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Photophysics and photochemical oxidation of yohimbine in moderately concentrated sulfuric acid methanol–water media

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Abstract

In the present paper, we have examined the photophysics and the photochemical oxidation of the indole alkaloid yohimbine in moderately concentrated sulfuric acid methanol–water media. The primary photophysical processes of yohimbine resemble those of indole. The differences can mainly be attributed to the presence of its exocyclic piperidinic ring. In the presence of light, the acid solutions of yohimbine are sensitive to atmospheric oxygen and they oxidize to give 3,4-dehydroyohimbine. The disappearance of yohimbine and the formation of dehydroyohimbine follow first order kinetics whose rate constants increase linearly with the concentration of acid and with the intensity of the exciting radiation. A two-step mechanism is proposed for this photochemical reaction. In the first step, excited yohimbine reacts with ground state oxygen to give hydroperoxoindolenine. This intermediate slowly rearranges in a second acid catalyzed step to yield 3,4-dehydroyohimbine.

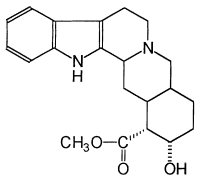
Keywords: Yohimbine; 3,4-Dehydroyohimbine; Photophysics; Photo-oxidation; Kinetics

1. Introduction

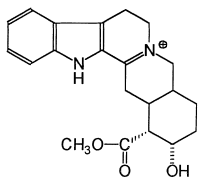
The Rauwolfia alkaloid yohimbine (**Y)** [1], is an adrenoceptor blocking agent acting selectively at α_2-receptors [2,3]. This alkaloid has been medically used in the treatment of angina pectoris and arteriosclerosis and as a veterinary aphrodisiac. Yohimbine has been also employed in the pharmacological treatment of impotence in men, but with questionable results [4,5].

Because **Y** contains in its basic structure the indolic ring [1], it possesses physicochemical properties similar to those observed in simplest indoles. Nevertheless, as in the case of other Rauwolfia alkaloids, such as reserpine [1], the presence of the piperidinic ring in these molecules confers them a distinctive behaviour. Thus, although Rauwolfia alkaloids oxidize to give reaction products structurally similar to those reported for other indolic compounds [6,7], they can also be oxidized to their partially or totally aromatized derivatives. These last oxidation reactions have a special interest because, apart from being specific of these alkaloids, they can be used for their quantitative determination.

Interestingly, while in the chemical oxidation of **Y** by different oxidizing agents in acid media, its partially aromatized derivative 3,4-dehydroyohimbine (**DH)**, has been reported as one of the oxidation products [8–11],



Yohimbine (Y)



3,4-dehydroyohimbine (DH)

this compound has never been found in its photosensitized oxidation [6]. This could be so, because the photochemical oxidation was carried out in nonacidic media and it is now well known that, at least in the chemical oxidation, an acid media is needed for **DH** to be formed [8,12]. In fact, to our experience, **DH** is an usual photo-oxidation product of the acid aqueous yohimbine solutions longstanding at the laboratory daylight. The appearance of **DH** in these aged solutions of **Y** is clearly recognizable by the presence of an absorption band at 350 nm in their UV–Vis spectra and by the intense emission at 435 nm in their fluorescence spectra [13]. Moreover, this type of dehydro derivative is a well

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known photo-oxidation product of the structurally related alkaloid reserpine [7,14].

Thus, to ascertain the factors that favour the formation of **DH** as the photo-oxidation product of **Y**, in this paper we have carried out a study of the direct photochemical oxidation of **Y** into **DH**. We have analyzed the influence that factors such as acidity, presence of oxygen, irradiation wavelength and irradiation intensity have on this reaction. To complement partial studies carried out previously by us and other authors [15,16] on the spectroscopic properties of this compound, we have also systematically examined the UV–Vis absorption, fluorescence and phosphorescence spectra of **Y** in neutral and acidic methanol–water solutions.

2. Experimental

2.1. Chemicals

Yohimbine (**Y)** 98% was purchased from Sigma–Aldrich Quimica and was used as received. Methanol–water 40% v/v solutions of **Y** were freshly prepared and stored in the dark. Perchloric and sulfuric acid solutions were prepared by dilution with distilled water of reagent grade concentrated acids. Appropriate mixtures of boric acid (0.1 M) and sodium hydroxide (0.1 M) were used as buffers. The pH values were measured in a Radiometer Copenhagen pHM82 standard pH meter.

2.2. Spectral measurements

Absorbances were measured on a Perkin-Elmer Lambda-5 spectrophotometer equipped with thermostatted cell holders. Steady state fluorescence or phosphorescence emission and excitation measurements were made in a Perkin-Elmer 650-40 spectrofluorometer equipped with a phosphorescence accessory Perkin Elmer 650-0175 for recording the phosphorescence spectra and phosphorescence decays. The emission spectra were corrected by using a Perkin Elmer Data Processor 650-0178 (Rhodamine as quantum counter). All the spectra were obtained in 1 cm quartz cells at $25.0 \pm 0.1^{\circ}$C. Sample absorbances for fluorescence measurements were adjusted to <0.1 at the corresponding excitation wavelengths to avoid inner filter effects and reabsorption phenomena.

