Formation of substituted 6-hydroxy-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine upon photochemical transformation of nifedipine

*V. P. Krivopalov, V. F. Sedova, and O. P. Shkurko**

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383 2) 34 4752. E-mail: oshk@nioch.nsc.ru

Long-term exposure of nifedipine to daylight in ethanol gives 2,2´-bis[3,5-bis(methoxycarbonyl)-2,6-dimethylpyridin-4-yl]azoxybenzene and 6-hydroxy-1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine as the major products.

Key words: 4-(2-nitrophenyl)-3,5-dimethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine, 4-(2-nitrosophenyl)-3,5-dimethoxycarbonyl-2,6-dimethylpyridine, 2,2´-bis[3,5-bis(methoxycarbonyl)-2,6-dimethylpyridin-4-yl]azoxybenzene, 6-hydroxy-1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine, intramolecular cyclization, photochemistry, nifedipine.

Nifedipine (dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**1**)) is widely used in practical medicine to treat cardiovascular diseases. It easily undergoes transformations when treated with oxidants or reducing agents[1—4] and is also capable of intra- and intermolecular transformations induced by ultraviolet and visible light.[5—7]

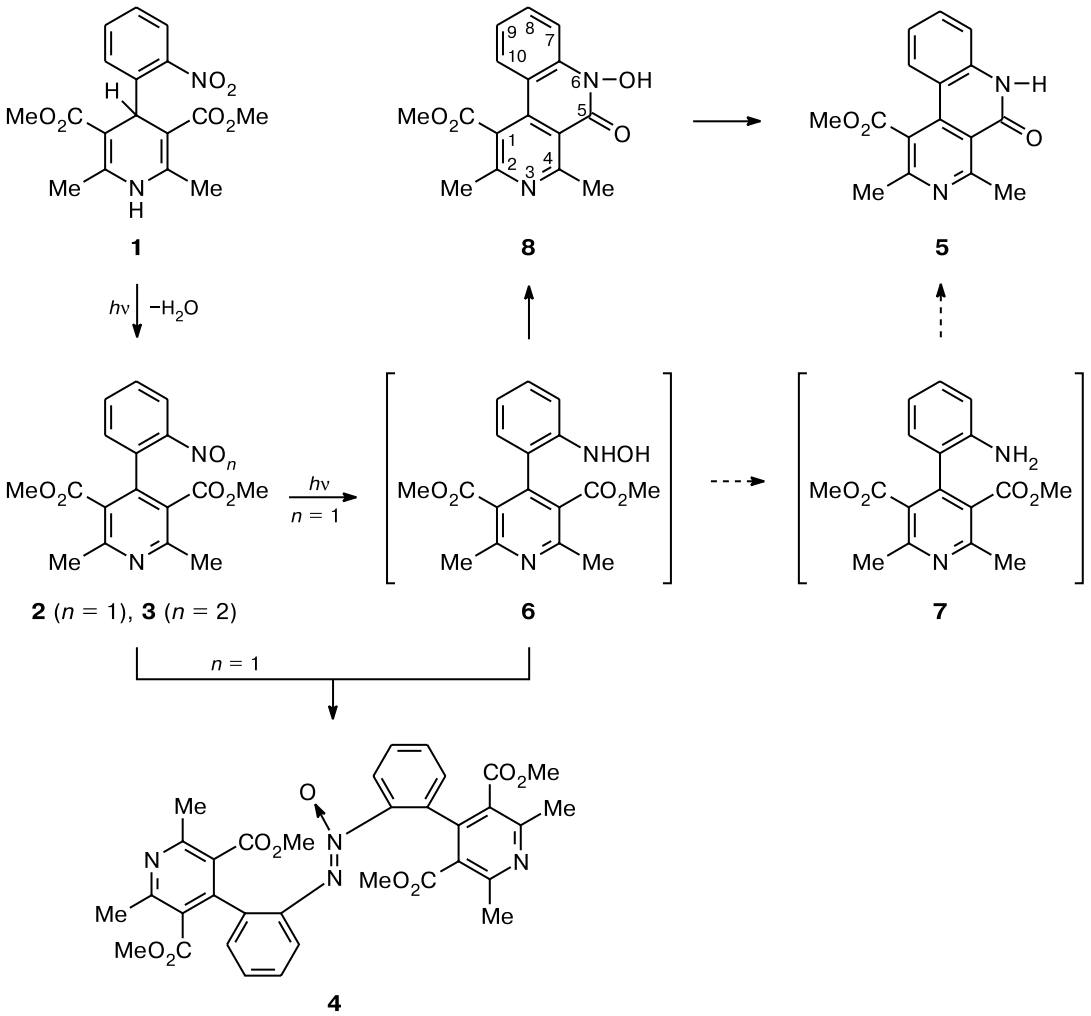
A number of studies[8—13] have been devoted to the composition and structure of the products of photochemical transformations of nifedipine and its pelleted forms. It was found that the reaction may proceed to different extents depending on the conditions applied, thus giving different sets of products. Thus, on exposure to daylight or soft UV light, nifedipine (**1**) gives dimethyl 2,6-dimethyl-4-(2-nitrosophenyl)pyridine-3,5-dicarboxylate (**2**) as the major product of the primary phototransformation, while harder UV radiation results in the formation of dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (**3**).[8,9] For longer exposure time, the process goes further giving rise to other compounds due to subsequent transformations of the primary phototransformation products. Japanese researchers[12] studied the composition of a complex mixture of compounds produced upon a 30-day exposure of nifedipine and its pelleted forms to daylight. In addition to nitroso compound **2** (30%) and azoxy derivative **4** (20%), they isolated trace amounts of nitro compound **3** and 1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine (lactam **5**). The pattern of transformations they proposed assumes the formation of nitroso derivative **2**, its reduction first to hydroxylamino derivative **6** and then to amino derivative **7**, and, finally, intramolecular cyclization of **7** to give lactam (**5**) (Scheme 1).

