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Degradation of lansoprazole and omeprazole in the aquatic environment

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Dedicated to the memory of Professor Gaspare Barone (1943–2005)

Abstract

Lansoprazole and omeprazole degrade in water leading to sulfides, benzimidazolones and a red complex material. Degradation is accelerated in acid medium and by solar simulator irradiation. Benzimidazoles, dianilines and pyridines have also been identified.

Keywords: Lansoprazole; Omeprazole; Hydrolysis; Phototransformation; Sulfoxide deoxygenation

1. Introduction

The occurrence of pharmaceuticals in surface waters and the question as to whether they pose a risk to the environment are receiving considerable attention (Kümmerer, 2001). Most of the literature on this subject concerns the occurrence of drugs and their effects on selected aquatic organisms, while few data are reported on the transformation products of drugs. In this context, we have recently studied the abiotic transformation of selected anti-inflammatory drugs in the aquatic environment and we have found that some degradation products are more harmful than the parent compounds (DellaGreca et al., 2004).

In recent years, the importance of non-biological alteration in the breakdown of drugs has been widely noticed and there are in progress a large number of researches concerning degradation mechanisms, kinetics, isolation and toxicity of degradation products. The last aspect is of particular interest since the metabolites may be even more toxic than the parent molecule. Our objective in this study was to determine the main products of hydrolytic and photolytic cleavage of two substituted pyridylmethylsulfinyl benzimidazole derivatives: lansoprazole (**1a**) and omeprazole (**1b**), proton pump inhibitors (PPIs) widely used for treatment of acid-related diseases (Horn, 2000) (Fig. 1). Omeprazole has been recently found in surface waters of the Lambro river (Calamari et al., 2003). Stability studies have been conducted especially on omeprazole and have revealed that it is acid labile and sensitive to light and heat (Wallmark and Lindberg, 1987), suggesting the possible

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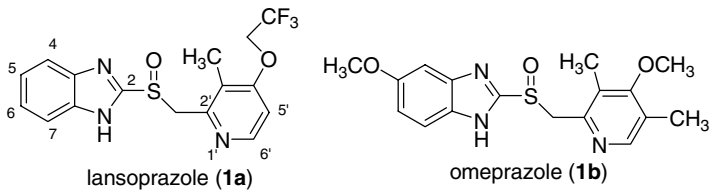


Fig. 1. Drug structures.

formation of degradation products. Indeed some problems have been observed in the establishment of the analysis of the pharmaceuticals and corresponding impurities (Castro et al., 1999; El-Kousy and Bebawy, 1999; Karljikovic-Rajic et al., 2003). However, in these studies there is no characterization of the degradation products.

2. Material and methods

2.1. Chemicals

Lanzoprazole (**1a**) and omeprazole (**1b**) were obtained from (Sigma) and used as received. All the other chemicals have been purchased from Aldrich.

2.2. Equipment and methods

Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz for [^{1}H] and 125 MHz for [^{13}C] on a Fourier Transform NMR Varian 500 Unity Inova spectrometer. Carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^{1}H–^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences.

Electronic impact mass spectra (EI-MS) were obtained with a HP 6890 spectrometer equipped with a MS 5973 N detector. Infrared spectra (IR) were determined on a Fourier Transform Infrared Perkin–Elmer 1740 spectrometer in $CHCl_3$ solutions (0.025 M). Ultraviolet spectra (UV) were recorded in ethanol (10^{-4} M) on a Perkin–Elmer LAMBDA 7 spectrophotometer. Irradiation experiments were performed with a 150 W solar simulator equipped with a Xenon lamp. The lamp had a spectral output 200–2.400 nm and an irradiance at 0.5 m higher than 10 mW m^{-2} nm^{-1}; a filter was used to simulate irradiation at the earth surface (Oriel Instruments).

2.3. Experimental procedure

Dispersions were prepared by suspending the drug (40 mg) in milliQ water (500 ml). Experiments at pH 7.1 were carried out using the same concentration in pure water, buffered with NaH_2PO_4/Na_2HPO_4, and at pH 4.0 or 9.0 by adjusting the pH values using HCl 2 M or KOH 2 M, respectively.

