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Journal of Photochemistry and Photobiology B: Biology 82 (2006) 79–93

Journal of Photochemistry and Photobiology B:Biology

www.elsevier.com/locate/jphotobiol

Effect of chlorine as substituent on the photochemistry and acid–base properties of β-carboline alkaloids

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Received 7 April 2005; received in revised form 19 August 2005; accepted 19 September 2005
Available online 2 November 2005

Abstract

The UV-absorption, fluorescence excitation and emission spectra of the 6-chloro-, 8-chloro-, 6,8-dichloro-derivatives of nor-harmane, harmane and harmine and the 8-chloro-derivative of harmol were studied. These studies were performed in EtOH and in EtOH + 1% perchloric acid solutions (pa). Furthermore, fluorescence quantum yields (ϕ_f) in both media and in acetonitrile and acetonitrile + 1% perchloric acid solutions at 298 K were measured. The HOMO and LUMO energy, the positions (λ_{max}) and oscillator strength (*f*) of the $^1S_1 \leftarrow {}^1S_0$ band for all the neutral and protonated β-carbolines studied were calculated and compared with the experimental data. The pK_a values in aqueous solution for for 6-chloro-, 8-chloro- and 6,8-dichloro-nor-harmane, harmane and harmine and 8-chloro-harmol were spectrophotometrically measured (p$K_{a(H_2O)}$). The change of the acid–base character of these compounds on going from the ground state (pK_a) to the first electronic excited singlet state (pK_a^*) as $\Delta pK_a = pK_a^* - pK_a$, in ethanol solution at 298 K were calculated ($\Delta pK_{a(EtOH)}$). Ground-state proton affinity (PA) for all the compounds studied defined as minus the enthalpy change of the reaction $M + H^+ \rightarrow MH^+$ (gas state) were calculated. Basicity relative to pyridine (ΔH_{rPy}) defined as the enthalpy change of the isodesmic reaction $MH^+ + Py \rightarrow M + PyH^+$ in gas state and in water solution, were also calculated (ab initio calculations). The effect of chlorine as substituent on the photochemistry and acid–base properties of the β-carboline alkaloids is discussed.

Keywords: Chloro-β-Carbolines; Chloro-nor-harmane; Chloro-harmane; Chloro-harmine; Chloro-harmol

1. Introduction

As part of our study of the effect of halogens as substituents on the photochemistry and acid–base properties of β-carbolines alkaloids (9*H*-pyrido[3,4-*b*]indole alkaloids) [1–8] we decided to examine chloro β-carbolines. Recently, we have described the effect of bromine as substituent in β-carbolines alkaloids [8]. As it is known, for aromatic molecules halogens as substituents might induce modifications on the acid–base properties in the ground and electronic excited state and on the nature (π,π*; n,π*), multiplicity (singlet, S_1; triplet, T_1), time of life (τ_{S1}; τ_{T1}) and efficiency of population (ϕ) of the electronic excited states [9,10] without affecting much their photostability.

Since the discovery that antidepressant activity of β-carbolines is due to its high in vivo monoamine oxidase (MAO) inhibition, the preparation of different derivatives has been attempted in order to study the electronic and steric effect of different β-carboline substituent groups on the MAO, at molecular level [11]. Among other β-carboline derivatives, the effect of 6-chloro-nor-harmane was studied [11]. The synthesis of 6-chloro- and 8-chloro-nor-harmane, and 6-chloro- and 8-chloro-harmane were attempted by Nakano et al. [12], in order to study the co-mutagenicity of chlorinated-β-carbolines.

Furthermore, chloro-β-carboline alkaloids have been isolated from plant tissues. Thus, the chloro-β-carboline alkaloids called bauerines A–C have been isolated from terrestrial blue-green alga *Dichothrix baueriana* GO-25-3 [13] and its activity against herpes has been shown. These *N*-methyl-7-chloro- and *N*-methyl-7,8-dichloro-nor-harmanes

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doi:10.1016/j.jphotobiol.2005.09.001

were full synthesized as well as the 7,8-dichloro-nor-harmane [14].

