Synthesis and Isolation of Chloro-β-carbolines Obtained by Chlorination of β-Carboline Alkaloids in Solution and in Solid State

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Received October 7, 2002

β-Carbolines (**1**-**5**) undergo electrophilic aromatic substitution with *N*-chlorosuccinimide and *N*-chlorobenzotriazole under different experimental conditions. Although 6-chloro and 8-chloro-nor-harmane (**1a** and **1b**) and 6-chloro and 8-chloro-harmane (**2a** and **2b**) obtained by chlorination with sodium hypochlorite of nor-harmane (**1**) and harmane (**2**) were isolated and fully characterized recently, other chloroderivatives of nor-harmane and harmane have never been described. The preparation and subsequent isolation, purification and full characterization of the dichloroderivatives **1c** and **2c** are reported (mp, R_f, ^1H nmr, ^{13}C nmr and ms) together with the preparation, isolation and charaterization, for the first time, of the chloroderivatives obtained from harmine (**3a**-**3c**), harmol (**4a**-**4b**) and 7-acetylharmol (**5a**-**5c**). As chlorinating reagent *N*-chlorosuccinimide and *N*-chlorobenzotriazole in solution as well as the β-carboline -*N*-chlorosuccinimide solid mixture have been used and their uses have been compared. Gc (t_R) and gc-ms (m/z) data for other monochloro derivative of nor-harmane (**1d**) and monochloro- and dichloroderivatives of harmane (**2d** and **2e**-**2f**), obtained in trace amounts, are also included (Scheme 1 and Table I). Semiempirical AM1 and PM3 calculations have been performed in order to predict reactivity in terms of the energies of HOMO-LUMO difference and in terms of the charge density of β-carbolines (**1**-**5**) and chloro-β-carbolines (**1a**-**1c**, **2a**-**2c**, **3a**-**3c**, **4a**-**4b**, and **5a**-**5c**) (Scheme 1). Theoretical and experimental results are discussed briefly.

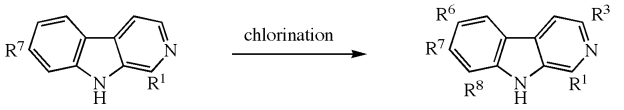
J. Heterocyclic Chem., **40**, 419 (2003).

Introduction.

As part of our study of the photochemistry of commercially available azacarbazoles (β-carbolines) [1] and their potential use as matrices (photosensitizers) in matrix assisted ultraviolet laser desorption/ionization time-of-flight mass spectrometry (uv-maldi-tof ms) [2], we decided to examine the behavior of substituted β-carbolines. To begin with, preparation of nitro-β-carbolines [3], bromo-β-carbolines [4] and chloro-β-carbolines was selected because, as it is known, for aromatic molecules these groups as substituents induce strong 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 [5,6].

The present study reports the preparation in solution of chloro derivatives from β-carbolines (Scheme 1, nor-harmane (**1**), harmane (**2**), harmine (**3**), harmol (**4**) and 7-acetylharmol (**5**)) using *N*-chlorobenzotriazole and *N*-chlorosuccinimide as chlorinating reagents. Thus, providing for the first time chloro-β-carbolines **1c**, **2c**, **3a**, **3b**, **3c**, **4a**, **4b**, **5a**, **5b**, and **5c**. Furthermore, we firstly report the chlorination of β-carbolines **1-5** in solid state with *N*-chlorosuccinimide and the results obtained are compared with those obtained in solution. We also describe in detail the use of chromatographic methods (tlc, preparative chromatographic folders and column chromatography, gc) in order to (i) follow the chlorination reaction, (ii) determine the yield of the reactions and (iii) isolate for complete characterization (elemental analysis, t_R, R_f, mp, ^1H nmr, ^{13}C nmr and ms) of the above mentioned chloro-β-carboline derivatives as well as the derivatives **1a**, **1b**, **2a**, and **2b** previously described [7]. Additionally, semiempirical calculations at AM1 and PM3 level have been performed in order to predict reactivity in terms of the charge density of the β-carbolines **1-5** and in terms of the energies of HOMO-LUMO difference (Scheme 1, Table I and Table II).

Scheme 1



Compound	R_1	R_7	Compound	R_1	R_3	R_6	R_7	R_8
1	H	H	**1a**	H	H	Cl	H	H
			1b	H	H	H	H	Cl
			1c	H	H	Cl	H	Cl
2	Me	H	**2a**	Me	H	Cl	H	H
			2b	Me	H	H	H	Cl
			2c	Me	H	Cl	H	Cl
3	Me	MeO	**3a**	Me	H	Cl	MeO	H
			3b	Me	H	H	MeO	Cl
			3c	Me	H	Cl	MeO	Cl
4	Me	HO	**4a**	Me	H	Cl	HO	H
			4b	Me	H	H	HO	Cl
5	Me	AcO	**5a**	Me	H	Cl	AcO	H
			5b	Me	H	H	AcO	Cl
			5c	Me	Cl	Cl	AcO	H