Absolute fluorescence quantum yields, ϕ, were determined at 280 nm excitation wavelength by comparison of the corrected emission spectra with the spectrum of tryptophan. Sample quantum yields were calculated by using a value of 0.14 for tryptophan [17], in phosphate buffered solutions of pH = 7, and by means of Eq. (1),

$$\phi_x = \frac{D_x}{D_r}\frac{A_r(\lambda_r)}{A_x(\lambda_x)}\phi_r \quad (1)$$

where the subscripts r and x refer to the reference and unknown solutions respectively, ϕ is the quantum yield, $A(\lambda)$ is the absorbance per centimetre of the solution at the excitation wavelength and D is the integrated area under the corrected fluorescence spectra.

Fluorescence decays were collected by time correlated single photon counting on a FL-900CD Edinburg Analytical Instrument. The excitation source was a nanosecond nF900 flash lamp filled with H_2, 0.4 bar, and operating at 40 kHz with ~6 kV applied across 1 mm electrode gap. Fluorescence decays from the samples were acquired from 1×10^4 to 1.5×10^4 counts in the peak. Fluorescence decay data were fitted by reference deconvolution to a sum of exponentials. Goodness of the individual fits was judged by the magnitude of the reduced χ_r^2 and the shape of the autocorrelation function of the weighted residuals. To analyze the lifetime data at different pH, a global analysis program based on the Marquardt algorithm was used [18].

2.3. Photochemical studies

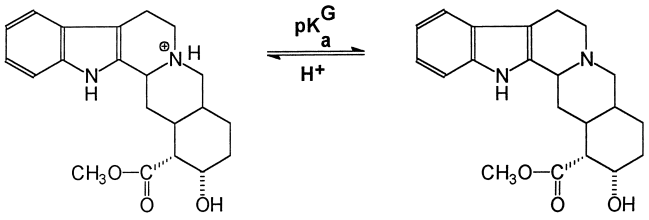
The source of irradiation for the photochemical studies was the 250 W Hamamatsu xenon lamp of our spectrofluorometric system. As photoreactor we used a micro quartz cell Hellma (model 75.050). The small volume of the cell ensured the total irradiation of the solutions and minimized the problems derived from the diffusion of the reagents. The solutions of **Y** were placed in the cell holder of the spectrofluorimeter and their fluorescence spectra were recorded periodically to analyze the evolution of the reaction mixture with time. The high absorbances of the solutions used in the photochemical experiments ensured the total absorption of the incident light.

The light intensity of the irradiation was varied by changing the slit of the excitation monochromator and it was evaluated with an actinometer of potassium ferrioxalate [19]. The actinometer solution was irradiated before and after the irradiation of the sample for an appropriate time(≈30 min). Usually, during the time of irradiation, about 2–4 h, the intensity of the lamp remained practically constant. However, when meaningful drifts in the lamp intensity were observed, the experimental measurements were rejected. All the kinetic experiments were carried out under temperature controlled conditions at $25 \pm 0.1^{\circ}$C. Always, the measured rate constants, at fixed oxygen and proton concentrations, were the same over a range of **Y** concentrations.

3. Results and discussion

3.1. Absorption and emission electronic spectra of yohimbine

Owing to the basic properties of its piperidinic nitrogen atom, **Y** can exist in aqueous solutions as neutral or cationic species (Scheme 1). In 40% v/v methanol–aqueous solutions, the spectrum of the cationic species is characterized by



Scheme 1.

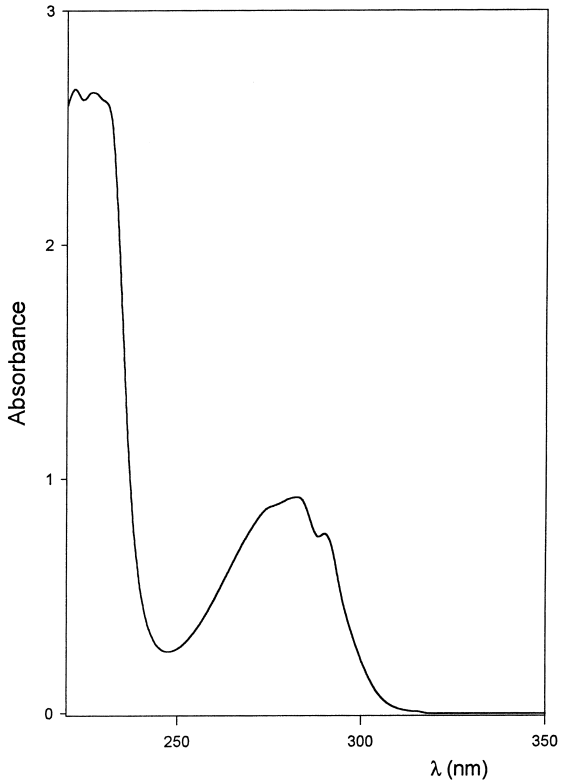


Fig. 1. Absorption spectrum of yohimbine in 40% v/v methanol–water solutions.

