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Photochemistry of Oxazolidinone Antibacterial Drugs†

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ABSTRACT

The photochemistry of six *N*3-(3-fluoro-4-dialkylaminophenyl)-oxazolidinones known for their antimicrobial activity has been examined. All of these compounds are defluorinated in water ($\Phi_{dec} \approx 0.25$) and in methanol ($\Phi_{dec} \approx 0.03$), reasonably *via* the triplet. The chemical processes observed are reductive defluorination and solvolysis, depending on the structural variation introduced (thus, tethering the dialkylamino group to the aromatic ring and introducing a highly polar group in the oxazolidinone moiety have an effect). A likely mechanism involves the fragmentation of the C–F bond yielding the corresponding triplet phenyl cation. This intermediate either is reduced or, under appropriate conditions, intersystem crosses to the singlet state that adds the solvent. These data demonstrate a sizeable photodecomposition of these drugs that causes a decrease in the therapeutic activity. Furthermore, the likely formation of phenyl cations may cause a photogenotoxic effect.

INTRODUCTION

In the last decades, the development of antibacterials has been largely based on the improvement of existing classes, as the introduction of a new family requires major investments. Therefore, the emerging of oxazolidinones after a long interval and after brilliant work by chemists and biologists is to be considered a major advancement (1–5), culminating in the licensing of the first clinically useful antibacterial of this class, linezolid **1**. In this molecule the heterocyclic moiety bears an aliphatic side chain in position 5 (*S* configuration necessary for drug activity) and a phenyl group on the nitrogen atom, likewise required for activity. In turn, the phenyl moiety is functionalized by fluorination (that increases the potency and enhances the oral pharmacokinetic performance) and by introducing an electron donating group (morpholino), well tolerated and improving the safety profile. This drug is used for the treatment of infections caused by multi-resistant bacteria including streptococci (6) and methicillin-resistant *Staphylococcus aureus* (7) and has many therapeutic indications, including the treatment of tuberculosis. Although this is a rather expensive drug, treatments are considered more cost effective than using competing drugs (8).

Linezolid is considered a relatively safe drug and the main toxicity issue reported to date refers to the possible development of thrombocytopenia upon prolonged treatment (9–11). However, the presence of the fluoroaminophenyl motif is reminiscent of the high photoreactivity of fluoroanilines (12) and of the fact that other antimicrobials likewise with a fluorine atom flanking an amino group such as lomefloxacin and other fluoroquinolones are known for their high photolability (13,14) and phototoxicity (15). Linezolid is known to be liable to degradation under photochemical conditions (16–18) and a recent detailed study has shown that the main photoprocess does in fact involve the aromatic fluorine (19). The reaction proceeded from the triplet state and was well rationalized on the basis of a phenyl cation as the intermediate. As mentioned above, the research on new oxazolidinones is quite active at present (20–25) and several new derivatives are candidates to the introduction in therapy. This encouraged us to extend the photochemical study on some further derivatives in order to understand whether structural variations had an important effect on the photochemical properties. The choice of the derivatives for the study was based on the significance of the pharmacological properties.

MATERIALS AND METHODS

H (300 MHz) and C (75.4 MHz) NMR spectra were registered by means of a Brucker instrument and IR spectra by using a Perkin Elmer Fourier transform spectrophotometer. Flash silica gel was used for column chromatographic separation. Reverse-phase HPLC analysis was carried out by using a C_{18} PHENOMENEX Gemini, 25 cm × 4.6 mm, 5 μm column and eluting with H_2O/MeCN 70/30 for **2**, **6** and **7**, 60/40 for **4** and **5**, 50/50 for **3**. The same setup was used for HPLC/MS experiments. Fluorescence and phosphorescence spectra were measured by means of a Perkin Elmer LS 55 luminescence spectrometer under the conditions indicated in Table 4.

Starting materials. (*S*)-3-[3′-Fluoro-4′-(*N*-morpholino)phenyl]-5-(*N*-acetamidomethyl)-oxazolidin-2-one (linezolid, **1**) was prepared according to the published procedure (5). *N*1-{(5*S*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-yl}methylacetamide **2** and *N*1-{(5*S*)-3-[(6a*S*)-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-yl}methylacetamide **7** were prepared essentially according to the published procedure (26) but because of low yields and difficult application two of the intermediates involved were synthesized in a different way as indicated below.