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

Table I
Chlorination of β-Carbolines (**1-5**) by using Different Methods

β-Carboline (t_R/min)	Method [b]	β-Carboline :ClA (molar ratio) [c]	Conversion (%)	Products (% Yield) [a] **a** (t_R/min)	**b** (t_R/min)	**c** (t_R/min)	Other products (t_R/min)
1				**1a**	**1b**	**1c**	
(5.21)				(7.75)	(5.76)	(8.14)	
	(i)	NCB / 1:1.6 (solution)	97	83	13	1	
	(ii)	NCS / 1:1.6 (solution)	100	85	15	-	
	(iii)	NCS / 1:1.2 (solid)	63	55	7	0.6	Monochloro-nor-harmane **1d**, yield 0.4%, (5.68)
2				**2**	**2b**	**2c**	
(2.91)				(4.29)	(3.18)	(4.05)	
	(i)	NCB / 1:1.6 (solution)	93	74	14	5	
	(i-i)	NCB / 1.1:2.7 (solution)	100	13	-	80	Polymers; dichloro-harmane **2e** (5.71) and dichloro-harmane **2f** (6.54) [d]
	(ii)	NCS / 1:1.6 (solution)	100	85	15	-	
	(iii)	NCS / 1:1.2 (solid)	32	27	4	-	Monochloroharmane **2d**, yield 1%, (4.55)
3				**3a**	**3b**	**3c**	
(4.34)				(5.97)	(4.65)	(5.42)	
	(i)	NCB / 1:1.6 (solution)	100	25	5	70	
	(ii)	NCS / 1:1.6 (solution)	99	55	10	34	
	(iii)	NCS / 1:1.2 (solid)	99	60	30	9	
4				**4a**	**4b**	-	
(4.49)				(4.43)	(4.22)		
	(i)	NCB / 1:1.6 (solution)	100	-	25	-	Polymers
	(ii)	NCS / 1:1.6 (solution)	95	-	16	-	Polymers
	(ii-i) 22° 3 hs	NCS / 1:1.6 (solution)	98	[e]	97	-	
	(iii)	NCS / 1:1.2 (solid)	74	-	74	-	
5				**5a**	**5b**	**5c**	
(4.52)				(6.96)	(5.42)	(6.71)	
	(i)	NCB / 0.6:1.3 (solution)	100	3	33	-	Polymers
	(ii)	NCS / 0.4:1.2 (solution)	90	32	58	[f]	
	(iii)	NCS / 1:1.2 (solid)	26	-	-	-	**4a** (19%) and **4b** (7%)
	(iii-i) 22° 1 month	NCS / 1:1.2 (solid)	97	-	-	-	**4a** (21%), **4b** (23%) and **4** (53%)

[a] Quantitative gc analysis; capillary column: Zebron ZB-5; t_R (min) data are displayed. Reaction time: 3 hs; additional controls were performed after 4 and 24 hs and after 1 month. Products **a-c** were fully characterized (see Experimental). Products **d-f** were characterized only by gc and gc-ms (see Experimental). [b] Method: (i) NCB/solution; T: 22°; reaction time: 3 hs; (ii) NCS/ solution; T: 55°; reaction time: 3 hs; (iii) NCS/ solid sate; T: 22°; reaction time: 3 hs. [c] β-Carbolines to chlorinating agent (ClA) molar ratio. [d] gc-ms analysis of isolated 6,8-dichloroharmane showed the presence, as traces, of two additional dichloroharmane derivatives (see Results and Discussion and ms data in Experimental). [e] gc-ms analysis of the reaction mixture when reaction was conducted in solution at room temperature after 24 hs showed the presence as traces of another mono-chloro-harmol, characterized as 6-chloro-harmol (see Results and Discussion and Experimental). [f] gc-ms analysis of isolated 8-chloro-7-acetylharmol showed the presence, as traces, of dichloro-7-acetylharmol derivative characterized as 6,8-dichloro-7-acetylharmol (see ^{1}H nmr and ms in Experimental section).

has been attempted in order to study the electronic and steric effect of different β-carboline substituent groups on the MAO, at molecular level. Among others, the synthesis of 6-chloro-nor-harmane was attempted for the first time, by dehydrogenation of the 6-chloro-1,2,3,4-tetrahydro-β-carboline and characterized by mp, uv-visible absorption spectrum and elemental analysis [8]. Similar procedures were used to prepare 6-chloro- and 8-chloro-nor-harmane [9], 1-chloro-nor-harmane [10] and 3-chloro-nor-harmane [11]. Recently, in order to study the co-mutagenicity of chlorinated-β-carbolines Nakano *et al* [7] described the preparation of 6-chloro- and 8-chloro-nor-harmane and 6-chloro- and 8-chloro-harmane by treatment of nor-harmane and harmane with sodium hypochlorite. These new compounds were characterized by mp, high resolution mass spectrometry (hrms), ^{1}H and ^{13}C nmr. The authors added that dichlorinated products were detected as minor products in the gc-ms analysis of the reaction mixtures, but that they were not isolated. The mentioned ms (m/z and % data) and the gc-ms results (t_R data and experimental conditions) were not included in the mentioned paper [7].

Chloro-β-carboline alkaloids called bauerines A-C have been isolated from terrestrial blue-green alga *Dichothrix baueriana* GO-25-3 [12] and its activity against herpes has been shown. These *N*-methyl-7-chloro- and *N*-methyl-7,8-dichloro-nor-harmanes were synthesized as well as the 7,8-dichloro-nor-harmane [13].

Table II

Static Charge Distribution for β-Carbolines and Chloro-β-carbolines and Energy values of LUMO relative to HOMO [a]