In a typical procedure, each dispersion of the drug was kept in the dark or irradiated at room temperature (in the latter case, the sample was irradiated from the top and maintained in a thermostated pyrex beaker). The water was then evaporated, and the residue was first analyzed by ^{1}H NMR and then chromatographed by TLC with Merck Kieselgel 60 F_{254} plates with 1 mm film thickness. The dispersions investigated at pH 4.0 or 9.0 were neutralized before water evaporation.

Experiments in the presence of humic acids (5 ppm) and KNO_3 (10 ppm) were carried out using the same concentration of the drug and then analyzing the mixture in the dark or by irradiation as above.

Experiments were carried out using the same concentration of the drug in closed pyrex tube after saturating with oxygen or argon and then analyzing the mixture in the dark or by irradiation, as above.

2.3.1. Hydrolysis products isolation

The dispersion of lansoprazole (40 mg) in water milliQ (500 ml), kept in the dark for 72 h, led, after evaporation of water, to a red-coloured residue (30 mg). The latter was chromatographed on preparative TLC [$CH_2Cl_2/(CH_3)_2CO$ (9:1)] affording sulfide **2a** (10%), lansoprazole (**1a**) (57%), a red fraction (17%) and benzimidazolone **3a** (3%) at decreasing R_fs.

The dispersion of omeprazole (**1b**), kept in the dark for 43 h, led, after water evaporation, to an intense red-coloured residue which was separated on preparative TLC [CH_2Cl_2/CH_3OH (95:5)], giving compound **2b** (25%), omeprazole (20%), an intractable red fraction (15%) and compound **3b** (10%), at decreasing R_fs.

The red fractions deriving from both drugs consisted of diverse products (TLC and ^{1}H NMR, data not shown). Attempts to separate and/or characterize the red materials failed due to their alteration over time or during chromatographic processes.

2.3.2. Photoproducts isolation

The dispersion of lansoprazole (40 mg) in milliQ water (500 ml), irradiated by solar simulator for 72 h, after water evaporation, gave a residue (38 mg) which was purified on preparative TLC [$CHCl_3/CH_3OH$ (95:5)] giving sulfide **2a** (10%), dianiline **5a** (8%), fraction

A (16 mg), a red fraction (15%), benzimidazole **4a** (5%) and benzimidazolone **3a** (5%) at decreasing R_fs. Fraction A (16 mg) was purified on preparative TLC [CH_2Cl_2/CH_3OH (97:3)] giving dianiline **5a** (11%), pyridine **6a** (5%), lansoprazole (24%) at decreasing R_fs.

A suspension of omeprazole (80 ppm) in water milliQ was exposed to the solar simulator for 43 h. After evaporation of water, the residue (25 mg) was chromatographed on TLC [CH_2Cl_2/CH_3OH (95:5)] leading, at decreasing R_fs, to dianiline **5b** (10%), sulfide **2b** (16%), benzimidazolone **3b** (20%), pyridine **6b** (traces, <1%) benzimidazolone **4b** (traces, <1%) and a red fraction (20%).

2.4. Photostability of derivatives 2, 3, and 4

Suspensions of benzimidazoles **3a**, **4a**, **3b** and **4b** (10 ppm) in MilliQ water were exposed to the solar simulator for 72 or 43 h. Each experiment was performed in duplicate, with one set of dark controls. Each reaction mixture was evaporated in vacuum and each residue was analysed by ^{1}H NMR and TLC showing only the starting material.

When sulfides **2a** and **2b** were treated in the same way, analysis of dark samples showed only starting materials, while by irradiation they led to a mixture of products. The mixture from **2a** (8 mg) was subjected to preparative TLC [CH_2Cl_2/CH_3OH (93:7)] affording dianiline **5a** (30%) and benzimidazole **4a** (38%). The mixture (7 mg) deriving from irradiation of **2b** was subjected to preparative TLC [CH_2Cl_2/CH_3OH (93:7)] giving dianiline **5b** (43%) and benzimidazole **4b** (28%).