(6aS)-1-fluoro-6a,7,8,9-tetrahydro-6H-azolo-[1,2-d]benzo[b][1,4]oxazine-3-amine: To a solution of 9.00 g (37.8 mmol) of (6a*S*)-1-fluoro-3-nitro-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4]oxazine (26) in 50 mL of tetrahydrofuran and 90 mL of methanol, ammonium formate was added (19.00 g). The flask was maintained under argon atmosphere and cooled to 0°C. Ten percent palladium on carbon (0.44 g) was added and the suspension was stirred overnight. The reaction was monitored by TLC, water and ethyl acetate were added, the phases separated, and the aqueous portion was extracted with ethyl acetate. The combined organic portions were washed with saturated

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sodium chloride, dried ($MgSO_4$) and evaporated to give 7.2 g of the title compound (90%) as a brown solid that was sufficiently pure for the following steps, through which it was transformed into (5*R*)-3-[(6a*S*)-1-fluoro-6a-7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4] oxazine-3-yl]-5-azidomethyl-1,3-oxazolan-2-one according to the reported method (26).

Compound 2: To a solution of 0.90 g (2.68 mmol) of the above azide in 80 mL of ethyl acetate 10% palladium on carbon was added (0.25 g) and the vessel was alternatively evacuated and filled with nitrogen; then hydrogen was introduced. The mixture was stirred overnight, then evacuated, flushed with nitrogen and cooled at 0°C, when 0.25 mL (3.08 mmol) of pyridine and 0.80 mL (8.3 mmol) of acetic anhydride were added. The mixture was stirred for 30 min and then removed from the ice bath and stirred at room temperature (r.t.) for 1 h, filtered and concentrated to give an orange solid which was purified on a silica gel column by chromatography to obtain 0.6 g (64%) of acetamide **2**.

The corresponding intermediates for the synthesis of compound **7** were prepared by the same method.

*N*1-{(5*S*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d] benzo[b][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-yl}methyl-*O*-methylthiocarbamate **3** and *N*1-{(5*S*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-yl}methylthiourea **4** were prepared according to the published procedure (26).

(*S*)-*N*-{[3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolan-5-yl] methyl}-*O*-methylthiocarbammate **5** and (*S*)-*N*-{[3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolan-5-yl]methyl}thiourea **6** were prepared analogously to **3** and **4** from (*S*)-5-Aminomethyl-[*N*-3-(3-fluoro-4-morpholinophenyl)]oxazolidine-2-one as indicated below.

(R)-{[N-3-(3-fluoro-4-morpholinophenyl)-2-oxo-oxazolidin-5-yl} methyl]isothiocyanate: Thiophosgene (1.25 mL) was added dropwise to a solution of (*S*)-5-Aminomethyl-*N*-[3-(3-fluoro-4-morpholinophenyl)]oxazolidine-2-one (4.7 g, 14.13 mmol) (27) in dry dichloromethane (100 mL) in an ice bath under argon. The reaction mixture was allowed to react at r.t. over 3 h and then the volatile components were removed. The residue obtained was chromatographed onto a silica gel column and afforded 2 g of the title compound (40%). ^{1}H NMR ($CDCl_3$) δ 3.15 (t, J = 4.5 Hz, 4H), 3.90 (t, J = 4.5 Hz, 4H), 3.80–4.04 (m, 3H), 4.15 (t, J = 9 Hz, 1H), 4.85 (m, 1H), 6.95 (t, J = 9 Hz, 1H), 7.15 (dd, J = 9, 2.5 Hz, 1H), 7.45 (dd, J = 14–2.5 Hz, 1H).

Compound 5: A solution of the above isothiocyanate (1.7 g, 5 mmol) in methanol (100 mL) was heated to 80–100°C while monitoring by TLC. When the consumption of the starting material was complete, the reaction mixture was allowed to cool to r.t. The residue was then filtered, washed with ether and dried to afford a crude which was crystallized from isopropanol/water to give 1.3 g of **5** (70%), the spectroscopic properties of which corresponded to those reported in the literature (27).

Compound 6: Ammonia gas was bubbled into a solution of the above isothiocyanate (300 mg, 0.89 mmol) in THF (100 mL) at −10°C over 20 min. The resultant mixture was stirred at r. t. for 1 h and then diluted with ethyl acetate. The organic layer was extracted with water and brine and dried. The solvent was evaporated and the residue obtained was passed through a column of silica gel to afford 170 mg of thiourea **(6)** (54%), the spectroscopic properties of which corresponded to those reported in the literature (28).