Comp.	1-C	3-C	4-C	4a-C	4b-C	5-C	6-C	7-C	8-C	8a-C	9a-C	Δ(LUMO-HOMO/eV)
1	-0.0722	-0.1034	-0.0854	-0.0499	-0.0874	-0.0327	-0.1376	-0.0674	-0.1226	-0.1172	-0.1787	7.951998
	(-0.0943)	(-0.1096)	(-0.1228)	(-0.0489)	(-0.0914)	(-0.0651)	(-0.1665)	(-0.0916)	(-0.1649)	(0.0528)	(-0.0114)	
1a	-0.0598	-0.0878	-0.0935	-0.0386	-0.0668	-0.0421	-0.1493	-0.0761	-0.0959	-0.1174	-0.1759	7.966643
	(-0.0863)	(-0.1022)	(-0.1239)	(-0.0451)	(-0.0812)	(-0.0619)	(-0.0951)	(-0.0889)	(-0.1506)	(0.0399)	(-0.0251)	
1b	-0.0588	-0.0881	-0.0943	-0.0388	-0.0673	-0.0402	-0.1173	-0.0740	-0.1369	-0.1179	-0.1757	7.972938
1c	-0.0581	-0.0873	-0.0912	-0.0419	-0.0557	-0.04273	-0.1418	-0.0783	-0.1271	-0.1213	-0.1753	9.8477841
2	-0.0336	-0.0829	-0.1051	-0.0305	-0.0786	-0.0406	-0.1277	-0.0739	-0.1089	-0.1140	-0.1745	8.060012
	(-0.0323)	(-0.1029)	(-0.1279)	(-0.0456)	(-0.0917)	(-0.0649)	(-0.1673)	(-0.0919)	(-0.1656)	(0.0529)	(-0.0137)	
2a	-0.0326	-0.0819	-0.1020	-0.0338	-0.0672	-0.0421	-0.1495	-0.0765	-0.0963	-0.1166	-0.1742	7.9280247
	(-0.0289)	(-0.1002)	(-0.1261)	(-0.0459)	(-0.0853)	(-0.0588)	(-0.0997)	(-0.0863)	(-0.1577)	(0.0535)	(-0.0144)	
2b	-0.0313	-0.0822	-0.1029	-0.0339	-0.0677	-0.0401	-0.1178	-0.0748	-0.1369	-0.1171	-0.1743	7.935285
2c	-0.0305	-0.0813	-0.1000	-0.0369	-0.0562	-0.0436	-0.1420	-0.0786	-0.1271	-0.1203	-0.1739	7.8156371
3	-0.0303	-0.0790	-0.1114	-0.0169	-0.1179	-0.0060	-0.1663	0.1207	-0.1982	-0.0756	-0.1822	8.1382094
	(-0.0288)	(-0.0983)	(-0.1346)	(-0.0319)	(-0.1275)	(-0.0344)	(-0.1918)	(0.1197)	(-0.2477)	(0.0879)	(-0.0222)	
3a	-0.0298	-0.0782	-0.1086	-0.0198	-0.1059	-0.0116	-0.1929	0.1235	-0.1899	-0.0773	-0.1813	7.9642356
	(-0.0209)	(-0.0909)	(-0.1362)	(-0.0279)	(-0.1164)	(-0.0345)	(-0.1229)	(0.1271)	(-0.2361)	(0.0747)	(-0.0369)	
3b	-0.0298	-0.0804	-0.1046	-0.0304	-0.0793	-0.0275	-0.1339	0.0864	-0.1679	-0.1059	-0.1759	7.9206005
3c	-0.0293	-0.0797	-0.1019	-0.0332	-0.0668	-0.0340	-0.1629	0.0857	-0.1589	-0.1094	-0.1751	7.787911
4	-0.0301	-0.0785	-0.1114	-0.0167	-0.1201	-0.0018	-0.1688	0.1311	-0.2131	-0.0704	-0.1821	8.1462078
4a	-0.0192	-0.0916	-0.1374	-0.0287	-0.1172	-0.0327	-0.1251	0.1285	-0.2459	0.0807	-0.0350	7.967043
4b	-0.0281	-0.0784	-0.1101	-0.0192	-0.1222	0.0024	-0.1653	0.1413	-0.2454	-0.0722	-0.1835	8.0514542
5	-0.0296	-0.0781	-0.1057	-0.0270	-0.0923	-0.0181	-0.1406	-0.0872	-0.1700	-0.0888	-0.1771	8.0394192
5a	-0.0291	-0.0774	-0.1033	-0.0302	-0.0801	-0.0253	-0.1742	0.0891	-0.1604	-0.0923	-0.1763	7.8695982
5b	-0.0283	-0.0793	-0.1023	-0.0343	-0.0732	-0.0253	-0.1334	0.0732	-0.1712	-0.1063	-0.1752	7.876008
5c	-0.0281	-0.0783	-0.1002	-0.0364	-0.0621	-0.0324	-0.1672	0.0753	-0.1642	-0.1082	-0.1753	7.742057

[a] Calculations were performed using PM3 method and data in parenthesis by using AM1 method.

Results and Discussion.

Chlorination with *N*-Chlorobenzotriazole (NCB) and *N*-Chlorosuccinimide (NCS) in Solution.

In order to investigate the chlorination reactions of β-carbolines **1**-**5** and taking into account the high reactivity shown by this family towards nitrating [3] and brominating reagents [4] a standard set of experimental conditions was adopted when experiments were conducted in solution. Thus, the solvent chosen as reaction medium was, depending on the substrate employed, ethyl acetate or mixtures of dichloromethane – ethyl acetate – ethanol, and the chlorination reaction was run, depending on the chlorinating reagent employed, at room temperature, at 55° or heating at reflux the reaction mixture to get a high yield of the chloro-β-carbolines (see Experimental and Table I). As chlorinating reagents we decided to use N-chlorobenzotriazole (NCB) and N-chlorosuccinimide (NCS) in comparative way (Table I).

When nor-harmane (**1**) was treated at room temperature with the chlorinating reagent (NCB) in molar ratio 1:1.6 the monochloro derivatives **1a** and **1b** were obtained as the main products (Table I, β-carboline **1**, method (i), 6-chloro-nor-harmane (**1a**) 83% and 8-chloro-nor-harmane (**1b**) 13%). Also in the reaction mixture 6,8-dichloro-nor-harmane (**1c**) was detected (1%). Similar results were obtained when the reaction was conducted at 22° during 3 hs and refluxed an additional hour (results not shown). When harmane (**2**) was treated at room temperature with NCB in molar ratio 1:1.6, the mono-chloro derivatives **2a** and **2b** were obtained as main products (Table I, compound **2**, method (i), 74 % and 14 %) together with the 6,8-dichloro derivative **2c** in minor yield (5 %). When after keeping the system at 22° during 3 h the reaction mixture was refluxed during 1 h the product yields obtained were similar. When harmane (**2**) was treated at room temperature with NCB in molar ratio 1.1:2.7, as main products **2a** as the only mono-chloro derivative was obtained together with the 6,8-dichloro-derivative **2c** (Table I, compound **2**, method (i-i), 13 % and 80 % respectively). In this experimental conditions two additional dichloro-harmane derivatives, **2e** and **2f**, were obtained in trace amounts. These two dichloro-harmane derivatives were only characterized by cg and cg-ms analysis showing t_R at 5.71 and 6.54 min (6,8-dichloro-harmane **2c**, t_R 4.05 min). In **2e** and **2f** mass spectra (ms) the molecular ions showed the same m/z value than that for compound **2c** and also a similar fragmentation pattern was observed in the three mass spectra (see in Experimental the ms data for 6,8-dichloro-harmane **2c** and for the dichloro-harmanes **2e** and **2f**).

The presence of a third mono-chloro-β-carboline derivative was observed in experiments performed with

nor-harmane in solid state (Table I, β-carboline **1**, method (iii), **1d** 0.4%; t_R = 5.68) and with harmane in solid sate (Table I, β-carboline **2**, method (iii), **2d** 1%, t_R = 4.55). These mono-chloro derivatives were only characterized by gs and gs-ms analysis (see Experimental).