2.5. Products characterization

Compounds **3a** and **4a** were identified by comparing spectral data with those of commercial samples (from Aldrich). Compounds **4b** and **6b** were identified by ^{1}H NMR and LC-MS due to their low amounts.

Compound **2a**: EIMS *m/z* 353 $[M]^+$; IR ($CHCl_3$): ν_{max}3100 (NH), 1581 (C=N), 1168 (CF_3) cm^{-1}; UV λ_{max} 208, 292 nm; ^{1}H NMR: δ (CD_3OD) 8.27 (1H, d, $J = 5.6$ Hz, H-6′), 7.50 (2H, br s, H-4, H-7), 7.22 (2H, m, H-5, H-6), 7.02 (1H, d, $J = 5.6$ Hz, H-5′), 4.70 (2H, q, $J = 8.4$, CH_2CF_3), 4.59 (2H, s, CH_2S), 2.29 (3H, s, CH_3). ^{13}C NMR: δ (CD_3OD) 163.0 (C-4′), 155.5 (C-2′), 149.4 (C-6′), 147.5 (C-2), 139.8 (C-8, C-9), 122.1 (C-5, C-6), 123.0 (C-3′), 122.0 (CF_3), 113.0 (C-4, C-7), 106.4 (C-5′), 64.8 (CH_2CF_3), 36.1 (CH_2S), 9.3 (CH_3).

Compound **6a**: EIMS *m/z* 221 $[M]^+$; IR ($CHCl_3$): ν_{max} 3357 (OH), 1592 (C=N), 1170 (CF_3) cm^{-1}; ^{1}H NMR: δ (CD_3OD) 8.33 (1H, d, $J = 5.5$ Hz, H-6′), 7.06 (1H, d, $J = 5.5$ Hz, H-5′), 4.82 (2H, q, $J = 8.4$, CH_2CF_3), 4.62 (2H, s, CH_2OH), 2.13 (3H, s, CH_3). ^{13}C NMR: δ (CD_3OD) 164.2 (C-4′), 160.3 (C-2′), 148.7 (C-6′), 122.6 (C-3′), 120.0 (CF_3), 108.3 (C-5′), 67.2 (OCH_2), 64.5 (CH_2OH), 10.3 (CH_3).

Compound **2b**: EIMS *m/z* 329 $[M]^+$; IR ($CHCl_3$): ν_{max} 3100 (NH), 1591 (C=N), cm^{-1}; UV λ_{max} 214, 300 nm; ^{1}H NMR: δ (CD_3OD) 8.13 (1H, s, H-6′), 7.38 (1H, d, $J = 8.8$, H-7), 7.00 (1H, d, $J = 2.4$, H-4), 6.81 (1H, dd, $J = 8.8$, 2.4 Hz, H-6), 4.54 (2H, s, CH_2S), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 2.24 (3H, s, CH_3), 2.22 (3H, s, CH_3). ^{13}C NMR: δ (CD_3OD) 166.4 (C-4′), 158.1 (C-5), 155.6 (C-2′), 149.8 (C-6′), 150.3 (C-2), 140.8 (C-9), 135.0 (C-8), 127.7 (C-3′), 127.3 (C-5′), 116.1 (C-4), 113.1 (C-6), 97.8 (C-7), 60.6 (OCH_3), 56.2 (OCH_3), 37.8 (CH_2S), 13.4 (CH_3), 11.3 (CH_3).

Compound **3b**: EIMS *m/z* 164 $[M]^+$; IR ($CHCl_3$): ν_{max} 3140 (NH), 1720 (C=O) cm^{-1}; ^{1}H NMR: δ (CD_3OD) 6.92 (1H, d, $J = 8.0$, H-7), 6.66 (1H, d, $J = 2.5$, H-4), 6.63 (1H, dd, $J = 8.5$, 2.5 Hz, H-6), 3.77 (3H, s, OCH_3). ^{13}C NMR: δ (CD_3OD) 158.4 (C-2), 157.0 (C-5), 131.6 (C-9), 124.7 (C-8), 110.7 (C-7), 108.6 (C-6), 96.9 (C-4), 56.2 (OCH_3).