Photochemical reactions. Explorative experiments: 5×10^{-4} M Solutions of the investigated compounds were flushed by nitrogen and irradiated by means of six external phosphor-coated lamps (15 W, center of emission, 310 nm), monitoring the course of the reaction by HPLC. Under these conditions, the light flux measured by a radiometer fitted by a UV-31 calibrated sensor was 61 W m^{-2}. Tests were carried out also by using lamps with center of emission at 360 nm in the same setup (flux measured by a radiometer fitted by a UV-36 calibrated sensor was 50 W m^{-2}).

Preparative experiments: 1×10^{-3} M Solutions of the investigated compounds were flushed by nitrogen and irradiated under either of the two conditions, *viz*. (1) in an immersion well apparatus (125 mL) by means of a 125 W medium pressure mercury arc through Pyrex or (2) in a number of quartz tubes (each containing 10 mL) by means of four external phosphor-coated lamps (15 W, center of emission, 310 nm). The course of the reaction was monitored by HPLC. When the starting material was consumed, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (cyclohexane-ethyl acetate as eluent). New products were identified on the basis of their analytical and spectroscopic properties. The most informative evidence was offered by H, C NMR spectra as reported below.

9 ^{1}H NMR ($CDCl_3$): δ 1.5–2.2 (m, 4H), 3.25 (q, J = 9 Hz, 1H), 3.45 (t, J = 10 Hz, 1H), 3.6 (m, 1H), 3.75–4.15 (m, 5H), 4.05 (s, 3H), 4.45 (dd, J = 10, 3 Hz, 1H), 4.95 (m, 1H), 6.50 (d, J = 8.5 Hz, 1H), 6.90–7.05 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 23.5 (CH_2), 28.2 (CH_2), 47.6 (CH_2), 47.9 (CH_2), 48.3 (CH_2), 55.1 (CH), 57.5 (CH_3), 68.6 (CH_2), 70.1 (CH), 108.2 (CH), 112.2 (CH), 113.5 (CH), 127.0 (C), 132.6 (C), 142.8 (C), 154.6 (C = O), 192.5 (C = S).

10 ^{1}H NMR ($CDCl_3$): δ 1.5–2.25 (m, 4H), 2.60 (q, J = 9 Hz, 1H), 3.80 (s, 3H), 4.05 (s, 3H), 3.30–4.10 (m, 8H), 4.85 (m, 1H), 6.45 (d, J = 2.5 Hz, 1H), 6.95 (bs, 1H), 7.05 (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.0 (CH_2), 26.0 (CH_2), 47.6 (CH_2), 47.8 (CH_2), 51.8 (CH_2), 54.1 (CH), 55.7 (CH_3), 57.6 (CH_3), 64.8 (CH_2), 71 (CH), 95.5 (CH), 100.0 (CH), 120.7 (C), 131.6 (C), 146.5 (C), 153.1 (C), 154.6 (C = O), 192.5 (C = S).

16 ^{1}H NMR ($CDCl_3$): δ 3.10 (t, J = 4.5 Hz, 4H), 3.85 (t, J = 4.5 Hz, 4H), 4.0 (s, 3H), 3.75–4.10 (m, 4H), 4.95 (m, 1H), 6.90 (d, J = 9 Hz, 2H), 7.25 (bs, 1H), 7.40 (d, J = 9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 47.50 (CH_2), 47.60 (2 CH_2), 48.10 (CH_2), 57.50 (CH_3), 66.70 (2 CH_2), 71.10 (CH), 116.0 (2 CH), 120.0 (2 CH), 130.3 (C), 148.2 (C), 154.6 (C = O), 192.6 (C = S).

17 ^{1}H NMR [$(CD_3)_2CO$]: δ 2.85 (t, J = 5 Hz, 4H), 3.90 (s, 3H), 3.80 (t, J = 5 Hz, 4H), 3.80–4.10 (m, 4H), 4.95 (m, 1H), 7.0 (dd, J = 9, 2.5 Hz, 1H), 7.25 (d, J = 9 Hz, 1H), 7.3 (d, J = 2.5 Hz, 1H), 7.8 (bs, 1H), 8.5 (bs 1H); ^{13}C NMR [$(CD_3)_2CO$]: δ 48.9 (CH_2), 49.1 (CH_2), 53.6 (2 CH_2), 57.8 (CH_3), 67.8 (CH_2), 71.7 (CH), 106.5 (CH), 110.7 (CH), 122.0 (CH), 136.8 (C), 137.5 (C), 152.9 (C = O), 193.9 (C = S).