However, another study[13] calls in question the participation of amino ester **7** in the formation of lactam **5**, as this amino ester is a stable compound and requires more rigorous conditions for cyclization.[3] Lactam **5** is formed upon irradiation of nifedipine in the presence of $TiCl_3$ [5] or on treatment of nitroso derivative **2** with a reducing agent such as glutathione in the dark.[13] On the basis of the foregoing, it has been assumed[13] that lactam **5** is formed from *N*-hydroxylactam **8** rather than from amino ester **7**. However, the researchers cited did not succeed in detecting the formation of *N*-hydroxylactam **8** during the phototransformation of nifedipine, although this product is a well-known compound, first prepared[5] by careful reduction of nitro derivative **3** with zinc.

We succeeded in identifying the conditions of photodecomposition of nifedipine to give *N*-hydroxylactam **8**. It was found that this compound is formed, together with azoxy derivative **4**, under usual laboratory conditions when a mixture of primary photodecomposition products of nifedipine (**1**) is kept in the light for many months. Thus a solution of nifedipine in MeOH was kept for 6 months and a solution in EtOH, for 10 months. Both solutions turned bright-green several hours after the preparation, which indicated the formation of nitrosophenylpyridine **2**. Subsequently, the color gradually changed from green to yellow-brown and a finely-crystalline colorless precipitate gradually accumulated on the walls. The precipitate formed in each case was isolated, while the major components of the supernatant were separated by preparative

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2307—2310, November, 2003.

Scheme 1



TLC on silica gel (Table 1). In both cases, this resulted in isolation of *trans*-azoxy derivative **4** and nitroso derivative **2** containing (according to TLC and ^{1}H NMR spectroscopy) traces of nitro derivative **3** difficult to separate.

Table 1. Values of R_f (TLC) for compounds **1**—**4** and **8**

Compound	Conditions[a]	
	I	II
1	0.63	0.24
2	0.86	0.68
3 [b]	0.85	0.62
4	0.50	0.30
8	0.54	~0

[a] I — SiO_2 (Silufol UV-254)/CH_2Cl_2—$MeOBu^t$—C_6H_{14}, 2 : 2 : 1. II — Al_2O_3 (DC Alufolien E)/CH_2Cl_2—C_6H_{14}, 1 : 1.

