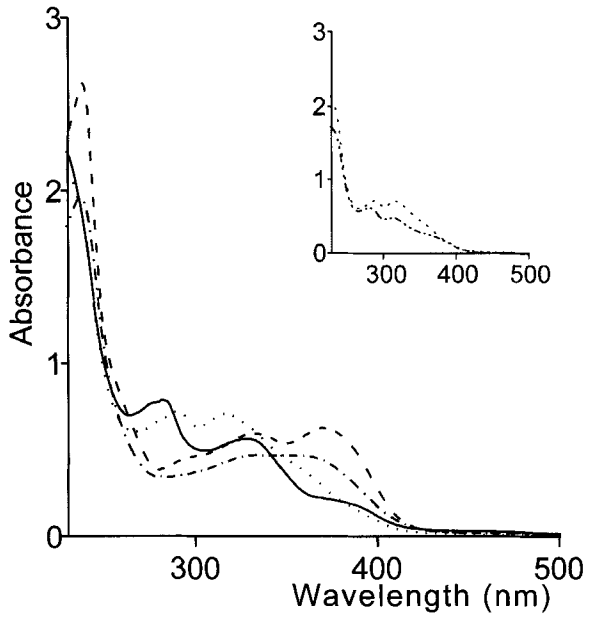


Figure 3. Absorption spectrum of a 1×10^{-4} *M* solution of nifedipine 1 in ethanol (degassed under vacuum): (-•-•-) at 293 K; (– – – –) at 90 K; (———) at 90 K after 5 min irradiation at 366 nm; (- - - -) as above, brought to 293 K. Inset: 1×10^{-4} *M* solution of nifedipine 1 in ethanol (degassed under vacuum) (-••-••-••) after 43 s irradiation at 366 nm at 293 K; (- - - -) after 5 min irradiation at 366 nm at 90 K, brought to 293 K.

around 0.3, with small dependence on the solvent and the exciting wavelength. The reaction does not follow a radical course and the quantum yield was found to be insensitive to the presence of oxygen (saturated solution) or to 1-dodecanethiol (0.1 *M*).

Further evidence was sought by irradiation in a matrix at low temperature. Thus, a 1×10^{-4} *M* solution of Compound 1 in ethanol was degassed by freeze-pump-thaw cycles and frozen at 90 K. Under these conditions the long-wavelength band was split in two well-defined bands with maxima at 325 and 375 nm (see Fig. 3). Irradiation at 366 nm caused a decrease of the absorption in the near-UV region and the formation of a different system with bands around 330 and 280 nm. Upon melting the glass, the spectrum changed again and the maxima now were at 315 and 290 nm. The last spectrum remained unchanged upon refreezing the sample. HPLC analysis at this point showed that ~50% of Compound 1 was consumed and that the nitroso derivative was the primary product. Indeed, the spectrum after melting resembled that obtained by irradiation of Compound 1 at 293 K at a similar conversion (see Fig. 3, inset). Thus, some intermediate was formed in the glass that transformed into the final product upon melting. The rate of photoconversion at 90 K was about seven times lower than at 293 K.

In methyltetrahydrofuran, glass irradiation again caused a blue-shift in the UV region, although to a lower degree than in the previous case, but also to the development of an intense blue color, corresponding to a broad band with maximum 710 nm (Fig. 4). This color was stable at 90 K. Allowing the temperature to rise slowly caused the band to shift somewhat to the red at ~100 K and to disappear when the glass softened at ~110 K. At this point a spectrum closely similar to that resulting from melting the ethanol glass was observed, and refreezing the solution did not restore the blue color or induce any change in the spectrum. HPLC analysis confirmed a partial conversion into Compound 3, similar to what was obtained in ethanol. Carrying out the same experiment in a 3-methylpentane glass led to a modification of the UV part of the spectrum. In this case, melting of the glass caused only a slight modification. At this point, HPLC analysis confirmed the formation of Compound 3. No colored intermediate was formed.