Finally, when the 7-methoxy-1-methyl β-carboline called harmine (**3**) was treated with NCB in 1:1.6 molar ratio in solution, at room temperature, the 6,8-dichloro-harmine derivative **3c** was obtained in high yield (70 %) together with 6-chloro-harmine **3a** (25 %) (Table I, compound **3**, method (i)) while the 8-chloro-harmine **3b** was obtained as the minor product only in 5 % yield.

The chlorination reaction of the β-carboline **1**-**3** was also carried out in solution with N-chlorosuccinimide (NCS) in 1:1.6 molar ratio. In all the cases, when the reaction mixtures were kept in the dark during 3 hs at room temperature, low conversion of the β-carbolines was observed (< 10 %) and only the corresponding 6-chloro derivative was obtained as product. Although in this experimental conditions chlorinations were almost regioselective, the conversion and yields were low. Higher conversions of the β-carbolines were obtained when the solutions were kept at 55° during 3 hs. As it is shown in Table I (see method (ii)) nor-harmane (compound **1**) yielded 6-chloro-nor-harmane **1a** in 85 % and 8-chloro-nor-harmane **1b** in 15 %, harmane (compound **2**) yielded 6-chloro-harmane **2a** in 85 % and 8-chloro-harmane **2b** in 15 % and harmine (compound **3**) yielded 6-chloro-harmine **3a** in 55 %, 8-chloro-harmine **3b** in 10 % and 6,8-dichloro-harmine **3c** in 34 %.

As conclusion, NCB showed to be more reactive than NCS for β-carboline chlorination at room temperature, yielding dichloro-β-carbolines in high yield when NCB was used in excess (1.1:2.7 molar ratio). In the same experimental conditions, room temperature and molar ratio 1:1.6, NCS yielded regioselectively the 6-chloro derivative in low yield being necessary to keep the reaction mixture at 55° for 3 h in order to reach higher conversion of the starting β-carboline.

The different reactivity of NCB and NCS was also evident when harmol (**4**) was treated with each reagent. As shown in Table I, when compound **4** was treated with NCB at room temperature (method (i)), only the 8-chloro-derivative was isolated (**4b**, 25 %) in spite of the high conversion of the starting harmol (100 %). Oxidized polymeric compounds were produced in high yield. Similar result was obtained when the experiments were performed with NCS at 55° (Table I, compound **4**, method (ii)). On the contrary, when harmol was treated with NCS at room temperature (Table I, method (ii-i), the oxidized polymeric products were not formed and together with the 8-chloro-derivative **4b** (97 %), in a very clean reaction, 6-chloro-harmol **4a** was detected in trace amount.

6-Chloro-7-acetyl-harmol **5a** and 8-chloro-7-acetyl-harmol **5b** were obtained in high yields (32 % and 58 %) together with traces of a dichloro-7-acetyl-harmol derivative, in a quite clean chlorination reaction, when **5** was treated with NCS according to the conditions of method (ii) (Table I, compound **5**, method (ii)), while by treatment of **5** with NCB the oxidative-polymerization process was also observed (Table I, compound **5**, method (i)). From 6-chloro-7-actyl-harmol (**5a**), the 6-chloro-harmol **4a** was easily obtained by hydrolysis of the acetyl group.

Solid State Chlorination with *N*-Chlorosuccinimide.

N-Chlorosuccinimide (NCS) is an important reagent not only for chlorination but also for a host of other reactions [14]. NCS in solution is used extensively in chlorination reactions involving radical substitution; electrophilic addition and substitution pathways while oxidation reactions is not that uncommon [14]. Recently, we have described the results obtained when β-carbolines were treated with *N*-bromosuccinimide in solution and in solid state and we showed that when the brominations were performed in solid state, the oxidation reactions were eliminated [4]. Similar results were described by Satish Goud and Desiraju [15] and by Sarma and Nagaraju [16] for the bromination in solid state of phenols [15,16], hydroquinones [15], anilines [16] and nitro aromatic compounds [16]. Thus, the aim of the present study is to compare the chlorination reaction of β-carbolines in solution and in solid state.

Reaction Conditions.

One of the important postulates for any solid state reaction is that optimum yield is obtained when the reaction temperature is well below the melting point of the reactant (preferably below by ~ 30°) [16-19]. As the melting point of β-carbolines and their chloroderivatives are high (> 200°; see Experimental), experiments were performed at room temperature, without external control of the reaction temperature.

When a very active substituent such as the methoxy group is present in the β-carboline moiety (harmine; Table I, compound **3**) a higher conversion of the starting β-carboline was observed and several chloro derivatives in higher yield were obtained (Table I, compound **3**, method (iii)).

Reducing the activity of the β-carboline moiety in the form of a methyl substituent or a milder hydrogen substitution the results were a bit different. Thus, when the unsubstituted β-carboline species nor-harmane (**1**) was treated with NCS (1:1.6 molar ratio) and kept at room temperature in the dark, the regioselectivity of the reaction improved although the conversion of the starting β-carboline diminished (Table I, compound **1**, method (iii)). Similar results were observed with harmane (**2**). Thus, the 6-chloro- to 8-chloro-derivative % yield ratio obtained was for harmine 60:30 for nor-harmane 55:7 and for harmane 27:4 (Table I, compounds **3**, **1** and **2**, method (iii) respectively).

The oxidizing character of NCS observed when the phenolic β-carboline **4** (harmol) was treated with NCS in solution at 55° disappeared when the treatment was performed in solid state. As it is shown in Table I, compound **4** yielded regioselectively **4b** in high yield in a very clean reaction (Table I, compound 4, method (iii)).

Finally, when the 7-acetyl-harmol **5** in solid state was treated with NCS instead of the mono-chloro derivatives of 7-acetyl-harmol **5a** and **5b** the corresponding deacetylated compounds **4a** and **4b** were obtained (Table I, compound **5**, method (iii)). After the electrophilic substitution in **5** the production of hydrogen chloride in the surroundings of the 7-acetyloxy group would produce the removal of the acetyl group yielding the phenol. When the solid mixture was kept in the dark during 1 month, the hydrolysis of the acetyl group of **5** competed with the electrophilic substitution and as consequence compound **4**, harmol, was also obtained in high yield (53 %) (Table I, compound **5**, method (iii-i)).