[b] The sample of compound **3** was synthesized by a known procedure.[2]

Both crystalline precipitates isolated from the methanol and ethanol solutions were identical but differed in properties from lactam **5**, which was described in detail previously.[12] We determined the composition and the structure of the compound obtained based on spectroscopic data. Its IR spectrum contains intense bands at 1714 cm^{-1} due to the ester group and at 1646 cm^{-1} due to the hydroxamic group and a broad band at 3100 cm^{-1} for the HO group. No band at 1675 cm^{-1} characteristic of lactam **5** [12] is present. The most intense peak in the mass spectrum of **5** has m/z 298, which corresponds to the molecular ion of *N*-hydroxylactam **8**. The ^{1}H and ^{13}C NMR spectra also confirm structure **8**, having one ester group and two methyl groups in the pyridine fragment; the spectra also exhibit the appropriate set of other signals. The signals were assigned based on the assignment of signals for the corresponding acid.[14] The sample of **8** that we isolated from the ethanol solution contained a slight amount (~5%) of the ethyl ester of this acid

Table 2. Products of phototransformation of nifedipine

Solvent	τ/days	Yield (%)		
		2	**4**	**8**
MeOH	~180	51	22	3
EtOH	~300	4	52	23

Note. τ is the exposure time.

(MS peak with *m/z* 312) formed as a result of transesterification. As compared to other products of nifedipine transformation, *N*-hydroxylactam **8** has substantially different mobilities on SiO_2 and Al_2O_3 (see Table 1), which facilitates its identification.

Table 2 shows the yields of the isolated products of nifedipine transformation in MeOH and EtOH for different photoexposure times of solutions. For low degrees of transformation, nitroso derivative **2** is the major product, while *N*-hydroxylactam **8** is present in a small amount. The ratio of the products changes for longer exposure times. The formation of azoxy compound **4** and *N*-hydroxylactam **8** indicates participation of two intermediates in the transformations, namely, nitroso derivative **2** and hydroxylamino derivative **6**. The latter may be produced from nitroso derivative **2** with participation of other components of the mixture in conjugated redox processes, including photochemical reactions.[15]

Thus, we showed that upon long exposure of an ethanol solution of nifedipine **1** to the light, 6-hydroxy-1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine (**8**) is formed as one of the two major products. Recently, a similar derivative, 6-hydroxy-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine, was prepared by UV irradiation of 3-methoxycarbonyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine.[16]

Experimental

IR spectra of the compounds were recorded on a Bruker Vector 22 spectrophotometer for KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AM-400 spectrometers. Mass spectra were obtained on a Finnigan MAT-8200 spectrometer (EI, 70 eV). The separation of compounds was monitored by TLC on Silufol UV-254 plates (Chemapol, Czechia) and DC Alufolien E plates (Merck, Germany); the spots were visualized in the UV light and compared with authentic samples of compounds **1**—**4**. All operations were carried out in air.

Phototransformation of nifedipine in methanol. A solution of nifedipine (**1**) (1.04 g, 3.0 mmol) in 30 mL of MeOH was kept in a closed glass flask at room temperature (~20 °C) under usual room light (a combination of the natural daylight and artificial light from a luminescent lamp). After 6 months, the yellow-brown solution was concentrated by half and left in a refrigerator (+4 °C). The resulting light-gray precipitate was separated, washed with MeOH, and dried *in vacuo* to give **6-hydroxy-1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine (8)**, yield 0.03 g (3%), m.p. 193—195 °C (from 96% EtOH). The compound developed an intense brown-violet color with $FeCl_3$ and was identical to the product obtained by phototransformation of nifedipine in 96% EtOH.

After separation of the crystalline precipitate, the solution was concentrated to dryness, the residue was dissolved in benzene, and the solution was passed through a layer of Al_2O_3 (1 cm) and concentrated. The residue was separated by preparative TLC on silica gel (Silica gel LL_{254} 5—40 μm, ~1.5 mm thick layer, elution with CH_2Cl_2—MeOBu^t—C_6H_{14}, 6 : 1 : 1) with detection in the UV light. Two main zones were collected, namely, R_f 0.6—0.7 (green zone) and 0.4—0.5 (yellow zone); they were eluted with $CHCl_3$. The eluates were filtered and concentrated *in vacuo* and each product was subjected once again to chromatography.