a weakly structured band with a maximum absorption in the 270–290 nm region (Fig. 1). This band embodies the spectral characteristics of the indole chromophore [20]. Piperidinic ring has only a minor effect on the indole chromophore of **Y**. Thus, by analogy with the parent indole, this band can be assigned to the two overlapping π–π transitions $^1L_a \leftarrow {}^1A$ and $^1L_b \leftarrow {}^1A$. Otherwise, by changing the pH conditions so that the absorbing species are the neutral species an almost unappreciable red shift and a decrease in the vibrational structure are observed. This shows that the protonation of the piperidinic nitrogen atom does not affect the energies of the electronic states responsible for absorption.

The changes with the pH of the fluorescence spectrum of **Y** are shown in Fig. 2. The individual emissions of the cationic and neutral species can be observed below pH = 7 and above pH = 10, respectively. Outside the pH range, we have previously reported the very weak fluorescence

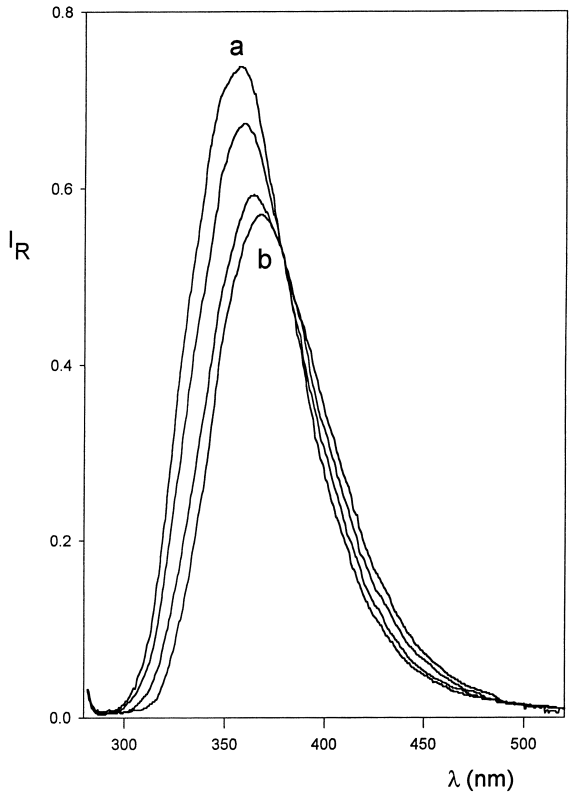


Fig. 2. Changes in the fluorescence spectra of yohimbine on increasing pH from 7 (a) to 10 (b).

emissions of the pyrrolic deprotonated anions, [21], and the pyrrolic protonated dications [22].

The steady-state fluorescence emission spectra of the neutral and cationic species are broad and featureless. The emission maximum occurs at 369 nm in the neutral species ($\phi = 0.29$), shifting to 356 nm in the cation ($\phi = 0.38$). Singlet excited neutral and cationic species decay monoexponentially at 298 K with lifetimes of 4.6 and 6.0 ns, respectively. Desoxygenation of the solutions has very little effect on the fluorescence quantum yields and the fluorescence lifetimes.

In the protonation region (pH values between 7 and 10), the fluorescence of **Y** decays biexponentially with lifetimes practically independent of pH and very close to that of the neutral and cationic species. These decay curves were globally fitted to the biexponential equation

$$I(t) = A_C \exp\left(\frac{-t}{\tau_C}\right) + A_N \exp\left(\frac{-t}{\tau_N}\right) \quad (2)$$

where τ_C and τ_N are the lifetimes of the cationic, 6.0 ns, and neutral, 4.6 ns, species respectively, and A_C and A_N stand for the corresponding amplitudes. Data in Table 1 show that these amplitudes are pH dependent. Thus, the contribution of the cationic component to the total fluorescence, A_C, decreases and that of the neutral component, A_N, increases with the increase of the pH. This behaviour, already observed for the related compound tetrahydroharmane [16], indicates that the excited state proton transfer rates are slow compared

Table 1
Global analysis of the fluorescence decay curves to Eq. (2) of 40% methanol–water buffered solutions of yohimbine at different pH

pH	A_C	A_N	χ^2	χ^2_g
7.50	0.059	0.007	1.176	1.108
7.73	0.055	0.012	1.086	
7.84	0.052	0.014	1.058	
8.27	0.047	0.020	0.883	
8.85	0.043	0.024	0.937	
9.65	0.038	0.031	0.966	

with fluorescence emission: i.e. the prototropic equilibrium is not established within the lifetime of the lowest excited singlet state.