Quantum yield measurements. Reaction quantum yields were measured by irradiating 2 mL samples of 5×10^{-4} M solutions of **1**–**7** in a quartz spectrophotometric cuvette on an optical bench. The light source was a collimated beam from a 100 W high-pressure mercury arc fitted with an interference filter (transmittance maximum, 280 nm). The reaction was monitored by HPLC and the consumption of the starting material (limited to < 20%) was determined (a known volume, 20 μL, injection loop was used). The light flux was measured by ferrioxalate actinometry (29).

Fluorescence quantum yields were measured using quinine sulfate as the standard (Φ_F = 0.54) (30).

RESULTS

First reported by Dupont researchers in 1987 (3) oxazolidinone antimicrobials have been the subject of extensive investigation and development at the Upjohn (then Pharmacia) laboratories (4,5). A member of this family, linezolid, was approved by the Food and Drug Administration in April 2000 and has acquired a significant therapeutic role. In the following years, the success of this drug fostered structure–activity relationship (SAR) studies for the optimization of the pharmaceutical activity of molecules having as the base skeleton a *N*-(aminophenyl)-oxazolidinone and bearing a polar group tethered through a methylene in position 5. These studies showed that important elements are the introduction of a conformational constraint in the aminophenyl moiety, the introduction of a fluoro substituent on the phenyl ring and the nature of the polar group (31). Due to our interest in the photochemistry of drugs and in particular of those containing a fluorinated aromatic moiety, we decided to examine the photochemistry of some of these compounds, as a contribution to the pharmacological profile of such highly useful drugs. Thus, we compared the photochemistry of some fluorophenyloxazolidinones that appeared promising for the biological activity. In these the structural modifications that the above SAR analysis had indicated as significant were introduced. Thus, the polarity of the side chain was varied, the

rotation of the dialkylaminophenyl group was hindered and fluorinated and fluorine-free derivatives were compared. The first group of oxazolidinones included tricyclic compounds **2**, **3** and **4**, where an oxymethylene bridge hinders the rotation of the morpholino group with respect to the aromatic ring; these compounds bear an acetamido, a thiocarbamate or a thiourea polar group, respectively. The second group included the corresponding derivatives lacking the oxymethylene bridge, *viz*. compounds **1** (the previously examined linezolid), **5** and **6** (Scheme 2). The photochemistry was systematically investigated in water and in methanol by irradiating at 310 nm; tests with compounds **1** and **2** showed a significant photodecomposition also by using lamps centered at 360 nm (*ca* 3% of the decomposition observed with the 310 nm lamps). Exposure of a similar aqueous solution of **1** and **2** to an integrated near-UV energy of 200 W m^{-2} (360 nm centered lamps) caused a decomposition, respectively, of 56% and 65% for the two drugs. For some derivatives the photoreactivity was tested also in nonpolar solvents and found to be very low; therefore, such conditions were not further investigated.

*N*1-{(5*S*)-3-[(6a*S*)-1-Fluoro-6a,7,8,9-tetrahydro-6*H*-azolo-[1,2-d]benzo[b][1,4]oxazin-3-yl]-2-oxo-1,3-oxazolan-5-yl}methylacetamide **2** was prepared through a modification of the published procedure (see Materials and Methods). Irradiation (phosphor-coated lamps, emission centered at 310 nm) of this compound (1×10^{-3} M) in a nitrogen-flushed aqueous solution led to extensive degradation (85% in 15 min), as indicated by HPLC. A single main product was formed and was separated by column chromatography (a few highly polar peaks were revealed, but not separated). This was demonstrated to be the corresponding fluorine-free phenyloxazolidinone **7** by comparison with an authentic sample prepared according to the literature (26) (see Scheme 1 and Table 1).

When the same compound was irradiated in methanol, reduced **7** was again the main photoproduct and was accompanied by a lower amount of another phenyloxazolidinone that was separated. The evidence obtained allowed to assign the structure of methyl ether **8** to this compound.

Two further oxazolidinones, **3** and **4**, were prepared through modifications of the published procedure (see Materials and methods). These differed from compound **2** by having a different group attached to the aminomethyl chain in position 4, and contained a methylthiourethane and a thioureide function. Irradiation of compound **3** gave fluorine-free **9** as the only isolated product in water and as the main one in methanol, where methyl ether **10** was also formed. As for thiourea **4**, the HPLC profile of the irradiated solution in both water and methanol was almost identical to that obtained from **3** under the same conditions and it was assumed that the photoproducts were **11** and **12**, the analogs of those from **3**.