Electrostatic Charges.

The absence of chloromethyl derivatives as products formed by chlorination of methyl-β-carbolines (harmane, harmine, harmol and 7-acetylharmol) together with the observation of nuclear chlorination in all cases and the dependence of the reactivity of the β-carbolines on the nature of their substituents, indicate that in both solution and in solid state an electrophilic substitution occurs as the most important process. If this is indeed the case, then the partial atomic charges on the ring C-atoms should correlate with the chlorination selectivity. In all compounds, it is invariably observed that mono-chlorination is effective on the most electron-rich ring C-atom. The charge of the ring C-atoms are given in Table II and in agreement with calculated values the negative charge is higher where mono-chlorination is effective. Thus, the 6-chloro-β-carboline is the monoderivative obtained in higher yield from nor-harmane (**1**), harmane (**2**) and harmine (**3**) while the 8-chloro-β-carboline is preferentially formed from harmol (**4**) and 7-acetylharmol (**5**). Similar distribution of mono-substituted products, also supported by partial atomic charge calculations, was previously described for the bromination of β-carbolines with *N*-bromosuccinimide in solution and in solid state [4].

About di-chlorinated products, the formation of the 6,8-dichloro derivatives **1c**, **2c** and **3c** are also in agreement with the partial atomic charge calculated for the C-atoms of the corresponding mono-chloro precursors (Table II). As is shown in Table I and was previously discussed, only harmine (compound **3**) yielded in mild conditions the 6,8-dichloro-derivative in high yield. For nor-harmane (**1**) and harmane (**2**) more drastic experimental conditions (higher temperature and/or excess of chlorinating reagent) were necessary in order to increase the efficiency of the formation of the corresponding 3,6-dichloro-derivative.

The higher reactivity of the harmine towards the electrophilic chlorination reaction expressed as higher calculated static charge values at 6-C and 8-C (Table II, compare the values for compounds **1**, **2** and **3**) support the experimental behavior observed (Table I). In the same way, as it is shown in table II, the calculated high static charge values at 8-C in the 6-chloro-harmine **3a** and at 6-C in the 8-chloro-harmine **3b** agree with the efficient formation of the 6,8-dichloro-harmine derivative **3c** observed (Table I, compound **3**).

HOMO-LUMO Energies.

The molecular orbital energies have been computed in order to distinguish the relative reactivity of the β-carbolines studied. If the reaction follows a well-defined electrophilic subtitution pathway, the HOMO and LUMO levels should be able to give an insight into the reactivity and assist in predicting the feasibility of such reaction. As it is shown in Table II, for the the β-carbolines **1**-**5** difference calculated between the HOMO and LUMO levels is in between 7.951998 and 8.1462078 eV. Sarma and Nagaraju have recently suggested that when the substrate HOMO – LUMO energy difference is low (7.9 to 9.1 eV), the bromination of this substrate in solid state is feasible and when the LUMO – HOMO gap widens (9.1 to 9.8 eV), the reaction is more difficult [16]. In agreement with this suggestion, the HOMO – LUMO differences calculated for β-carbolines match with the former group. Besides, it is interesting to note that among the many solid-solid and solid-gas reactions studied so far in the literature, the chlorination here described together with brominations previously described [4,16] is one of the few reactions where a molecular property contributes significantly to the solid state reactivity.

EXPERIMENTAL

Thin layer chromatography (tlc) analysis was performed with aluminum silica gel sheets (0.2 layer thickness, silica-gel 60 F254). Mass spectra (ms) were obtained under electron impact (70 eV). The ratios m/z and the relative intensities (%) are reported. Gas chromatography (gc) analysis was conducted with a Zebron ZB-5 capillary column (5% Phenylpolysiloxane; 30m x 0.25mm x 0.50 μm film). Gas chromatography-mass spectra (gc-ms) analysis was conducted with the same column. Gc and gc-ms experiments were performed as follows: T_0 = 250 °; T_f = 330 °; heating rate = 6°/min.

Products were isolated by preparative thick layer chromatography and flash - column chromatography which was carried out using silica gel 200-400 mesh 60 Å and hexane, hexane-ethyl acetate and ethyl acetate-ethanol as eluents. Melting points are uncorrected; ^{1}H- and ^{13}C-nmr spectra were run in dimethylsulfoxide-d_6 at 200 MHz the former and at 500 MHz the latter. Chemical shifts are reported in ppm values, using tetramethylsilane as internal standard. ^{13}C-nmr assignments were confirmed by using DEPT pulse sequence.

Dichloromethane, chloroform, ethanol, hexane, ethyl acetate and other reagents used were analytical grade. Solvents were

freshly distilled and dried before using. Nor-harmane (**1**), harmane (**2**), harmine (**3**), harmol (**4**), N-chlorosuccinimide (NCS) and *N*-chlorobenzotriazole (NCB) were purchased from Aldrich. 7-Acetylharmol (**5**) was prepared according to the procedure described elsewhere [4].

General Procedure for the Chlorination Reaction of β-Carbolines (**1-5**) in solution, with *N*-Chlorobenzotriazole (NCB) (Table I, method (i)) and with *N*-Chlorosuccinimide (NCS) (Table I, method (ii)).