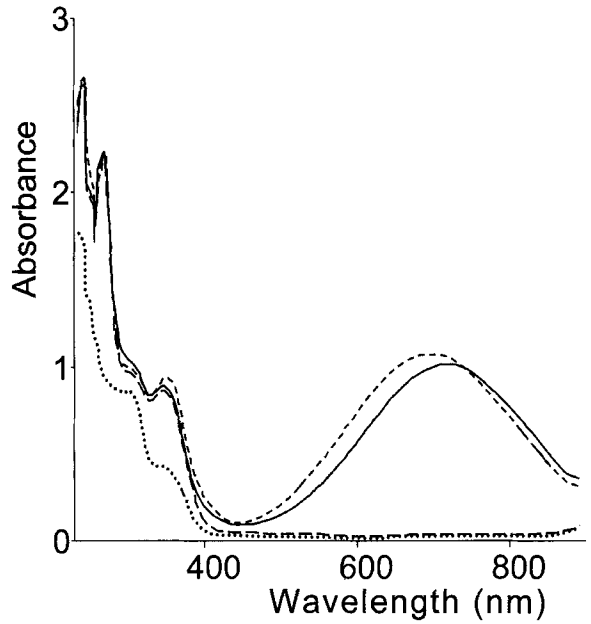


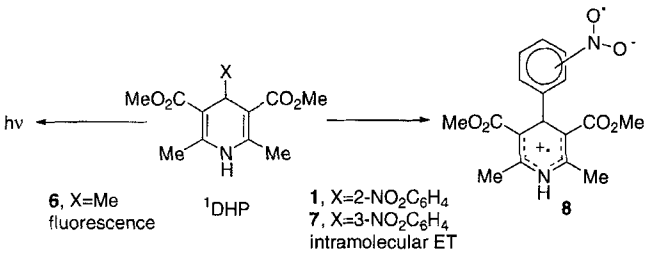
Figure 4. Absorption spectrum of a 1×10^{-4} *M* solution of nifedipine 1 in MTHF (degassed under vacuum): (– – – –) at 77 K, (- - - -) after 20 min irradiation at 366 nm to 77 K, (———) after 20 min irradiation at 366 nm at 77 K and brought to 100 K, (•••••••) after 20 min irradiation at 366 nm at 77 K and brought to 110 K.

For comparison, the parent dimethyl 2,4,6-trimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Compound 6) and the 3-nitrophenyl Derivative **7**, isomeric with Compound 1, were also investigated. Compound 6 turned out to be photostable ($\Phi < 1 \times 10^{-4}$) under all of the conditions tested, whereas Compound **7** was slightly reactive. The quantum yield of reaction for the latter compound depended on both solvent and irradiation wavelength, but in no case was higher than ~0.01 (see Table 1).

As for the photophysics, the parent Compound 6 was characterized by a blue fluorescence in solution (λ_{max} = 437 nm [compare ref. 28]). On the contrary, the nitrophenyl Derivatives 1, 2 and 7 showed no fluorescence.

DISCUSSION

4-Phenyl-1,4-dihydropyridines such as the presently considered derivatives contain two π chromophores separated by an sp^3 carbon. Kurfürst and Kufan (29) suggested that the absorption spectra of this type of compound can be understood as the sum of the independent absorptions by the two chromophores. In fact, Fig. 1 shows that the spectrum of Compound 1 is satisfactorily fitted by adding the spectra of Compound 6, in which only the dihydropyridine chromophore is present, and of nitrobenzene, the latter not absorbing above 300 nm. The long-wavelength band is broader than that in parent Compound 6, in which the only chromophore absorbing is the dienaminodicarboxylate system in the dihydropyridine ring, but has the same area. Thus, it can be inferred that the nitrophenyl group does not affect the character of the lowest singlet state in Compound 1 and its analogues, and that also in these compounds, S_1 is localized on the dihydropyridine moiety (^{1}DHP). However, nitrophenyl Derivatives 1 and 2 (as well as Derivative **7**) differ from that of Derivative 6 in that they do not fluoresce (see Scheme 2).