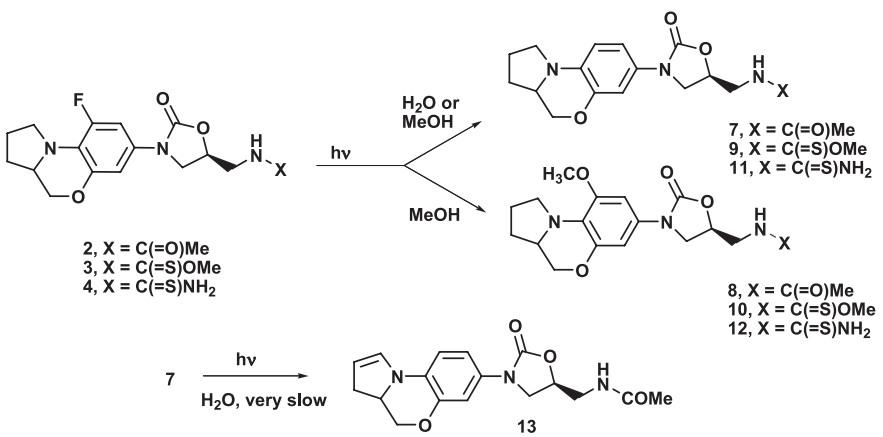
Table 1. Products from the irradiation of tricyclic oxazolidinones **2**–**4**.

Oxazolin	Solvent	Products (% yield)
2	H_2O	**7** (48)
	MeOH	**7** (35), **8** (18)
3	H_2O	**9** (34)
	MeOH	**9** (28), **10** (13)
4	H_2O	**11** (35)
	MeOH	**11** (25), **12** (25)

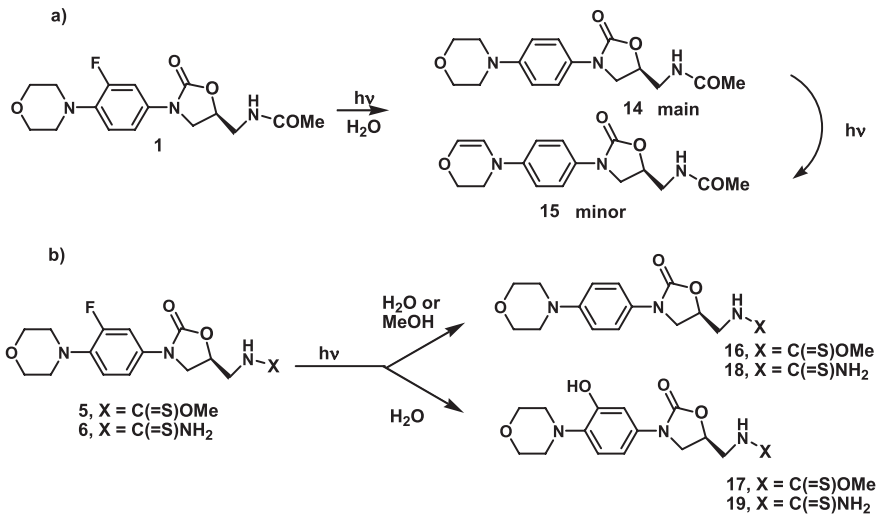
The nonfluorinated derivative **7** was irradiated under the same conditions and showed to be next to photostable. A single peak was detected in HPLC after prolonged irradiation. Examination by mass spectroscopy demonstrated the loss of 2 mass units with respect to the starting material and the compound was suggested to have structure **13**.

The photochemistry of *N*-[3-(3-fluoro-4-morpholinophenyl)-2-oxo-oxazolidin-5-yl]methylacetamide (**1**, linezolid) has, as mentioned, been examined previously (19) and found to give the defluorinated product **14** in 30% yield in water. For some further derivatives, like fluorine-free **14**, it had been demonstrated that the morpholine ring had undergone a slow oxidative degradation (structure **15** and three products derived from it). Minor, highly polar products were detected, but not further investigated. Reduced **14** and a trace of the methyl ether were obtained in methanol. For the convenience of the reader, the main results are reported again in Scheme 2a and Table 2.