To a stirred solution of β-carboline (100 mg, 0.50 mmoles) in ethyl acetate (or mixture dichloromethane - ethyl acetate – ethanol) (50 ml), a solution of NCS or NCB (100 mg, 0.15 to 0.60 mmole, depending on the stoichiometry used) in dichloromethane (50 ml) was added dropwise. The reaction was stirred for an appropriate time in the absence of light at room temperature (or at 55°, or refluxed) until tlc indicated that the reaction was complete (methods (i) and (ii), see additional details in footnotes of Table I). All of these reactions were carried out under normal (air) atmosphere. The reaction mixture was then filtered and the solid washed with dichloromethane (3 x 15 ml) and ethyl acetate – ethanol 1/1 (3 x 15 ml). The combined extracts were washed with sodium hydroxide 0.1 *N* (3 x 15 ml) and then with water (3 x 15 ml). The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo* to give a pale green solid residue. The residue was separated by flash column chromatography (silica gel-hexane-ethyl acetate-ethanol mixtures as eluent) to give as white solids (**1a**), (**1b**), (**1c**), (**2a**), (**2b**), (**2c**), (**3a**), (**3b**), (**3c**), (**4a**), (**4b**), (**5a**) and (**5b**) respectively (Scheme 1, Table I). The mono-chloro derivatives (**1d**) and (**2d**) (Scheme 1, Table I) obtained as traces in the reaction mixtures were only characterized by cg-ms. During the chlorination of harmane (Table I, compound **2**) two additional dichloro derivatives **2e** and **2f** were obtained as traces, when harmane to NCB molar ratio was 1.1:2.7 (see Table I, method (i-i)) and characterized only by cg-ms: compound **2e** t_R = 5.71 min and compound **2f** t_R = 6.54 min (for 6,8-dichloro-harmane **2c** t_R = 4.05 min) and ms. Compound **2e** t_R = 5.71 min, ms: m/z 254 (^{37}Cl ^{37}Cl, M^+, 12), 252 (^{37}Cl ^{35}Cl, M^+, 65), 250 (^{35}Cl ^{35}Cl, M^+, 100), 222(2), 217 (10), 215 (30), 195 (6), 179 (11), 151 (3), 125 (10), 107 (10). Compound **2f** t_R = 6.54 min, ms: m/z 254 (^{37}Cl ^{37}Cl, M^+, 12), 252 (^{37}Cl ^{35}Cl, M^+, 65), 250 (^{35}Cl ^{35}Cl, M^+, 100), 222(2), 217 (5), 215 (15), 195 (1), 180 (10), 179 (30), 151 (6), 125 (8), 107 (10). Compound (**5c**), a dichloro-derivative of acetylharmol **5**, also obtained in poor yield, was characterized by gc-ms and ^1H nmr. According to the experimental conditions used the percentage yield of the products obtained are different as it is shown in Table I and described in Results and Discussion.

The R_f values sequence for TLC of all the β-carbolines (**1-5**) and its reaction products were always: 6,8-dichloro-β-carboline > 8-chloro-β-carboline >> 6-chloro-β-carboline > β-carboline; as example for nor-harmane: 6,8-dichloro-β-carboline = 0.87; 8-chloro-β-carboline = 0.84; 6-chloro-β-carboline = 0.56; β-carboline = 0.53.

6-Chloro-nor-harmane (**1a**).

Compound **1a** has mp 238-240° (d) (benzene-ethanol) (lit 235° (d) [7], 270-271° [8]); ^1H nmr (dimethylsulfoxide-d_6) [7]: δ 11.75 (s, 1 H, NH), 8.94 (s, 1H, 1-H), 8.37 (d, 1H, 5-H, J = 1.8 Hz), 8.33 (m, 1H, 3-H), 8.15 (d, 1H, 4-H, J = 5.1 Hz), 7.63 (d, 1H, 8-H, J = 8.7 Hz) and 7.55 ppm (dd, 1H, 7-H, J = 8.7, 1.8 Hz); ^{13}C nmr (dimethylsulfoxide-d_6) [7]: δ 138.89 (9a-C), 138.29 (3-C), 135.44 (8a-C), 134.41 (1-C), 127.95 (7-C), 126.61 (6-C), 123.53 (4b-C), 121.86 (4a-C), 121.29 (5-C), 114.93 (8-C), 113.52 ppm (4-C); ms: m/z 204 (^{37}Cl, M^+, 33), 202 (^{35}Cl, M^+, 100), 174 (5), 167 (22), 147 (2), 139 (21), 113 (4), 101 (16).

8-Chloro-nor-harmane (**1b**).

Compound **1b** has mp 200-202° (benzene-ethanol) (lit 198-199° [7]); ^1H nmr (dimethylsulfoxide-d_6) [7]: δ 11.95 (s, 1 H, NH), 8.97 (broad s (bs), 1H, 1-H), 8.42 (d, 1H, 3-H, J = 4.7 Hz), 8.25 (d, 1H, 5-H, J = 7.6 Hz), 8.16 (d, 1H, 4-H, J = 4.7 Hz), 7.65 (d, 1H, 7-H, J = 7.6 Hz) and 7.27 ppm (t, 1H, 6-H, J = 7.6 Hz); ^{13}C-nmr (dimethylsulfoxide-d_6) [7]: δ 138.95 (9a-C), 138.63 (3-C), 134.92 (8a-C), 134.50 (1-C), 127.38 (7-C), 126.86 (4b-C), 122.59 (4a-C), 120.77 (6-C), 120.34 (5-C), 116.16 (8-C), 115.12 ppm (4-C); ms: m/z 204 (^{37}Cl, M^+, 33), 202 (^{35}Cl, M^+, 100), 174 (3), 167 (28), 147 (5), 140 (27), 113 (18), 101 (19).

6,8-Dichloro-nor-harmane (**1c**).

Compound **1c** has mp 268-270° (d) (benzene-ethanol); ^1H nmr (dimethylsulfoxide-d_6): δ 12.15 (s, 1 H, NH), 8.97 (bs, 1H, 1-H), 8.40 (d, 1H, 3-H, J = 4.8 Hz), 8.37 (d, 1H, 5-H, J = 1.8 Hz), 8.19 (d, 1H, 4-H, J = 4.8 Hz) and 7.75 (d, 1H, 7-H, J = 1.8 Hz); ^{13}C nmr (dimethylsulfoxide-d_6): δ 138.01 (9a-C), 137.48 (3-C), 134.50 (1-C), 134.18 (8a-C), 128.09 (6-C), 127.73 (7-C), 123.63 (4b-C), 121.34 (4a-C), 120.59 (5-C), 117.01 (8-C) and 115.41 ppm (4-C); ms: m/z 240 (^{37}Cl ^{37}Cl, M^+, 8), 238 (^{37}Cl ^{35}Cl, M^+, 75), 236 (^{35}Cl ^{35}Cl, M^+, 100), 208 (4), 201 (25), 182 (12), 165 (11), 138 (8).

Anal. Calcd. for $C_{11}H_6N_2Cl_2$: C, 55.72; H, 2.55; N, 11.82; Cl, 29.91. Found: C, 55.73; H, 2.54; N, 12.01; Cl, 29.72.