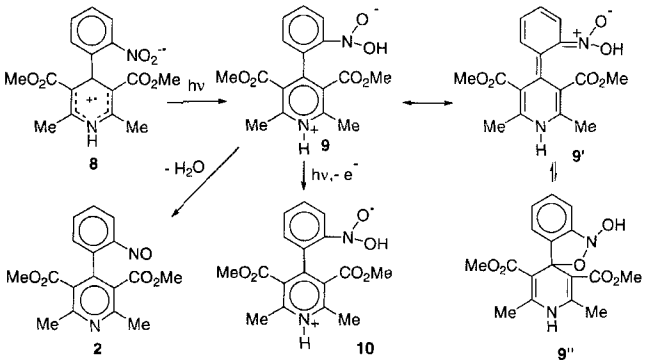


Scheme 2.

This difference can be understood as being due to the occurrence of intramolecular electron transfer from the excited DHP moiety to the nitrobenzene-accepting group. Indeed, intermolecular electron transfer quenching of singlet excited dihydropyridines analogous to that of Compound 6 (and of reduced nicotinamide-adenine dinucleotide, NADH) by electron acceptors such as paraquat has been previously reported (30), and theoretical support for intramolecular electron transfer has been found in empirical force field calculations (31).

Electron transfer from ^{1}DHP is markedly exothermic, with the ΔG°_{ET} = –26.1 kcal mol^{-1}, as calculated according to the Weller equation from the oxidation potential of the DHP chromophore (E_{ox} + 0.67 V *vs* Ag/AgNO$_3$ for Compound 6) (32), the reduction potential of the nitrotoluene moiety (E_{red} –1.25 V) and the energy of the singlet-excited state localized on the first moiety, ^{1}DHP (E_S 73 kcal mol^{-1}, from the fluorescence spectrum). Thus, emission from the singlet is suppressed in the nitrophenyl derivatives and intramolecularly bonded radical ion pairs are formed (see Formula 8 in Scheme 2).

With the 2-nitrophenyl Derivatives 1 and 2 the radical ion pair has an easy path available, because the hydrogen atom in position 4 is favorably located for bonding to the nitro group (deprotonation from the 4 position is the preferred path for 1,4-dihydropyridine radical cations) (33). The hindrance by the flanking ester groups in 3,5 keeps the phenyl ring noncoplanar to the DHP moiety (compare ref. 34) and the nitro oxygen atom is close to the H atom in 4. Therefore, proton transfer between the two oppositely charged moieties is likely (see Scheme 3).



Scheme 3.

The intermediate might be envisaged either as a zwitterion (Formulae 9, 9′), strongly stabilized by the attained aromaticity, or as a C–O bonded species (Formula 9″). The latter seems less likely, both because it is nonaromatic and because the process also occurs at cryogenic temperature in matrix, and therefore involves a limited atom motion, whereas arriving at Formula 9″ requires a 180° torsion of the nitro group. Indeed, the photoreaction occurs in matrix with a quantum yield that is lower than in fluid solution but still relatively large (0.07 rather than 0.35). This supports on one hand the importance of conformational factors in inducing the reaction of the short-lived radical ion pair 8, and on the other hand the reactive conformation is favored.

Loss of water from this intermediate leads to the primary photoproduct, nitrosophenylpyridine 3. The experiments in matrix clearly support the formation of an intermediate that is smoothly converted into Compound 3 upon melting of the glass (see, for example, Fig. 3), consistent with the assignment of Structure 9, for which splitting of a proton from the acidic pyridinium site and of a hydroxyl anion from the negatively charged nitro group is expected to easily occur. The zwitterion is sufficiently stable when the matrix is formed by an oxygen-containing solvent, such as MTHF or EtOH, where it is indefinitely stable at 90 K, because it is stabilized by hydrogen bonds. On the other hand, in a hydrocarbon matrix (MP) no distinct intermediate is formed and the reaction leads directly to Compound 3.

