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# Photochemistry of the alkaloids eudistomin N (6-bromo-nor-harmane) and eudistomin O (8-bromo-nor-harmane) and other bromo-β-carbolines

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**Abstract**

The UV-absorption, fluorescence excitation and emission spectra of the alkaloids eudistomin N (6-bromo-nor-harmane) and eudistomin O (8-bromo-nor-harmane) were described. In order to perform a comparative analysis, we also studied other bromo-β-carbolines and the corresponding non-substituted-carboline. Thus, 6-bromo-, 8-bromo-, 6,8-dibromo-, 3,6-dibromo- and 3,6,8-tribromo-derivatives of nor-harmane, harmane and harmine were studied. These studies were performed in EtOH and in EtOH + 1% perchloric acid solutions (pa). Furthermore, fluorescence quantum yields ($\phi_f$) in acetonitrile and acetonitrile + 1% perchloric acid solutions at 298 K were measured. The HOMO and LUMO energy, the positions ($\lambda_{max}$) and oscillator strength (*f*) of the $^1S_1 \leftarrow {}^1S_0$ band for all the neutral and protonated β-carbolines studied was calculated and compared with the experimental data. The p$K_a$ values in aqueous solution for eudistomin N and O (6-bromo- and 8-bromo-nor-harmane), for 6-bromo-, 8-bromo- and 6,8-dibromo-harmane, and for 6-bromo- and 8-bromo-harmine were spectrophotometrically measured ($pK_{a(H_2O)}$). 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 $\Delta pK_a = pK_a^* - pK_a = 0.625\Delta\bar{\nu}/T$, in ethanol solution at 298 K were calculated ($\Delta pK_{a(EtOH)}$). Proton affinities (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 ($\Delta H_{rPy}$) defined as the enthalpy change of the isodesmic reaction $MH^+ + Py \rightarrow M + PyH^+$ (gas state) was also calculated. The effect of bromine as substituent on the properties of the β-carboline moiety in nor-harmane, harmane and harmine is discussed.

*Keywords:* Eudistomin N; Eudistomin O; Bromo-β-carbolines; Bromo-nor-harmane; Bromo-harmane; Bromo-harmine

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## 1. Introduction

As part of our study of the photochemistry of β-carboline alkaloids, we decided to examine the photochemical behavior of bromo-carboline alkaloids called eudistomins [1]. The alkaloids eudistomin N (6-bromo-nor-harmane; Fig. 1, compound **1a**) and eudistomin O (8-bromo-nor-harmane; Fig. 1 compound **1b**), isolated from antiviral Caribbean tunicate *Eudistoma olivaceum*, were described by Rinehart et al. [1] as a yellow oil **1a**:**1b** 1:1 mixture.

These alkaloids together with the other eudistomins present in crude extract, collected from *E. olivaceum* samples, inhibited plaque formation by *Herpes simplex* virus, type 1 (HSV-1), in CV-1 cells (monkey kidney tissue) with little cytotoxicity at the level tested. They

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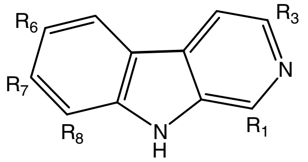

| β-Carboline | $R_1$ | $R_7$ | Bromo-β-carboline | $R_1$ | $R_3$ | $R_6$ | $R_7$ | $R_8$ |
|---|---|---|---|---|---|---|---|---|
| **1** | H | H | **1a** | H | H | Br | H | H |
| | | | **1b** | H | H | H | H | Br |
| | | | **1c** | H | H | Br | H | Br |
| | | | **1d** | H | Br | Br | H | H |
| | | | **1e** | H | Br | Br | H | Br |
| **2** | Me | H | **2a** | Me | H | Br | H | H |
| | | | **2b** | Me | H | H | H | Br |
| | | | **2c** | Me | H | Br | H | Br |
| | | | **2d** | Me | Br | Br | H | H |
| | | | **2e** | Me | Br | Br | H | Br |
| **3** | Me | MeO | **3a** | Me | H | Br | MeO | H |
| | | | **3b** | Me | H | H | MeO | Br |
| | | | **3c** | Me | H | Br | MeO | Br |
| | | | **3d** | Me | Br | Br | MeO | H |
| | | | **3e** | Me | Br | Br | MeO | Br |

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

also exhibited modest activity against *Saccharomyces cerevisiae*, a yeast, and *Bacillus subtilis*, a gram-positive bacterium [2].

As it is known that cytotoxicity in vitro and in vivo can be modified by light. This effect is quite critical when the compound assayed shows significant absorbance in the visible region ($\lambda_{\max} > 300$ nm) [3]. This aspect was not taken into account by Rinehart et al. [2] although they stated that eudistomins N and O contain a β-carboline (nor-harmane) UV chromophore but the two maxima at longest wavelength were shifted bathochromically (347 → 373 and 335 → 361 nm). It is interesting to note that nor-harmane shows in neutral solution the two above-mentioned maxima at wavelengths 339 and 350 nm and in slightly acidic solution shows the maxima at wavelength 376 nm (Table 1 and Fig. 2) [4] and although Rinehart et al. [1] reported first the synthesis of the 6- and 8-mono-bromo-derivatives of nor-harmane (Fig. 1, **1a** and **1b**) they did not attempt the isolation and purification of each.

In order to perform a comparative study of the photochemistry of eudistomins N and O and other bromo-β-carbolines, we initiated our study by re-examining the electronic spectroscopic properties of these substrates in solution. In view of the absence of data for this family of compounds, it was of interest first to examine comparatively the electronic spectra (absorption, fluorescence excitation and emission) of bromo-β-carbolines and the corresponding β-carboline in neutral and acidic solutions, exciting at different wavelength values. The preparation, purification and full characterization of the bromo-derivatives obtained from nor-harmane (**1**), harmane (**2**) and harmine (**3**) (Fig. 1, compounds **1a**–**e**, **2a**–**e** and **3a**–**e**) were described elsewhere [5] but the electronic spectra were not described in this previous report. Surprisingly, on the contrary that Rinehart and coworkers stated [2], we observed neither the two maxima at 361 and 373 nm for the bromo-β-carbolines **1a** and **1b** in neutral solution nor for the same compounds in acidic solutions (Table 1; Figs. 2 and 3; see details in Section 3) although all the maxima at longest wavelength were shifted bathochromically compared with the maxima for nor-harmane (Table 1, compound **1**). The notorious bathochromic shift of the maxima owing to the presence of bromine as substituent and a significant fluorescence emission detected at 298 K although the presence of a "heavy atom" as bromine in the chromophore nor-harmane moiety induced us to extend the study to provide examples of other mono-, di- and tribromo-β-carbolines (Fig. 1 and Tables 1–3, **1c**-**e**, **2a**–**e** and **3a**–**e**) and to compare its behavior with that of the corresponding β-carboline (Fig. 1 and Tables 1–3, **1**–**3**). The HOMO and LUMO energy, the position ($\lambda_{\max}$) 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 $\lambda_{\max}$ (Tables 4 and 5). Furthermore, fluorescence quantum yields ($\phi_f$) in acetonitrile and