Two analogs of compound **1** with a different polar group in position 5 were prepared by conventional syntheses (see Materials and Methods), *viz*. the methyl urethane **5** and the ureide **6**. Irradiation of compound **5** in water for 2 h led to a 45% decomposition. Two significant products were detected by HPLC and were separated by column chromatography and characterized. Analytical and spectroscopic examination showed that the minor one had undergone reductive defluorination (structure **16**) and the main one substitution of a



Scheme 1.



Scheme 2.

Table 2. Products from the irradiation of oxazolidinones **1**, **5** and **6**.

Oxazolin	Solvent	Products (% yield)
1	H_2O	**14** (30)*
	MeOH	**14** (70)†
5	H_2O	**16** (4), **17** (25)
	MeOH	**16** (33)
6	H_2O	**18** (4), **19** (25)
	MeOH	**18** (33)

*Products resulting from the oxidative degradation of the morpholino side chain, *viz*. enamine **15** and products resulting from it, were also obtained (*ca* 20%). †A 10% yield of the 3-methoxy-4-morpholino derivative was also obtained (19).

Table 3. Quantum yield of reaction of oxazolidinones **1**–**7**.*

Oxazolin	H_2O	MeOH
2	0.27	0.02
3	0.09	0.02
4	0.11	0.03
1	0.33	0.05
5	0.25	0.05
6	0.23	0.04
7	< 0.001	0.03

*Error within 10%.

hydroxyl group for a fluoro atom (structure **17**). In methanol compound **16** was the only product. As for ureide **7**, this showed a HPLC strictly analogous to that of **5** in both solvents and was assumed to follow the same course giving **18** and **19** (Scheme 2b, Table 2).

The quantum yield of reaction of the above compounds was measured in the solvents used for preparative reactions (see Table 3).

Some spectroscopic properties of representative compounds were measured. The absorbance spectra were quite similar, with a maximum at *ca* 250–270 nm. The data for tricyclic derivatives **2** and **3**, compounds **1** and **5** lacking the oxygenated ring and the related fluorine-free compounds **7** and **14** are reported in Table 4.

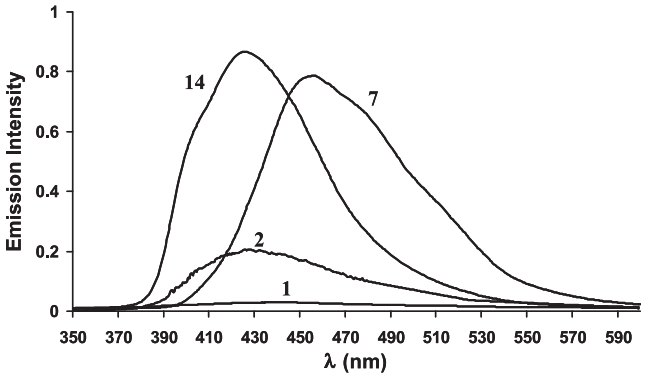


Figure 1. Phosphorescence spectra of compounds **1**, **2**, **7** and **14** in ether-pentane-alcohol (5/5/2) at 77 K.

Table 4. Key spectroscopic data on some oxazolidinones.

	Absorbance*	Fluorescence*		Phosphorescence†	
	λ_{max}, nm (log ϵ)	λ_{max}, nm	Φ_F‡	λ_{max}, nm	Relative intensity‡
2	247 (4.33)	377§	0.03	427§	0.23
7	264 (4.04)	358‖	0.11	454‖	0.9
1	252 (4.29)	377§	0.0004	445§	0.02
14	255 (4.29)	358§	0.07	427§	1
3	259 (4.16)				
5	246 (4.22)				

*In water at 20°C. †In ether-pentane-ethyl alcohol 5:5:2 mixed solvents at 77 K. ‡Error within 10%. §λ_{exc} 265 nm; slit bandwidths (nm) 10–10. ‖λ_{exc} 290 nm; slit bandwidths (nm) 10–10.

The emission properties of some of the above oxazolidinones were also examined. The fluorophenyl derivatives **1** and **2** were only weakly fluorescent in solution, while the fluorine-free analogs were 30 times more emissive. Likewise, fluorinated **2** phosphoresced weakly in glass at 77 K and the emission

from **1** was barely detectable, while the phosphorescence from fluorine-free **7** and **14** was much more intense (see Fig. 1 and Table 4).