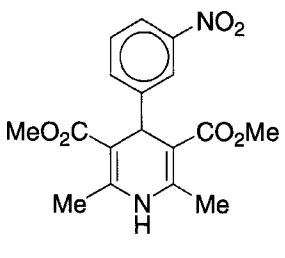
A further piece of information is given by the blue species that is formed in glassy methyltetrahydrofuran and is recognized as the solvated electron by comparison with the literature (35). This suggests the occurring of secondary ionization from the zwitterion, and more specifically the formally charged nitronato moiety.

Nitronates are known to be easily oxidized (36) and electron photoejection to form radical cation 10 appears likely. This is in accord with the fact that ionization occurs conspicuously in polar MTHF, but not in protic EtOH, where the anionic site is probably protonated. The "free" electron absorption actually is reported to occur at a longer wavelength in this solvent (35), thus it may be that the ejected electron remains vicinal to the radical cation in glassy solvent. Indeed, when the matrix is slowly heated while remaining stiff, the absorption shifts to the red by ~40 nm, before disappearing when the glass softens.

Comparison with the 3-nitro isomer **7** confirms the general picture. Intramolecular electron transfer is expected to be equally favored in this case, and accordingly, fluorescence from the ^{1}DHP state is completely quenched. However, the nitro group is far from the 4-hydrogen atom and thus the proton transfer observed with Compound 1 is inhibited. Accordingly, the quantum yield of the reaction at 366 nm drops by a factor of 10^2–10^3 with respect to Compound 1. Furthermore, the quantum yield of the intramolecular reaction of Compound 1 is independent of conditions, whereas Isomer **7** reacts more efficiently in MeOH than in MeCN. It is reasonable that the alcohol facilitates intermolecular proton transfer and thus reaction of radical ion pair 8.

Also, it is important to notice that Compound 7 is more photoreactive at 254 nm (by a factor of 3 to 5), whereas Compound 1 is less reactive (in average by 15–20%). As mentioned above, at this wavelength about a half of the impinging light is absorbed by the nitrobenzene chromophore. The inefficient hydrogen abstraction by the nitrobenzene localized triplet (in the parent compound Φ ~0.01) (37) then contributes, resulting in an enhanced reaction in the case of the even less photoreactive (via the intramolecular path) Compound 7, but in a decreased yield for the quite reactive (intramolecularly) Compound 1.

It should also be noted that irradiation of Compound 1 in glass solvent in the EPR cavity reveals the presence of two paramagnetic species, an alkyl $-CH_2$ radical and a nitro group–located radical anion (38). Despite the identification of the former intermediate, apparently arising from hydrogen abstraction from the methyl groups in the 2 or 6 position, or from the methyl ester, this must be a quite minor process, detected only thanks to the high sensitivity of the method, because no significant amount of products arising



7

Scheme 4.

from this path have been obtained from preparative photolysis or detected by HPLC. That only weak EPR signals are detected confirms the nonradical nature of the photochemical reaction. The fact that a radical path has no role is also indicated by the lack of effect by a radical trap such as a thiol.

On the other hand, flash photolysis studies (not reported) gave no indication of a transient at room temperature.

CONCLUSION

In conclusion, the evidence reported supports the operation of a fast intramolecular electron transfer path in nitrophenylpyridines. In the 2-nitro derivatives such as the drugs nifedipine and nisoldipine, this is followed by proton transfer, efficiently leading to a zwitterion. Although this suggestion has no experimental support in fluid solution, the zwitterion has been detected (and is stable) in matrix. The electron transfer path, due to the easy oxidation of the dihydropyridine moiety, distinguishes the photochemistry of such molecules from the atom-transfer intramolecular mechanism generally occurring with *o*-nitrobenzyl derivatives, even if the overall result is in both cases hydrogen transfer from the neighboring position.