The upper zone produced 0.5 g (51%) of a green crystalline product, which was **2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(2-nitrosophenyl)pyridine (2)**, m.p. 85—90 °C (Ref. 5: m.p. 93 °C). ^1H NMR (400 MHz, CCl_4), δ: 2.60 (s, 6 H, Me); 3.30 (s, 6 H, OMe); 6.37 (dd, 1 H, H(6′), $^3J_{5',6'}$ = 8.0 Hz, $^4J_{4',6'}$ = 1.2 Hz); 7.34 (ddd, 1 H, H(5′), $^3J_{5',6'}$ = 8.0 Hz, $^3J_{4',5'}$ = 7.6 Hz, $^4J_{3',5'}$ = 1.2 Hz); 7.45 (dd, 1 H, H(3′), $^3J_{3',4'}$ = 7.6 Hz, $^4J_{3',5'}$ = 1.2 Hz); 7.63 (td, 1 H, H(4′), $^3J_{3',4'}$ = $^3J_{4',5'}$ = 7.6 Hz, $^4J_{4',6'}$ = 1.2 Hz). The ^1H NMR and mass spectra also exhibited low-intense peaks coinciding with those in the spectra of an authentic sample of nitro compound **3** (*cf.* Refs. 2, 12). MS, *m/z*: 328 (19) $[M]^+$, 298 (34) $[M - NO]^+$, 269 (100) $[M - COOMe]^+$. High-resolution mass spectrum, *m/z*: 328.1063. $C_{17}H_{16}N_2O_5$. Calculated: 328.1059.

The lower zone produced 0.21 g (22%) of ***trans*-2,2′-bis[2,6-dimethyl-3,5-bis(methoxycarbonyl)pyridin-4-yl]azoxybenzene (4)**, m.p. 162—165 °C (from a benzene—hexane mixture) (Ref. 12: m.p. 163—165 °C). ^1H NMR (400 MHz, CCl_4), δ: 2.45 and 2.49 (both s, each 6 H, Me); 3.25 and 3.26 (both s, each 6 H, OMe); 7.00—7.04 (m, 2 H, Ar); 7.19 and 7.31 (both dt, each 1 H, Ar, ^3J = 8.5 Hz, ^4J = 1.5 Hz); 7.40—7.42, 7.80—7.86 (both m, each 2 H, Ar). ^{13}C NMR (100 MHz, CCl_4), δ: 20.84 (Me), 21.11 (Me), 49.32 (OMe), 119.56, 121.95, 122.60, 124.39, 124.86, 125.57, 126.32, 126.38, 127.47, 127.68, 129.69, 131.81, 139.03, 142.41, 142.85, 144.83, 153.41, 154.13, 164.51 (C=O), 164.86 (C=O). MS, *m/z*: 641 $[M + H]^+$, 581 $[M^+ - COOMe]$, 314 $[M^+ - C_{17}H_{16}N_3O_4]$, 298 $[M^+ - C_{17}H_{16}N_3O_5]$.

Phototransformation of nifedipine in ethanol. A solution of nifedipine (**1**) (0.25 g, 0.72 mmol) in 10 mL of 96% ethanol was kept in a closed glass flask for 10 months under the conditions described above. The pale-yellow-gray precipitate was separated, washed with 0.1 mL of 96% EtOH, and dissolved in $CHCl_3$. The solution was passed through a silica gel layer (1.5 cm) and eluted with $CHCl_3$. The eluates were concentrated *in vacuo* and the colorless crystalline precipitate was recrystallized from 96% ethanol to give **6-hydroxy-1-methoxycarbonyl-2,4-dimethyl-5-oxo-5,6-dihydrobenzo[*c*][2,7]naphthyridine (8)**, yield 0.05 g (23%), m.p. 193—195 °C. The product was identical to the compound (m.p. 194—196 °C) prepared by the reduction of dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate with zinc (**3**) according to a procedure described previously[5] (Ref. 5: m.p. 210 °C). IR, ν/cm $^{-1}$: 1252 (ester C—O), 1550, 1588, 1606 (conjug. C=C), 1646 (amide C=O), 1714 (ester C=O),