DISCUSSION

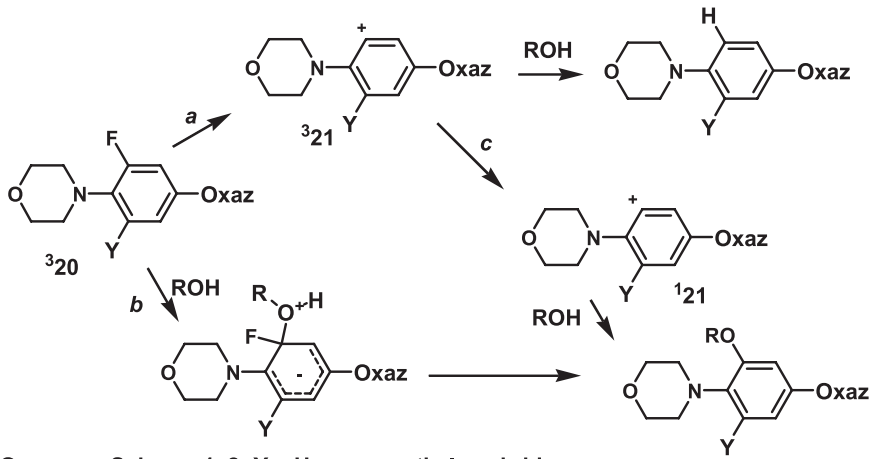
The absorption spectra of the oxazolidinones considered in this study show little difference among them (see Table 4). Oxazolidinones bearing no aromatic substituent do not absorb above 250 nm (32). When an aromatic substituent is present, as in the compounds above, the spectrum is essentially that of that moiety, with little if any modification by the oxazolidinone moiety. In fact, the spectra of the present compounds all are closely analogous to that of anilines. Likewise, the oxazolidinone moiety does not introduce any photochemical reactivity. *N*-phenyl derivatives such as compounds **7** and **14** are rather photostable and actually the only reaction occurring involves the morpholino group substituted at the phenyl ring (the usual oxidative side chain degradation previously observed in *N*-dialkylanilines), not the oxazolidinone moiety. Furthermore, such fluorine-free compounds exhibit both fluorescence in solution and phosphorescence in glass (see Table 4) and resemble anilines in their photophysical properties. Comparison with literature data shows that the fluorescence of parent aniline is at 334 nm ($\Phi_F = 0.15$ in MeCN) and the phosphorescence at 405 nm (in methyltetrahydrofuran glass at 77 K) (33). Thus, the emission from the present derivatives is somewhat redshifted and less intense, but qualitatively of the same type.

On the other hand, all of the fluorinated compounds tested are quite photolabile and the photoreaction consistently involves the fluoro atom through either of the two processes, reductive elimination or solvolysis. In all of the cases, the efficiency of the reaction strongly decreases in going from water to methanol as the solvent and decreases again in passing to acetonitrile. Thus it is likely that the reaction involves charged intermediates. Insertion of a fluorine decreases both the fluorescence and the phosphorescence of these compounds, thus no indication about the multiplicity of the reacting states comes from this fact. However, with simple anilines, including some fluorinated anilines (34), intersystem crossing in solution is quite efficient ($\Phi_{ISC} \approx 0.7$) and thus it seems possible that the photoreactions considered, with quantum yield up to 0.33, originates from the triplet (^{3}**20** in Scheme 3). The type of chemistry observed then supports this idea, as shown below.

Two mechanisms appear reasonable (19), that is monomolecular cleavage of the carbon–fluorine bond (SN1 process, path *a* in Scheme 3) and bimolecular [SN2 (Ar*) path *b*] reaction *via* the addition–elimination mechanism usual in the thermal chemistry of aromatics. Note that in a recent flash photolysis study on linezolid **1** (19), we documented a further process, photoionization. This was proved to be a reversible process and to cause no irreversible chemical change. This can thus be disregarded in the present chemical investigation.

In the S_N1 case, homolytic cleavage of the C–F bond is excluded because the energy of both singlet (E_S around 85 kcal mol^{-1}) and triplet (E_T around 75 kcal mol^{-1}) states, as measured from the emission spectra, are too low to make this a viable path ($E_{Ar\text{-}F} \approx 120$ kcal mol^{-1}). Thus, a monomolecular mechanism must involve heterolytic cleavage to form a phenyl cation. The two mechanisms are depicted in Scheme 3.