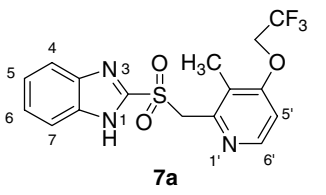
Compound **4b**: EIMS *m/z* 148 $[M]^+$; ^{1}H NMR: δ (CD_3OD) 8.04 (1H, s, H-2), 7.47 (1H, d, $J = 9.0$, H-7), 7.09 (1H, br s, H-4), 6.90 (1H, dd, $J = 9.0$, 2.5 Hz, H-6), 3.83 (3H, s, OCH_3).

Compound **5b**: EIMS *m/z* 138 $[M]^+$; IR ($CHCl_3$): ν_{max} 3290 and 3195 (NH_2 stretching), 1626 (NH_2 bending) cm^{-1}; ^{1}H NMR: δ (CD_3OD) 7.08 (1H, d, $J = 9.4$, H-6), 6.78 (2H, m, H-2, H-5), 3.79 (3H, s, OCH_3). ^{13}C NMR: δ (CD_3OD) 157.1 (C-1), 133.4 (C-3), 126.7 (C-4), 110.5 (C-6), 110.2 (C-5), 94.7 (C-2), 55.1 (OCH_3).

Compound **6b**: EIMS *m/z* 167 $[M]^+$; ^{1}H NMR: δ (CD_3OD) 8.14 (1H, s, H-6), 4.66 (2H, s, CH_2O), 3.80 (3H, s, OCH_3), 2.29 (3H, s, CH_3), 2.26 (3H, s, CH_3).

2.6. Synthesis of 2-((4-(2,2,2-trifluoroethoxy)-3-methylpyridin-2-yl)methylsulfonyl)-1H-benzo[d]imidazole (7a) (Fig. 2)

To a solution of compound **1a** (18 mg) in anhydrous dichloromethane (0.02 M), *m*-chloroperbenzoic acid (1 equiv.) was added and the resulting mixture kept at room temperature under magnetic stirring. After two hours, TLC showed that compound **1a** disappeared. Then, the mixture was washed with water and anhydrified with Na_2SO_4. After filtration and evaporation of dichloromethane, the sulfone **7a** was purified by TLC



7a

Fig. 2. Sulfone **7a** structure.

(eluent CH_2Cl_2/methanol 96:4): 64%; EIMS *m/z* 385 $[M]^+$; IR ($CHCl_3$): ν_{max} 3198 (NH), 1581 (C=N), 1341 (SO_2), 1172 (CF_3), 1144 (SO_2) cm^{-1}; ^1H NMR: δ ($CDCl_3$) 8.27 (1H, d, $J = 5.3$ Hz, H-6′), 7.65 (2H, br s, H-4, H-7), 7.37 (2H, m, H-5, H-6), 6.68 (1H, d, $J = 5.3$ Hz, H-5′), 5.10 (2H, s, SO_2CH_2), 4.37 (2H, q, $J = 8.4$, CH_2CF_3), 2.35 (3H, s, CH_3). ^{13}C NMR: δ ($CDCl_3$) 164.0 (C-4′), 162.5 (C-2′), 148.1 (C-6′), 147.5 (C-2), 147.3 (C-8, C-9), 128.1 (C-5, C-6), 125.4 (C-3′), 125.3 (CF_3), 115.0 (C-4, C-7), 106.5 (C-5′), 65.3 (CH_2CF_3), 60.2 (CH_2SO_2), 11.4 (CH_3).

When the sulfone was dispersed in milliQ water and kept in the dark, analysis by TLC and ^1H NMR after 72 h showed the sulfone unchanged.

3. Results and discussion

The drugs have been dispersed in water and kept in the dark or irradiated with a solar simulator. Table 1 reports all the experimental conditions used and the results of the most significant tests. The reaction mixtures were analyzed by NMR spectroscopy indicating the presence of different degradation products. Percentage yields of products were evaluated by chromatography of each mixture. The products (Scheme 1) were identified by their spectroscopic features and/or by comparison with authentic samples. Both lansoprazole and omeprazole were unstable in water decomposing in about 40% and 80%.