According to this model, the ground state pK_a can be directly obtained from fluorimetric titrations [23]. Because the fluorescence spectra of the acid–base pair strongly overlap, the measured fluorescence intensities of the cationic and neutral forms must be corrected for the intensity component due to the other form. The true fluorescence intensities (I_C and I'_C) are related to the measured intensities (I at 356 nm and I' at 369 nm) according to the equations [24],

$$I = I_C + k' I'_C \quad \text{and} \quad I' = I'_C + k I_C \tag{3}$$

where k and k', the overlap ratios of the cationic and neutral forms, respectively, can be obtained making measurements on solutions containing only one species in the excited state.

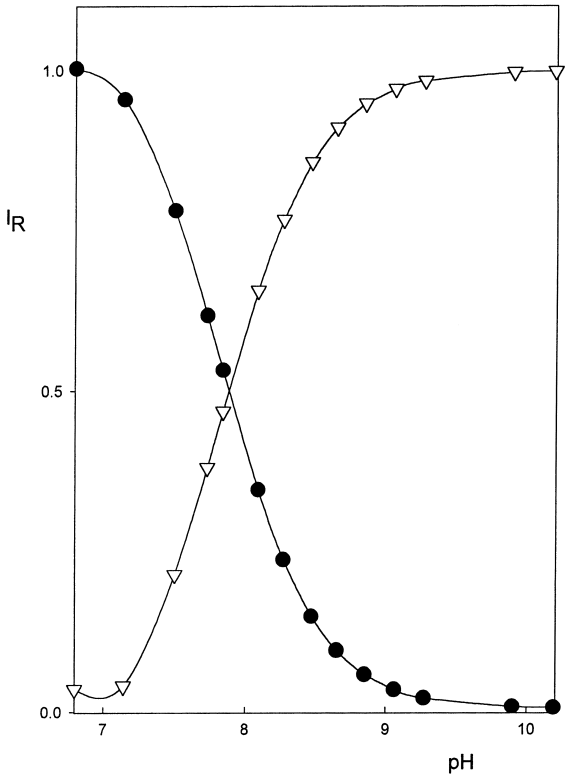


Fig. 3. pH dependence of the normalized fluorescence intensities at 356 (●) and 369 nm (▽).

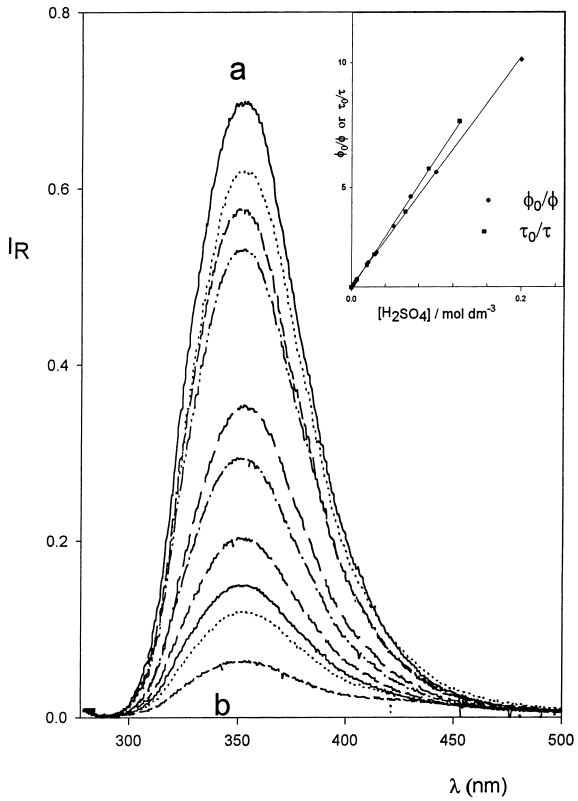


Fig. 4. Quenching of the yohimbine fluorescence by H_2SO_4: (a) $[H_2SO_4] = 0$; (b) $[H_2SO_4] = 1.8\,\text{mol dm}^{-3}$. In the inset, Stern–Volmer plots of ϕ_0/ϕ (●) and τ_0/τ (▭) vs. $[H_2SO_4]$.

Rearranging these equations we can obtain the true fluorescence intensities in terms of I and I', k and k',

$$I_C = \frac{I - k'I'}{I - kk'}, \qquad I'_C = \frac{I' - kI}{I - kk'} \tag{4}$$

The plot of the normalized intensities at 356 and 369 nm against the pH of the media is shown in Fig. 3. The two curves intercept at pH = 7.9. Therefore, this pH value can be taken as an estimate of the pK_a of **Y**. This pK_a value is, as expected from the tertiary character of the piperidinic nitrogen in **Y**, somewhat smaller than the value of 8.8 obtained for tetrahydroharmane [16].