No other mechanism competes with intramolecular charge transfer and proton transfer giving the nitrosopyridine. All the other products obtained in the present work or elsewhere (nitro derivatives such as Compound 3, azoxy compounds) result from further thermal or photochemical reactions of the nitroso derivatives. Such inherent intramolecular photoreactivity is little affected by conditions and is also observed in the crystal state (although the reaction stops at the first layer in that case). From the point of view of drug photostability, the title can be preserved only by protecting the drug preparation by means of an opaque outer shell or blister or by adding a suitable dye. On the other hand, a knowledge of the photochemical mechanism of nifedipine is important, because the high photosensitivity of this molecule has made it useful as a photoactivated probe for the study of biological mechanisms (39–41), as well for photoinitiated polymerizations (42). It would probably be informative to compare nifedipine with the 3-nitrophenyl isomer (**7**) in such applications in order to distinguish what is due to electron transfer and what is due to the subsequent reaction.

Acknowledgement—Financial support of this work by the Department of Education, Rome, in the frame of the PRIN program, is gratefully acknowledged.

REFERENCES

1. Tønnesen, H. H., editor (2004) *Photostability of Drugs and Drugs Formulations*, 2nd edition. CRC Press, Orlando, FL.
2. Albini, A. and E. Fasani, editors (1998) *Drugs: Photochemistry and Photobiology*. The Royal Society of Chemistry, Cambridge, UK.
3. Leonard, R. G. and R. L. Talbert (1982) Calcium-channel blocking agents. *Clin. Pharm.* **1**, 17–33.
4. Pontremoli, R., G. Leoncini and A. Parodi (2005) Use of nifedipine in the treatment of hypertension *Expert Rev. Cardiovasc. Ther.* **3**, 43–50.
5. Berson, J. A. and E. Brown (1955) Dihydropyridines. II. The photochemical disproportionation of 4-(2-nitrophenyl)-1,4-dihydropyridines. *J. Am. Chem. Soc.* **77**, 447–450.
6. de Vries, H. and G. M. Beijersbergen van Henegouwen (1998) Photoreactivity of nifedipine in vitro and in vivo. *J. Photochem. Photobiol. B Biol.* **43**, 217–221.
7. Shim, S. C., A. N. Pae and Y. J. Lee (1988) Mechanistic studies on the photochemical degradation of nifedipine. *Bull. Korean Chem. Soc.* **9**, 271–274.
8. Pietta, P., A. Rava and P. Biondi (1981) High performance liquid chromatography of nifedipine, its metabolites and photochemical degradation products. *J. Chromatogr.* **210**, 516–521.
9. Thoma, K. and R. Kerker (1992) Photoinstability of drugs. Part 4. The decomposition products of nifedipine. *Pharm. Ind.* **54**, 465–468.
10. Stasko, A., V. Brezova, S. Biskupic, K. Ondrias and V. Misik (1994) Reactive radical intermediates formed from illuminated nifedipine. *Free Rad. Biol. Med.* **17**, 545–556.
11. Alajarin, R., J. J. Vaquero, J. Alvarez-Builla, M. Pastor, C. Sunkel, M. Fau de Casa-Juana, J. Priego, P. R. Statkow, J. Sanz-Aparicio and