The two reactions observed, reduction and substitution, may result each from one of the mechanisms (path *a* or *b*) or both from path *a*, with a later branching through path *c* toward substitution. Several studies on halogenated anilines (35) have shown that reductive dehalogenation (including defluorination) *via* the triplet phenyl cation (here ^{3}**21**) formed from the cleavage of the triplet state is a viable path and it appears reasonable that this applies also to this case. Triplet phenyl cations do not add to n nucleophiles but rather abstract hydrogens. Ongoing computational studies on analogous reactions suggest that the triplet multiplicity is conserved during the bond formation sequence and is followed by intersystem crossing to the singlet end product. As for solvolysis this may arise either again from the cation, in this case the singlet (^{1}**21**, known to be the most stable spin state of cations of this type) (36), provided that intersystem crossing (path *c*) occurs efficiently, or *via* the addition–elimination mechanism (path *a*). It is difficult to assess the two possibilities, each of which has precedents for analogous compounds (37). However, some trends can be evidenced. Thus, the quantum yield of reaction is rather constant along the series, around 0.25 in water (except for compound **3** that has *ca* 0.1) and



Scheme 3.

0.02–0.05 in methanol, with a decrease by a factor of 5–10 in going to the latter solvent. The limited variation along the series suggests the primary photochemical step remains the same. The effect of structure can be evidenced in the type of chemical process, though. Thus, conformationally blocked derivatives **2**–**4** undergo no substitution in water, but only (as a minor process) in methanol, a fact that strongly supports the phenyl cation path. Substitution on the contrary is the main path in conformationally free compounds **5** and **6** in water, but not with **1**, and with these compounds no substitution takes place in methanol (again an exception is **1**, where this process occurs, though to a low extent, see Table 2). As the two former compounds are distinguished from the last one by a more polar side chain in 5 (the dipole moment of *N*-methylacetamide is 3.98 D in dioxane, while that of *N,N*'-dimethylthiourea is 5.31 D), an economic rationalization is that the photoreaction proceeds in any case *via* heterolytic cleavage in the triplet state (hence the much larger Φ_r in more polar water [$\varepsilon = 80.2$] than in MeOH [$\varepsilon = 32.6$]) to give the triplet cation. An optimal solvation of such strongly polar intermediate prolongs its lifetime. This is the case when the cationic site is easily accessible (that is in conformationally free compounds) and in the presence of highly polar groups (that is the case of compounds **5** and **6**). Under these conditions ISC to the singlet phenyl cation becomes competitive with reaction from the triplet, particularly in a nonreducing solvent such as water, and this is known to add to n nucleophiles. The polarity of the side chain has little importance with compounds **2**–**4**, where the determining factor seems to be sterical hindering around the reacting center. Apparently, the solvation in this case is such that solvolysis is competitive only in methanol.

The relatively high quantum yield of reactions of these molecules in water should be highlighted. Linezolid is approved for the use also by parenteral infusion and in particular under these conditions it should be protected from light in order to avoid a serious loss of activity. In fact the scission of F atom, that increases the potency of the drug, should affect the antibacterial activity. As shown above, the photodecomposition is significant also under ICH confirmatory test conditions (200 W h m^{-2}). Thus, one cannot count too much on the poor absorption of near-UV light by drug preparations with compound **1** as the active principle. A photoinduced lessening of the therapeutic activity of linezolid and oxazolidinones of similar structure that may in the future be used as drugs may result even after assumption. The photoreaction may be linked with some phototoxic effect, although this has not been reported as yet for the case of compound **1**, the only derivative presently used. The above chemical data suggest that a phenyl cation is formed, just as in the case of fluoroquinolones. In particular, the effective trapping with pyrrole strengthens the idea that a similar electrophilic intermediate is formed and attacks selectively electron-rich heterocycles and, by analogy, DNA bases. This points the attention (38) to the possible phototoxicity of the oxazolidinones and, on the other hand, photoactivated drugs based on this structure may be conceived.

CONCLUSION

Oxazolidinone antibacterials appear to be quite photoreactive in water and in polar organic solvents. The (rather efficient) reaction involves the moiety present in such molecules, probably *via* heterolysis of the C–F bond in the triplet state. The chemical paths from the thus formed triplet phenyl cation are then determined by the solvation and thus by the rigidity and the accessibility of the reacting center as well as by the presence of highly polar groups in the molecule. Although these compounds do not absorb significantly above 310 nm, exposure to UV-B light can cause a relevant decomposition and thus a loss of therapeutic activity. As the reaction leads to phenyl cations, suspected to have an important role in the phototoxicity of other drugs, in particular fluoroquinolones, the photobiological implications of these results should be taken into account and foster an appropriate investigation.

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