6-Chloro-harmane (**2a**).

Compound **2a** has mp 250-252° (d) (benzene-ethanol) (lit 246-248° [7]); ^1H nmr (dimethylsulfoxide-d_6) [7]: δ 11.76 (bs, 1 H, NH), 8.33 (d, 1H, 5-H, J = 1.8 Hz), 8.23 (d, 1H, 3-H, J = 5.4 Hz), 7.97 (d, 1H, 4-H, J = 5.4 Hz), 7.61 (d, 1H, 8-H, J = 8.7 Hz), 7.53 (dd, 1H, 7-H, J = 8.7, 1.8 Hz) and 2.76 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) [7]: δ 142.53 (1-C), 138.69 (9a-C), 137.69 (3-C), 134.98 (8a-C), 127.66 (7-C), 126.03 (4b-C), 123.45 (6-C), 122.31 (4a-C), 121.23 (5-C), 113.40 (8-C), 112.87 (4-C) and 20.34 ppm (CH_3); ms: m/z 218 (^{37}Cl, M^+, 33), 216 (^{35}Cl, M^+, 100), 188 (10), 181 (40), 161 (4), 154 (28), 140 (6), 127 (8), 113 (6).

8-Chloro-harmane (**2b**).

Compound **2b** has mp 213-215° (d) (benzene-ethanol) (lit 216-217° [7]); ^1H nmr (dimethylsulfoxide-d_6) [7]: δ 11.67 (bs, 1 H, NH), 8.26 (d, 1H, 3-H, J = 5.8 Hz), 8.19 (d, 1H, 5-H, J = 8.4 Hz), 7.96 (d, 1H, 4-H, J = 5.8 Hz), 7.62 (d, 1H, 7-H, J = 7.6 Hz), 7.24 (dd, 1H, 6-H, J = 7.6, 8.4 Hz) and 2.85 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) [7]: δ 143.17 (1-C), 138.13 (3-C), 137.36 (9a-C), 134.67 (8a-C), 127.30 (7-C), 126.73 (4b-C), 123.24 (4a-C), 120.53 (5-C), 120.30 (6-C), 116.29 (8-C), 112.81 (4-C) and 20.73 ppm (CH_3); ms: m/z 218 (^{37}Cl, M^+, 33), 216 (^{35}Cl, M^+, 100), 188 (8), 181 (24), 179 (10), 161 (1), 154 (15), 140 (4), 127 (5), 113 (4).

6,8-dichloro-harmane (**2c**).

Compound **2c** has mp 225° (d) (benzene-ethanol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.83 (bs, 1 H, NH), 8.36 (d, 1H, 5-H, J = 1.8 Hz), 8.28 (d, 1H, 3-H, J = 5.2 Hz), 8.01 (d, 1H, 4-H, J = 5.2 Hz), 7.72 (d, 1H, 7-H, J = 1.8 Hz) and 2.84 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 143.58 (1-C), 138.37 (3-C),

136.08 (9a-C), 135.17 (8a-C), 126.77 (7-C), 126.66 (4b-C), 123.83 (4a-C), 123.62 (6-C), 120.37 (5-C), 117.14 (8-C), 113.11 (4-C) and 20.75 ppm (CH_3); ms: m/z 254 (^{37}Cl ^{37}Cl, M^+, 12), 252 (^{37}Cl ^{35}Cl, M^+, 65), 250 (^{35}Cl ^{35}Cl, M^+, 100), 222(2), 217 (6), 215 (20), 195 (6), 179 (10), 151 (7), 125 (10), 107 (8).

Anal. Calcd. for $C_{12}H_8N_2Cl_2$: C, 57.39; H, 3.21; N, 11.16; Cl, 28.24. Found: C, 57.38; H, 3.20; N, 11.17; Cl, 28.25.

6-Chloro-harmine (**3a**).

Compound **3a** has mp 251-253° (isopropyl alcohol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.05 (bs, 1 H, NH), 8.13 (d, 1H, 3-H, J = 5.5 Hz), 8.06 (s, 1H, 5-H), 7.74 (d, 1H, 4-H, J = 5.5 Hz), 7.12 (s, 1H, 8-H), 4.01 (s, 3H, CH_3O) and 2.79 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 154.70 (7-C), 141.53 (1-C), 140.23 (9a-C), 137.93 (3-C), 134.52 (8a-C), 126.52 (4b-C and 5-C), 114.73 (6-C), 114.14 (4a-C), 112.21 (4-C), 94.93 (8-C), 56.11 (CH_3O) and 20.23 ppm (CH_3); ms: m/z 248 (^{37}Cl, M^+, 33), 246 (^{35}Cl, M^+, 100), 233 (10), 231 (30), 217 (1), 205 (13), 203 (40), 168 (10), 140 (7), 123 (9).

Anal. Calcd. for $C_{13}H_{11}N_2OCl$: C, 63.29; H, 4.49; N, 11.36; O, 6.49; Cl, 14.37. Found: C, 63.27; H, 4.49; N, 11.37; Cl, 14.38.

8-Chloro-harmine (**3b**).

Compound **3b** has mp 210-212° (isopropyl alcohol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.05 (bs, 1 H, NH), 8.22 (d, 1H, 3-H, J = 5.5 Hz), 8.20 (d, 1H, 5-H, J = 8.4 Hz), 7.89 (d, 1H, 4-H, J = 5.5 Hz), 7.13 (d, 1H, 6-H, J = 8.4 Hz), 3.97 (s, 3H, CH_3O) and 2.80 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 154.80 (7-C), 142.33 (1-C), 139.20 (9a-C), 138.22 (3-C), 134.93 (8a-C), 128.00 (4b-C), 120.92 (4a-C), 116.81 (5-C), 112.31 (4-C), 105.92 (6-C), 103.30 (8-C), 56.81 (CH_3O) and 20.52 ppm (CH_3); ms: m/z 248 (^{37}Cl, M^+, 33), 246 (^{35}Cl, M^+, 100), 233 (8), 231 (25), 215 (1), 205 (20), 203 (60), 168 (8), 140 (8), 123 (9).

Anal. Calcd. for $C_{13}H_{11}N_2OCl$: C, 63.29; H, 4.49; N, 11.36; O, 6.49; Cl, 14.37. Found: C, 63.30; H, 4.49; N, 11.35; Cl, 14.36.