As it is typically shown in Fig. 4, the fluorescence intensity of the cationic species is appreciably quenched in the presence of the strong acids as $HClO_4$ and H_2SO_4, albeit its absorption and excitation spectra remain unchanged. Moreover, the fluorescence spectrum is not affected when the inorganic counterion concentration is changed by the addition of Na_2SO_4 or $NaClO_4$ up to $2\,\text{mol dm}^{-3}$. This behaviour, already observed for other indole derivatives [16,25–27], has been attributed to an acid catalyzed protonation of the indole ring or to a collisional quenching by hydrogen ions in the excited state.

Although we have previously reported the formation of very weak fluorescent indoleninic dications of **Y** (λ_{em} = 440 nm) in highly concentrated sulfuric acid solutions

($18\,mol\,dm^{-3}$) [22], there are not pieces of evidences on the formation of such species in the range of acid concentration used in the present work. However, it is possible that the very weak fluorescent nature of these dications prevents its observation.

In the presence of sulfuric acid the fluorescence decay curves gave always good single exponential fits whose lifetimes decrease as the H_2SO_4 concentration increases. Again, neither SO_4^{2-} nor ClO_4^- anions have any effect on the lifetime of the cationic species. As shown in the inset of Fig. 4, the plots of ϕ_0/ϕ and τ_0/τ against $[H_2SO_4]$ (Eq. 5) are linear with slopes of $45.8 \pm 0.8\,dm^3\,mol^{-1}$ and $52 \pm 2\,dm^3\,mol^{-1}$ and intercepts at the origin of 0.99 ± 0.07 and 1.04 ± 0.1, respectively. Using $HClO_4$ instead of H_2SO_4 acid the results are entirely similar, but now the quenching constants obtained from the Stern–Volmer plots are somewhat smaller: 34.4 ± 0.6 and $33 \pm 1\,dm^3\,mol^{-1}$, respectively. Therefore, both the steady-state and time resolved fluorescence measurements show that the quenching of **Y** cations fluorescence by protons is a dynamic process. The average values for the quenching rate constants, k_q, calculated from the Stern–Volmer equation are 8.1×10^9 and $5.6 \times 10^9\,dm^3\,mol^{-1}\,s^{-1}$ in sulfuric and perchloric acids,

$$\frac{\phi_0}{\phi} = \frac{\tau_0}{\tau} = 1 + k_q \tau_0 [\text{Acid}] \quad (5)$$

respectively. These values are similar to those reported for the quenching by protons of other similarly charged indoles as tryptamine [26], $5.6 \times 10^9\,dm^3\,mol^{-1}\,s^{-1}$, and tetrahydroharmane [16], $5.9 \times 10^9\,dm^3\,mol^{-1}\,s^{-1}$.

The luminescence spectrum of **Y** in ethanol glasses at 77 K is shown in Fig. 5. It consists of fluorescence and phosphorescence emissions. As in the case of other simplest indoles, the fluorescence emission of **Y** at 77 K ($\lambda_{max} = 325$ nm) is blue shifted and intensified ($\phi = 0.43$) [15] with respect to that observed at 298 K. On the other hand, the phosphorescence emission of **Y** ($\phi = 0.05$) [15] displays well-resolved bands at 410, 437 and 464 nm characteristic of the indole nucleus [19]. In $1.8\,mol\,dm^3$ H_2SO_4 the luminiscence spectrum of **Y** is slightly blue shifted.

3.2. Photochemistry of aqueous acidic yohimbine solutions

As we have shown in the previous section, in 40% v/v methanol–water, yohimbine is protonated at the piperidinic nitrogen atom. The continuous irradiation of this solution with near-UV light leads to the photo-decomposition of the alkaloid but, as reported in earlier studies [6], the dehydroderivative, **DH**, is not formed, Fig. 6A. However, when these solutions are acidified with a strong acid such as $HClO_4$ or H_2SO_4 acids, the gradual disappearance of the fluorescence band of the cationic species at 356 nm is accompanied by the concomitant appearance of the emission band at 435 nm characteristic of **DH**, Fig. 6B. It is worth pointing out that experiments conducted in the dark or with deoxygenated solutions showed that the **Y** spectrum remains