Sulfides **2** and benzimidazolones **3** and a red-coloured mixture were isolated from the mixtures. Unfortunately, attempts to characterize the red material failed due to its complexity and changeable nature. However, the presence of diverse and labile substances in the degradation of these drugs has been previously reported (Brandstrom et al., 1989). Probably, this red material consists of a mixture of degradation products very labile and particularly sensitive to silica. Experiments conducted at different pHs indicated that degradation was accelerated in acid conditions, while according to previous results by Lagerström and Persson (1984) the drugs were quite stable at pH 9.0 or 7.0.

Degradation is accelerated by light (**1a** and **1b** exhibit absorption bands at λ_{max} 292 and 300 nm, respectively). After 72 h in milliQ water, lansoprazole was present only for 24% while after 43 h omeprazole was completely degraded. The photoinduced degradation is particularly evidenced if one compares the results at buffered pH 7.0 with those at the same conditions in the dark where the drugs are stable. Photodegradation was not affected by the presence of humic acids or nitrate, which are often found to act as photosensitizers (Zepp et al., 1985, 1987), indeed the same products in the same yields were obtained by irradiating the drugs in the presence of these additives.

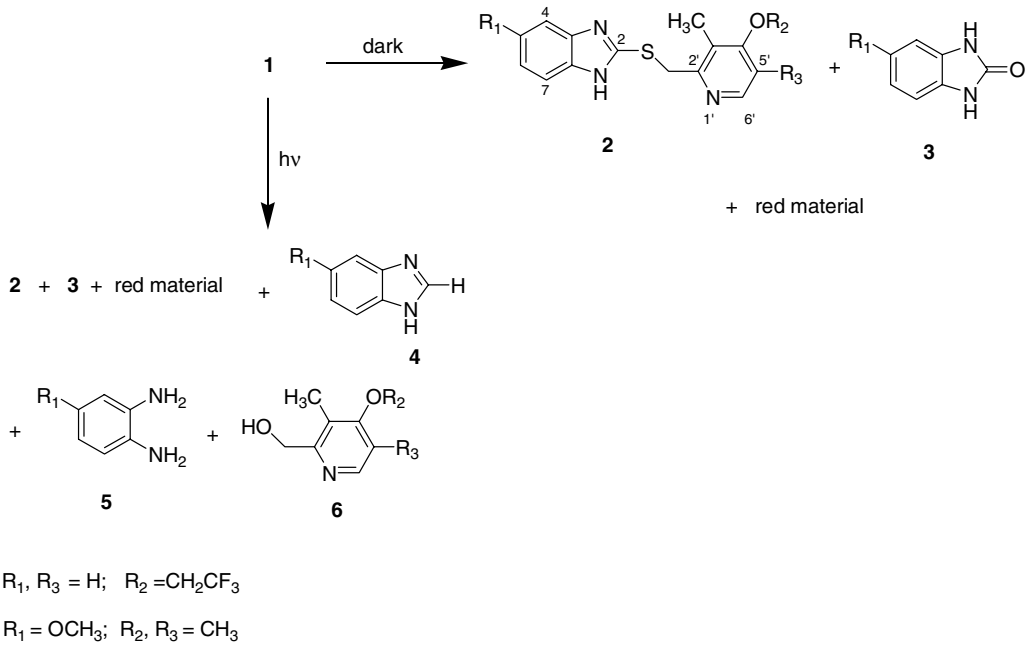
Product distribution either by hydrolysis or irradiation appeared not to be affected under argon-saturated conditions.