2820—3000 (C—H), 3100 (OH). MS, *m/z*: 298 (100) $[M]^+$, 281 (81) $[M - OH]^+$, 267 (21) $[M - OMe]^+$. High-resolution mass spectrum, *m/z*: 298.0952. $C_{16}H_{14}N_2O_4$. Calculated: 298.0953. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 2.66 (s, 3 H, C(4)C$\underline{H}_3$); 3.17 (s, 3 H, C(2)C$\underline{H}_3$); 3.99 (s, 3 H, OMe); 7.26 (ddd, 1 H, H(9), $^3J_{9,10}$ = 8.4 Hz, $^3J_{8,9}$ = 7.1 Hz, $^4J_{7,9}$ = 1.4 Hz); 7.66 (ddd, 1 H, H(8), $^3J_{7,8}$ = 8.4 Hz, $^3J_{8,9}$ = 7.1 Hz, $^4J_{8,10}$ = 1.0 Hz); 7.81 (dd, 1 H, H(7), $^3J_{7,8}$ = 8.4 Hz, $^4J_{7,9}$ = 1.4 Hz); 7.92 (dd, 1 H, H(10), $^3J_{9,10}$ = 8.4 Hz, $^4J_{8,10}$ = 1.0 Hz); 10.85 (s, 1 H, OH). ^{13}C NMR (50 MHz, $CDCl_3$), δ: 23.0 (Me), 26.9 (Me), 52.9 (OMe), 113.2 (C(7)), 114.6 (C(10a)), 115.1 (C(4a)), 121.4 (C(1)), 122.9 (C(9)), 125.7 (C(10)), 132.1 (C(8)), 134.7 (C(10b)), 137.1 (C(6a)), 155.6 (C(2)), 156.6 (C(4)), 162.8 (C(N)=O), 170.5 (C(O)=O).

After separation of the crystalline precipitate, the solution was concentrated, the residue was dissolved in benzene, and the solution was passed through an Al_2O_3 layer. The resulting mixture was separated by TLC as described above. From the upper zone, 0.01 g (4%) of nitrosophenyl derivative **2** was isolated, and 0.12 g (52%) of azoxy derivative **4** was isolated from the lower zone.

References

1. A. Sausin´sh and G. Dubur, *Khim. Geterotsikl. Soedinen.,* 1993, 579 [*Chem. Heterocycl. Compd.*, 1993 (Engl. Transl.)].
2. A. Kurfürst, P. Trška, and I. Goljer, *Collect. Czech. Chem. Commun.*, 1984, **49**, 2393.
3. J. M. Merillon, D. Liu, Y. Laurent, M. Rideau, and C. Viel, *Phytochemistry*, 1992, **31**, 1609.
4. N. Iqbal, C. R. Triggle, and E. E. Knaus, *Drug Dev. Res.*, 1997, **42**, 120.
5. K. Görlitzer and D. Buss, *Arch. Pharm. (Weinheim, Ger.)*, 1985, **318**, 97.
6. K. Görlitzer and D. Buss, *Arch. Pharm. (Weinheim, Ger.)*, 1985, **318**, 106.
7. L. Born, S. Goldmann, C. Wünsche, K. Görlitzer, and D. Buss, *Arch. Pharm. (Weinheim, Ger.)*, 1988, **321**, 855.
8. S. Ebel, H. Shütz, and A. Hornitschek, *Arzneim.-Forsch./Drug Res.*, 1978, **28**, 2188.
9. R. Testa, E. Dolfini, C. Reschiotto, C. Secchi, and P. A. Biondi, *Farmaco, Ed. Prat.*, 1979, **34**, 463; *Chem. Abstr.*, 1980, **92**, 51589.
10. K. Akimoto, K. Kurosaka, H. Nakagawa, and I. Sugimoto, *Chem. Pharm. Bull.*, 1988, **36**, 1483.
11. Y. Matsuda, R. Teraoka, and I. Sugimoto, *Int. J. Pharm.*, 1989, **54**, 211; *Chem. Abstr.*, 1990, **112**, 11831.
12. N. Hayase, Yu.-I. Itagaki, S. Ogawa, Sh. Akutsu, Sh.-I. Inagaki and Y. Abiko, *J. Pharm. Sci.*, 1994, **83**, 532.
13. H. de Vries and G. M. J. Beijersbergen van Henegouwen, *Photochem. Photobiol.*, 1995, **62**, 959.
14. E. Gössnitzer, K. Görlitzer, and H. J. Baltrusch, *Magn. Res. Chem.*, 2002, **40**, 467.
15. A. Staško, V. Brezova, S. Biskupič, K. Ondriaš, and V. Mišik, *Free Radical Biol. Med.*, 1994, **17**, 545.
16. K. Görlitzer and H. J. Baltrusch, *Pharmazie*, 2000, **55**, 747.

Received April 3, 2003;
in revised form July 1, 2003