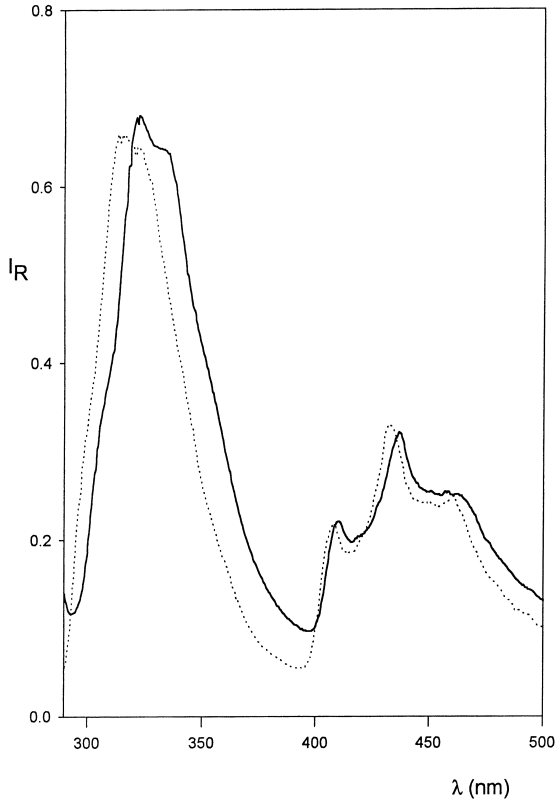


Fig. 5. Luminiscence spectra of yohimbine in ethanol glasses at 77 K. Full line $[H_2SO_4] = 0$; dotted line $[H_2SO_4] = 1.8\,mol\,dm^{-3}$.

unaffected. Therefore, apart from the acid media, both light and oxygen are necessary for this oxidation reaction.

UV–Vis absorption and TLC analysis of the irradiated solutions revealed that the yield of **DH** increases as the acidity increases. Thereby, at H_2SO_4 concentrations higher than $0.5\,mol\,dm^{-3}$, **DH** is the only photoproduct of the reaction. In these media, iodimetric titrations showed the stoichiometric formation of H_2O_2 among the reaction products being, therefore, the global reaction:

$$\mathbf{Y} + O_2 \rightarrow \mathbf{DH} + H_2O_2$$

Under these acidity conditions both, the disappearance of **Y**, k_{obs1} and the formation of **DH**, k_{obs2} follow first order kinetics whose rate constants increase linearly with the increase of acid concentration, Fig. 7. However, it must be noted that the values of k_{obs1} are always greater than those of k_{obs2}. Therefore, these kinetic processes are not coupled, i.e. **DH** is formed through a two step mechanism involving a long lived intermediate.

The rate constant for the first step, i.e. the disappearance of **Y**, k_{obs1}, also depends on the excitation wavelength. At wavelengths higher than 250 nm the reaction rates roughly correlate with the absorption molar coefficients of **Y** at the irradiation wavelengths. Thus, at those wavelengths where **Y** does not absorb, no reaction was observed. Furthermore, as Fig. 8 shows, there is a linear relationship between the

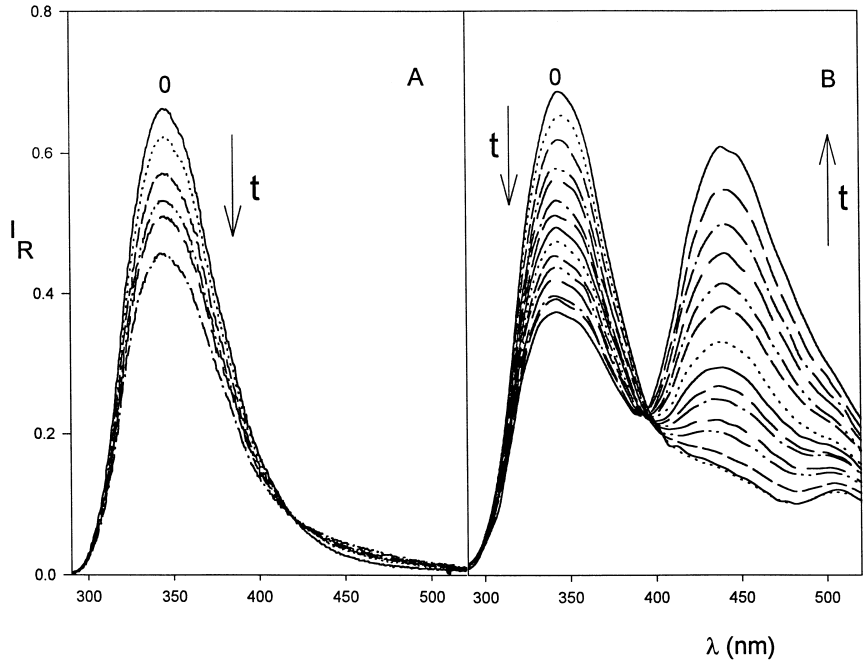


Fig. 6. Evolution with time of the fluorescence spectra of aerated 40% methanol–water solutions of yohimbine irradiated at 298 nm. (A) $[H_2SO_4] = 0$; (B) $[H_2SO_4] = 1.8\,mol\,dm^{-3}$.