I. Fonseca. (1995) Synthesis, structure, and pharmacological evaluation of the stereoisomers of furnidipine. *J. Med. Chem.* **38**, 2830–2841.
12. Barltrop, J. A., P. J. Plant and P. Shofield (1966) Photoremovable protecting groups. *J. Chem. Soc. Chem. Commun.* 822–823.
13. Yip, R. W., D. K. Sharma, R. Giasson and D. Gravel (1985) Photochemistry of the *o*-nitrobenzyl system in solution: evidence for singlet state intramolecular hydrogen abstraction. *J. Phys. Chem.* **89**, 5328–5330.
14. Rybalova, T. V., V. F. Sedova, Y. V. Gatilov and O. P. Shkurko (2003) Crystal structure of the azoxy compound formed by photochemical transformation of nifedipine. *J. Struct. Chem.* **44**, 870–873.
15. Krivopalov, V. P., V. F. Sedova and O. P. Shkurko (2003) Formation of substituted 6-hydroxy-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine upon photochemical transformation of nifedipine. *Russ. Chem. Bull.* **52**, 2440–2443.
16. Lehto, V. P., J. Salonen and E. Laine (1999) Real time detection of photoreactivity in pharmaceutical solids and solutions with isothermal microcalorimetry. *Pharm. Res.* **16**, 368–373.
17. Mielcarek, J. (1997) Photochemical stability of the inclusion complexes formed by modified 1,4-dihydropyridine derivatives with β-cyclodextrin. *J. Pharm. Biomed. Anal.* **15**, 681–686.
18. Al-Ajmi, H. S., R. S. Dawe, A. G. Renwick, B. S. Macklin, J. Ferguson and N. K. Gibbs (2000) The effect of whole-body sunbed ultraviolet A exposure on the pharmacokinetics of the photolabile drug nifedipine. *Photoderm. Photoimmunol. Photomed.* **16**, 111–115.
19. Taiwo, F. A., L. H. Patterson, E. Jaroszkiewicz, B. Marciniec and M. Ogrodowczyk (1999) Free radicals in irradiated drugs: an EPR study. *Free Radic. Res.* **31**, 231–235.
20. Fujii, H. and L. J. Berliner (1999) In vivo EPR evidence for free radical adducts of nifedipine. *Magn. Reson. Med.* **42**, 691–694.
21. Marinkovic, V. D., D. Agbaba, K. Karljikovic-Rajic, S. Vladimirov, J. M. Nedeljkovic and M. Jovan (2003) Photochemical degradation of solid-state nisoldipine monitored by HPLC. *J. Pharm. Biomed. Anal.* **32**, 929–935.
22. Marinkovic, V., D. Agbaba, K. Karljikovic-Rajic, J. Comor and D. Zivanov-Stakic (2000) UV derivative spectrophotometric study of the photochemical degradation of nisoldipine. *Farmaco* **55**, 128–133.
23. Yan, T., Y. Wu, Z. Jingqin, H. Nie, F. Yuan, H. Tang and S. Jin (1989) *Yaowu Fenxi Zazhi* **9**, 10–12. through *Chem. Abstr.* **110**, 237033.
24. Michelitsch, A., J. Reiner, M. Schubert-Zsilavecz and W. Likussar (1995) 2,2′-Bis(3-isobutyloxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-pyridyl)-azobenzene-N,N′-dioxide. A new degradation product of nisoldipine by UV light. *Pharmazie* **50**, 548–549.
25. Carabateas, P. M., R. P. Brundage, K. O. Gelotte, M. D. Gruett, R. R. Lorenz, C. J. J. Opalka, B. Singh, W. H. Thielking, G. L. Williams and G. Y. Lesher (1984) 1-Ethyl-1,4-dihydro-4-oxo-7-pyridyl)-3-quinolinecarboxylates: synthesis of 3- and 4-(3-aminophenyl) pyridines intermediates. *J. Heterocycl. Chem.* **21**, 1849–1856.
26. Shibanuma, T., M. Iwanami, M. Fujimoto, T. Takenaka and M. Murakami (1980) Synthesis of the metabolites of 2-(*N*-benzyl-*N*-methyl)ethyl methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate. *Chem. Pharm. Bull.* **28**, 2609–2613.