Control experiments showed that sulfides **2a** and **2b** were stable to hydrolysis while by irradiation they led to dianilines **5** and benzimidazoles **4** almost quantitatively, as expected, due to the absorption bands at λ_{max} 292 and 300 nm similar to those of the respective parent

Table 1
Photolysis and hydrolysis of lansoprazole (**1a**)[a] and omeprazole (**1b**)[b] in different conditions

Drug[c]	Products (%)[d]							
	Condition	**1a**	**2a**	**3a**	Red material	**4a**	**5a**	**6a**
1a	Light[e]	24	10	5	15	5	19	5
1a	Dark	57	10	3	17	–	–	–
1a	pH 7.0/light[e]	22	5	8	8	5	19	3
1a	pH 7.0/dark	100	–	–	–	–	–	–
1a	pH 4.0/dark	50	20	5	15	–	–	–
1a	pH 9.0/dark	100	–	–	–	–	–	–
		1b	**2b**	**3b**	Red material	**4b**	**5b**	**6b**
1b	Light[e]	–	16	20	20	<1	10	<1
1b	Dark	20	25	10	15	–	–	–
1b	pH 7.0/light[e]	5	12	20	15	<1	16	<1
1b	pH 7.0/dark	100	–	–	–	–	–	–
1b	pH 4.0/dark	–	50	28	14	–	–	–
1b	pH 9.0/dark	100	–	–	–	–	–	–

[a] Reaction time 72 h.
[b] Reaction time 43 h.
[c] 40 mg in 500 ml of milliQ water.
[d] By TLC.
[e] By a solar simulator.



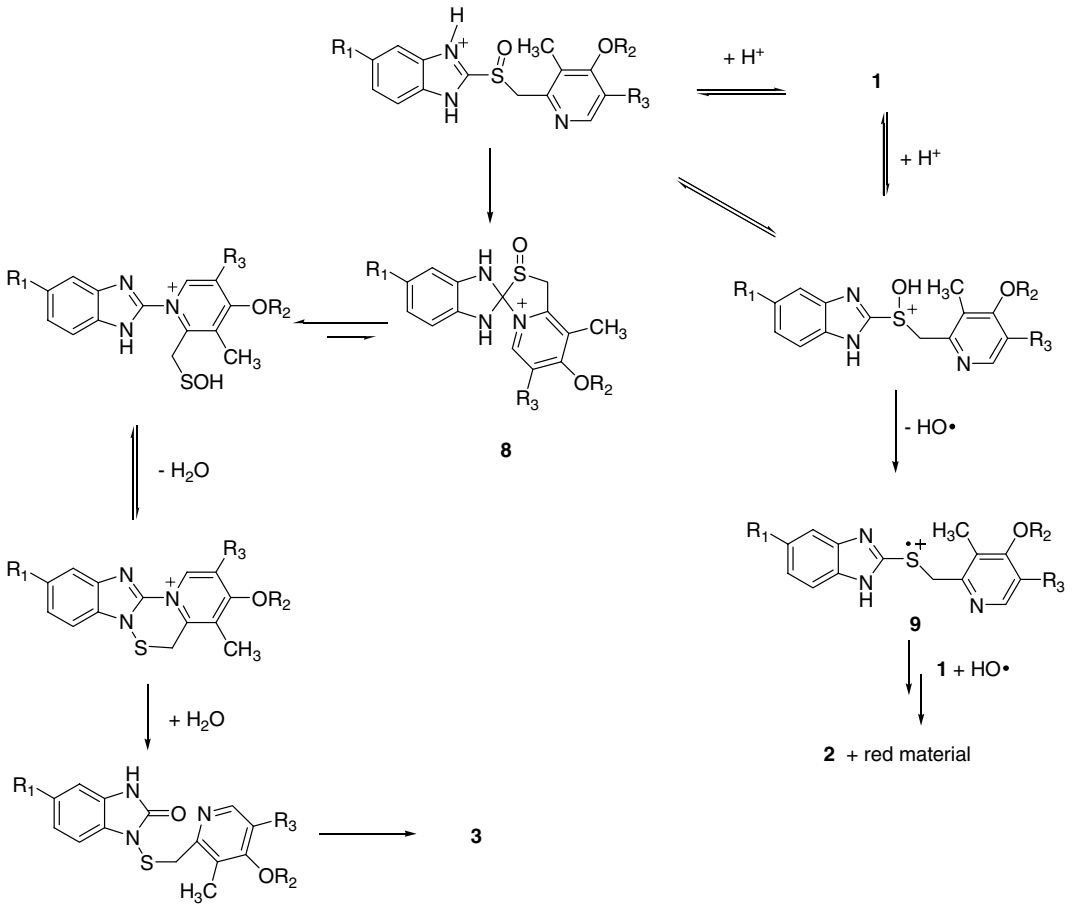
Scheme 1. Isolated degradation products from drugs **1** in aqueous suspension.

drugs. In contrast, benzimidazoles **4** and benzimidazolones **3** resulted stable both to hydrolysis and to photolysis.