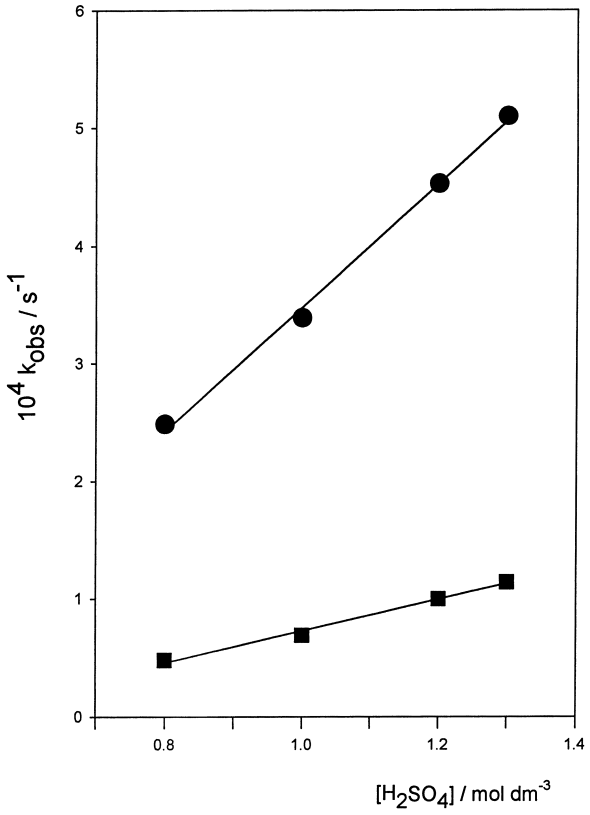


Fig. 7. Influence of $[H_2SO_4]$ on the pseudo first-order rate constants for the disappearance of yohimbine (●) and the formation of its 3,4-dehydro derivative (■). Excitation radiation 298 nm.

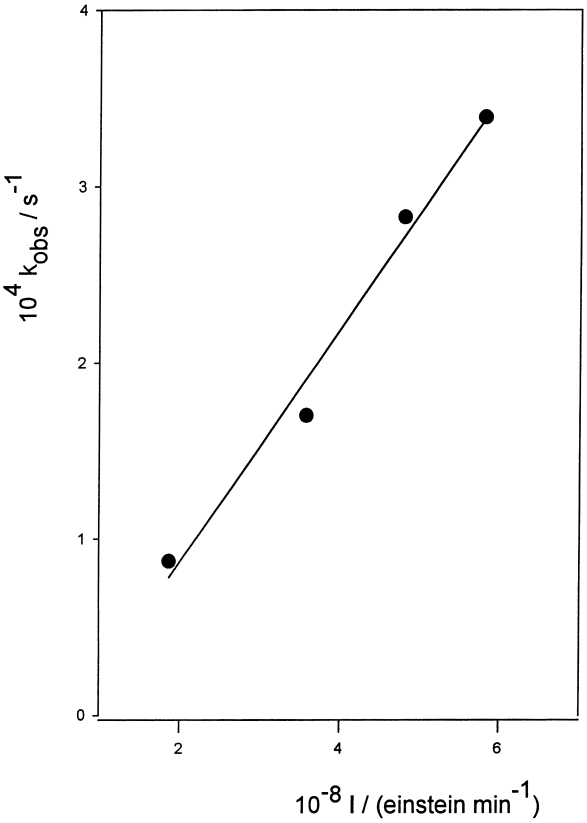


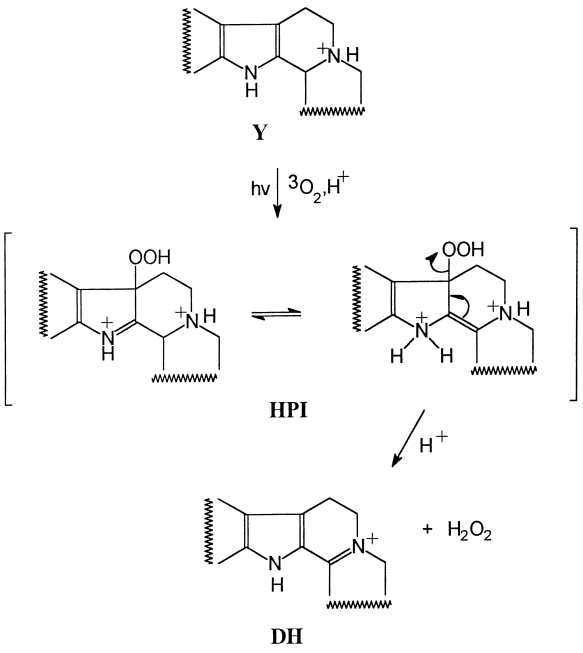
Fig. 8. Influence of the intensity of the excitating radiation at 298 nm on the pseudo-first order rate constants for the disappearance of yohimbine.

rate constant for the disappearance of **Y** and the intensity of the exciting radiation. Therefore, these results show that the oxidation of **Y** is not a thermal reaction, but it proceeds through an excited state of **Y** formed upon absorption of light.