27. Bonesi, S. M. and R. Erra-Balsells (2001) Electronic spectroscopy of carbazole and *N*- and *C*-substituted carbazoles in homogeneous media and in solid matrix. *J. Luminesc.* **93**, 51–74.
28. Deme, A. K., V. K. Lusis and G. Y. Dubur (1987) Fluorescence of 3,5-diethoxycarbonyl-1,4-dihydropyridine derivatives and their anions. *Khim. Geterotsikl. Soedin.* 67–70.
29. Kurfürst, A. and J. Kuthan (1983) Quantum chemical interpretation of electronic absorption spectra of the Hantzsch dihydropyridines. *Coll. Czech. Chem. Commun.* **43**, 1422–1428.
30. Martens, F. M., J. W. Verhoeven, C. A. G. O. Varma and P. Bergwerf (1983) Photooxidation of 1,4-dihydropyridines by various electron acceptors: a laser flash photolysis study. *J. Photochem.* **22**, 99–113.
31. Kovacic, P., W. D. Edwards, N. R. Natale, R. Sridhar, K. Rajagopalan and P. F. Kiser (1990) Theoretical calculations on calcium channel drugs: is electron transfer involved mechanistically? *Chem. Biol. Inter.* **75**, 61–70.
32. Lopez-Alarcon, C., J. A. Squella, D. Miranda-Wilson and L. J. Nunez-Vergara (2004) Spectroelectrochemical study on the electro-oxidation in aqueous medium of some 1,4-dihydropyridines: effect of substitution in 1-position and 4-position. *Electroanalysis* **16**, 539–546.
33. Zhu, X. Q., H. R. Li, Q. Li, T. Ai, J. Y. Lu, Y. Yang and J. P. Cheng (2003) Determination of the C4-H bond dissociation energies of NADH models and their radical cations in acetonitrile. *Chem. Eur. J.* **9**, 871–880.
34. Cotta-Ramusino, M. and M. R. Varì (1999) Force field and semi-empirical MO conformational analysis of dihydropyridine calcium-channel antagonists. *J. Mol. Struct. (Theochem.)* **492**, 257–268.
35. Abramczyk, H., B. Werner and J. Kroh (1992) Absorption spectra of the solvated electron in hydrocarbons. *J. Phys. Chem.* **96**, 9674–9677.
36. Garver, L. C., V. Grahaushas and V. Baum (1985) Catalytic oxidative nitration of nitronate salts. *J. Org. Chem.* **50**, 1699–1702.
37. Sundararajan, K., V. Ramakrishnan and J. C. Kuriacose (1984) Photoreduction of nitrobenzene by aliphatic amines. A mechanistic study. *Ind. J. Chem.* **23B**, 1086–1089.
38. Buttafava, A., A. Faucitano, E. Fasani, A. Albini and A. Ricci (2002) EPR evidence of a triplet biradical in the photolysis of nifedipine. *Res. Chem. Intermed.* **28**, 231–237.
39. Polyakov, N. E., M. B. Taraban and T. V. Leshina (2004) Photo-CIDNP study of the interaction of tyrosine with nifedipine. An attempt to model the binding between calcium receptor and calcium antagonist nifedipine. *Photochem. Photobiol.* **80**, 565–571.
40. Feldmeyer, D., P. Zoellner, B. Pohl and W. Melzer (1995) Calcium current reactivation after flash photolysis of nifedipine in skeletal muscle fibers of the frog. *J. Physiol.* **487**, 51–56.
41. Gurney, A. M., J. M. Nerbonne and H. A. Lester (1985) Photoinduced removal of nifedipine reveals mechanisms of calcium antagonist action on single heart cells. *J. Gen. Physiol.* **86**, 353–379.
42. Yamaoka, T., S. Yokoyama, T. Omote and K. Naitoh (1994) Photochemical behavior of nifedipine derivatives and application to photosensitive polymers. *J. Photopolym. Sci. Technol.* **7**, 293–298.