As shown in Table 1, dark degradation is significant, leading mainly to sulfides **2**. A possible pathway is reported in Scheme 2 and is based on the literature data. Sulfides **2** have been evidenced mainly under physiological pH in the presence of thiols in a model for studying the mechanism of (H^+–K^+)-ATPase inhibition by sulfoxides (Im et al., 1985; Sturm et al., 1987; Brandstrom et al., 1989). Their formation was explained by assuming that the sulfoxides rearrange in acidic media to a spirointermediate **8** which through subsequent steps, involving reaction with thiols, leads to the sulfides, which contain the original molecular backbone (Lindberg et al., 1986). In our case, the formation of sulfides cannot be easily justified in this way, while benzimidazolones **3** could be formed by hydrolysis of spirointermediate **8** due to the easy N–S bond breakage (Umetsu et al., 1980). Another pathway is possible for formation of sulfides **2**. It is reported that aromatic sulfoxides are fragmented and/or reduced via cations or radical cations as **9** and the conversion which may be slow if the acid is weak, occurs more easily with heterocyclic compounds (Shine, 1967). So, the alteration of drugs **1** might be due to the mild acid medium (initially measured ca. pH 5.0) as foreseen on the basis of the pK_as at 3.83 for **1a** and 4.06 for **1b** (Shin et al., 2004). Therefore, it is likely that protonation leads to radical cation **9** and OH radical formation which might trigger oxidation reactions, presumably on the aromatic groups of the drugs, leading to sulfides **2** and the red material. This hypothesis agrees with recent studies which have evidenced the anti-oxidant role of lansoprazole and omeprazole as OH-radical scavengers during ulceration in addition to their acting as proton pump inhibitors (Biswas et al., 2003). The authors identified only sulfones among four oxidation products formed by incubation of the drug with Cu^{2+}-ascorbate system. In our experiments no sulfone was detected. This was evidenced by control experiments showing that sulfone **7a** (ad hoc prepared) was found to be stable in dark conditions. The faster degradation of omeprazole might be due to the presence of activating groups such as 5-OMe or Me on the pyridinium moiety which should favor the oxidation.

When irradiated, the degradation of both drugs is accelerated. The identified products are benzimidazoles **4**, dianilines **5** and pyridines **6** in addition to sulphides **2**, benzimidazolones **3** and the red material. By irradiation, the excited drug undergoes a series of fragmentations which are difficult to rationalize due to the low concentration of other unidentified products and low mass balance. It has been ascertained that photodegradation does not involve oxygen. So, compounds **6** might form by decomposition of an unstable sulfenate intermediate (Still, 1988; Hogg, 1990).

Compounds **4** and **5** might form via simple homolytic benzimidazole–sulfoxide and/or -sulfide bond cleavage (Still, 1988) or photoinduced water addition to the benzimidazole moiety.



Scheme 2. Mechanistic hypothesis for hydrolysis products.

4. Conclusion

The work reports the chemical and photochemical behaviour of lanzoprazole and omeprazole in the aquatic environment. Both drugs result stable enough at pH 7.0 or higher while mild acid medium or solar light induce significant degradation, so justifying the difficulty of their determination (Karljikovic-Rajic et al., 2003). Redox reactions and fragmentations are mainly involved and do not require oxygen. This aspect is of particular interest and fits in with recent observations that these drugs act as both proton pump inhibitors (Horn, 2000) and as anti-oxidant and anti-apoptotic agents (Biswas et al., 2003).

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