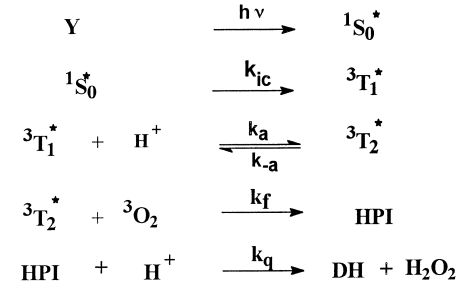
Owing to its short lifetime, it is rather improbable that the singlet excited state of **Y** could be involved in the reaction. Moreover, the quenching of **Y** singlets by O_2 must be ruled out since the fluorescence of **Y** is not appreciably quenched in aerated methanol–water solutions. It seems, therefore, more plausible that the reacting species are the triplets of **Y** or other species formed from them in the acid media where the photooxidation reaction takes place. In this context, it should be mentioned that flash photolysis experiments have shown that, upon excitation of indole and tryptophan in 1–3 mol dm^{-3} H_2SO_4 solutions, a new transient is formed [28]. Since no photoionization apparently occurred, it is believed that these transients are the triplets of their pyrrolic protonated cations. Thus, the acid dependence observed for the disappearance of **Y** probably arises from the formation of the similar triplets of **Y**.

In relation with the oxygen species involved in the oxidation reaction, it should be mentioned that the addition up to 0.5 mol dm^{-3} of sodium azide, an efficient singlet oxygen quencher, has no effect on the k_{obs1} values. Therefore, the reaction studied in this work is a Type I process. That is, molecular oxygen, $^3O_2$ reacts with the triplets of protonated **Y**, formed in an acid catalyzed step, to give a reaction intermediate.

Due to the nature of the substrate and the oxidizing agent, we assume that the reaction intermediate is the nonfluorescent 7-hydroperoxo-7H-yohimbine, **HPI (**Scheme 2). It



Scheme 2.



Scheme 3.

must be taken into account that this type of intermediate has been isolated as the primary product of the photosensitized oxidation of **Y** in neutral media [6]. The indolenine **HPI** is, on the other hand, a key intermediate in the formation of many other typical chemical and photochemical oxidation products of indoles and tetrahydrobetacarbolines, such as oxoindoles or dioxetanes [29–31].

Once this indolenine intermediate is formed, an internal reorganization step followed by acid catalyzed hydrolysis of the leaving group gives **DH**. The disappearance of this intermediate is not a photochemical process but a chemical reaction. Thus, when the samples are irradiated and subsequently the light is cut off **DH** is still being formed for a long period of time. Moreover, the nonphotochemical character of this step has already being checked for other indolenine derivatives. Thus, we have recently studied the direct transformation of two indolenines of **Y**, namely, 7-acetoxy and 7-methoxy-7H-yohimbine into **DH** [12]. Under strong acidity conditions both indolenines reorganize, in the absence of light, to give **DH** as the unique reaction product. The rate constants for these reactions depend linearly with proton concentration with slopes of $(2.3 \pm 0.6) \times 10^{-4}$ mol^{-1} dm^3 s^{-1} and $(9.1 \pm 0.6) \times 10^{-4}$ mol^{-1} dm^3 s^{-1} for acetoxy and methoxy yohimbine, respectively.

According to these results, we propose as the most probable mechanistic route for this oxidation reaction, which is shown in Scheme 3. Thus, as mentioned before, the reacting species are the triplets, $^3T_2^*$ formed, in an acid catalyzed step, from the triplets $^3T_1^*$. Applying the equilibrium condition to the formation of $^3T_2^*$ k_{obs1} can be expressed by,

$$k_{obs1} = h\nu \frac{k_a k_f}{k_{-a}} [^3O_2][H^+] \quad (6)$$

and the rate law for the formation of **DH** is given by

$$k_{obs2} = k_q[H^+] \quad (7)$$

Both equations are in agreement with the experimental results. From the k_{obs1} versus $[H^+]$ plot, a value of 1.3×10^{-4} mol^{-1} dm^3 s^{-1} can be obtained for k_q. As mentioned before, this value is in excellent agreement with those obtained for 7-acetoxy and 7-methoxy 7H-yohimbine.

We conclude that, as in the case of other Rauwolfia alkaloids such as reserpine, **Y** can be photochemically oxidized to its partially aromatized derivative. The two-step mechanism postulated for this reaction, which involves the initial formation of **HPI**, is completely similar to that proposed when **DH** is formed in a chemical oxidation. In fact, in a recent study on the oxidation of **Y** by peroxodisulfate [12], we have shown that the reaction products always come from an indolenine intermediate. In this case, due to the nature of the electrophilic agent, the intermediate postulated was 7-sulfate-7H-yohimbine. Once the indolenine is formed, it reacts via competing parallel reactions giving rise to the formation of **DH** or other oxidation products. The rates of these steps and, therefore, the yields of the different reaction products are strongly dependent on the nature and acidity of the media. Thus, **DH** is the sole chemical or photochemical reaction product only when the reactions are carried out under strong acidity conditions.

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