As it is known cytotoxicity in vitro and in vivo can be modified by light because of photochemical and acid–base properties in the ground and electronic excited state are different. Light effect is quite critic when the compound assayed shows absorbance in the visible region ($\lambda_{max} >$ 300 nm) [15]. This aspect was not taken into account in any of the above mentioned studies because the shortage of spectroscopic data available [11–13]. Thus, to begin with our study we decided to re-examining the electronic spectroscopic properties of 6-chloro- and 8-chloro-nor-harmane and 6-chloro- and 8-choro-harmane in solution. The significant fluorescence emission detected at 298 K although the presence of a "heavy atom" as chlorine in the β-carboline moiety (Fig. 1 and Tables 1–4, **1a**–**b**, **2a**–**b**, **3a**–**b** and **4b**) induced us to extend the study to provide examples of dichloro-β-carbolines (Fig. 1 and Tables 1–4, **1c**, **2c** and **3c**). Furthermore, taking into account that in nature alkaloids are generally present in tissues in the protonated form and as is described in the present paper all the protonated chloro-β-carbolines show significant absorption in the 300–400 nm region, we also studied the electronic spectroscopic properties in ethanol + 1% perchloric acid (pa) (Tables 1–4). Fluorescence quantum yields (ϕ_f) in ethanol and ethanol + 1% perchloric (results not shown) and in acetonitrile and acetonitrile + perchloric acid 1% were measured (Table 6).

The HOMO and LUMO energy, the position (λ_{max}) and oscillator strength (*f*) of the $^1S_1 \leftarrow {}^1S_0$ band for all the neutral and protonated β-carbolines studied were also verified by quantum chemical calculations and compared with the experimental λ_{max} (Tables 5a and 5b). Furthermore, fluorescence quantum yields (ϕ_f) in acetonitrile and acetonitrile + perchloric acid 1% solution (pa) at 298 K were measured (Table 6).

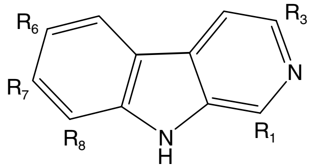
A knowledge of the acid–base properties of these compounds in ground and electronic excited state might be helpful in understanding its antivirus and/or phototoxic behaviour. Thus, the change of the acid–base character of these compounds on going from the ground state (pK_a) to the first electronic excited singlet state (pK_a^*) as $\Delta pK_a = pK_a^* - pK_a = 0.625\Delta\bar{\nu}/T$, in ethanol solution at 298 K were calculated (Table 7, $\Delta pK_{a(EtOH)}$). Besides, the pK_a values in aqueous solution were spectrophotometrically measured (Table 8, $pK_{a(H_2O)}$).

Finally, the ground-state proton affinity (PA) for all the β-carbolines studied defined as minus the enthalpy change of the reaction "β-carboline + $H^+ \rightarrow$ β-carboline protonated" (gas state), and the basicity relative to pyridine (ΔH_{rPy}) defined as the enthalpy change of the isodesmic reaction $MH^+ + Py \rightarrow M + PyH^+$, in gas state and in water solution were also calculated (Table 8).

2. Experimental

2.1. Chemicals

Nor-harmane (**1**), harmane (**2**) harmine (**3**) and harmol (**4**) were purchased from Sigma–Aldrich Chemicals Co. The chloro-derivatives **1a**–**c**, **2a**–**c**, **3a**–**c** and **4b** were synthesized according to procedures previously described



β-Carboline	R1	R7	Chloro-β-carboline	R1	R3	R6	R7	R8
1 (nor-harmane)	H	H	**1a**	H	H	Cl	H	H
			1b	H	H	H	H	Cl
			1c	H	H	Cl	H	Cl
2 (harmane)	Me	H	**2a**	Me	H	Cl	H	H
			2b	Me	H	H	H	Cl
			2c	Me	H	Cl	H	Cl
3 (harmine)	Me	MeO	**3a**	Me	H	Cl	MeO	H
			3b	Me	H	H	MeO	Cl
			3c	Me	H	Cl	MeO	Cl
4 (harmol)	Me	OH	**4b**	Me	H	H	OH	Cl

Fig. 1. Structure of the β-carbolines studied.