6,8-Dichloro-harmine (**3c**).

Compound **3c** has mp 222-224° (benzene-isopropyl alcohol; ^1H nmr (dimethylsulfoxide-d_6): δ 11.25 (bs, 1 H, NH), 8.17 (d, 1H, 3-H, J = 5.5 Hz), 7.93 (s, 1H, 5-H), 7.64 (d, 1H, 4-H, J = 5.5 Hz), 3.93 (s, 3H, CH_3O) and 2.76 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 150.90 (7-C), 143.13 (1-C), 137.10 (9a-C), 138.62 (3-C), 135.20 (8a-C), 126.72 (4b-C), 121.20 (5-C), 119.41 (4a-C), 118.90 (6-C), 112.72 (4-C), 111.30 (8-C), 60.91 (CH_3O) and 20.72 ppm (CH_3); ms: m/z 284 (^{37}Cl ^{37}Cl, M^+, 10), 282 (^{37}Cl ^{35}Cl, M^+, 75), 280 (^{35}Cl ^{35}Cl, M^+, 100), 267 (25), 265 (75), 253 (2), 239 (30), 237 (90), 202 (5).

Anal. Calcd. for $C_{13}H_{10}N_2OCl_2$: C, 55.54; H, 3.59; N, 9.96; O, 5.69; Cl, 25.22. Found: C, 55.55; H, 3.59; N, 9.98; Cl, 25.24.

6-Chloro-harmol **(4a)**.

Compound **4a** was obtained by hydrolysis of 6-chloro-7-acetylharmol (**5a**). mp 260-262° (d) (benzene-ethanol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.30 (bs, 1 H, NH), 8.10 (s, 1H, 5-H), 8.03 (d, 1H, 3-H, J = 5.1), 7.90 (d, 1H, 4-H, J = 5.1 Hz), 7.50 (s, 1H, 8-H) and 2.79 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 154.44 (7-C), 141.02 (1-C), 139.23 (9a-C), 137.83 (3-C), 135.55 (8a-C), 127.11 (4b-C), 121.50 (5-C), 115.11 (4a-C), 114.15 (6-C), 110.80 (4-C), 96.66 (8-C) and 22.57 ppm (CH_3); ms: m/z 234 (^{37}Cl, M^+, 33), 232 (^{35}Cl, M^+, 100), 204 (10), 197 (25), 170 (13).

Anal. Calcd. for $C_{12}H_9N_2OCl$: C, 61.94; H, 3.90; N, 12.04; O, 6.88; Cl, 15.24. Found: C, 61.96; H, 3.90; N, 12.03; Cl, 15.26.

8-Chloro-harmol (**4b**).

Compound **4b** has mp 268-270° (d) (isopropyl alcohol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.31 (bs, 1 H, NH), 8.12 (d, 1H, 3-H, J = 5.1), 7.95 (d, 1H, 5-H, J = 8.4 Hz), 7.80 (d, 1H, 4-H, J = 5.1 Hz), 6.93 (d, 1H, 6-H, J = 8.4) and 2.79 ppm (s, 3H, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6): δ 153.54 (7-C), 142.12 (1-C), 139.44 (9a-C), 138.31 (3-C), 134.58 (8a-C), 128.13 (4b-C), 120.50 (5-C), 115.17 (4a-C), 111.80 (4-C), 110.01 (6-C), 94.61 (8-C) and 20.66 ppm (CH_3); ms: m/z 234 (^{37}Cl, M^+, 33), 232 (^{35}Cl, M^+, 100), 204 (20), 197 (17), 170 (22).

Anal. Calcd. for $C_{12}H_9N_2OCl$: C, 61.94; H, 3.90; N, 12.04; O, 6.88; Cl, 15.24. Found: C, 61.95; H, 3.90; N, 12.05; Cl, 15.23.

6-Chloro-7-acetylharmol (**5a**).

Compound **5a** has mp 213-215° (d) (benzene-ethanol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.81 (s, 1 H, NH), 8.48 (s, 1H, 5-H), 8.25 (d, 1H, 3-H, J = 5.2 Hz), 7.50 (s, 1H, 8-H), 7.98 (d, 1H, 4-H, J = 5.2), 2.77 (s, 3H, CH_3) and 2.39 (s, 3H, CH_3CO); ^{13}C nmr (dimethylsulfoxide-d_6): δ 168.57 (CO), 145.89 (7-C), 142.43 (1-C), 139.03 (9a-C), 137.73 (3-C), 135.25 (8a-C), 125.92 (4b-C), 122.52 (5-C), 119.89 (4a-C), 117.27 (6-C), 112.83 (4-C), 107.06 (8-C), 20.47 (CH_3) and 20.36 ppm (CH_3CO); ms: m/z 276 (^{37}Cl, M^+, 33), 274 (^{35}Cl, M^+, 100), 234 (33), 232 (100), 207 (18), 191 (5), 165 (3),133 (3), 114 (2).

Anal. Calcd. for $C_{14}H_{11}N_2O_2Cl$: C, 61.21; H, 4.04; N, 10.20; O, 11.65; Cl, 12.80. Found: C, 61.23; H, 4.04; N, 10.19; Cl, 12.79.

8-Chloro-7-acetylharmol (**5b**).

Compound **5b** has mp 238-240° (d) (benzene-ethanol); ^1H nmr (dimethylsulfoxide-d_6): δ 11.78 (s, 1 H, NH), 8.28 (d, 1H, 3-H, J = 5.2 Hz), 8.22 (d, 1H, 5-H, J = 8.5 Hz), 7.98 (d, 1H, 4-H, J = 5.2 Hz), 7.17 (d, 1H, 6-H, J = 8.5), 2.84 (s, 3H, CH_3) and 2.40 (s, 3H, CH_3CO); ^{13}C nmr (dimethylsulfoxide-d_6): δ 179.29 (CO), 146.29 (7-C), 143.09 (1-C), 138.42 (3-C), 138.21 (9a-C), 135.21 (8a-C), 127.33 (4b-C), 120.84 (5-C), 115.37 (6-C), 120.76 (4a-C), 112.75 (4-C), 109.35 (8-C), 20.65 (CH_3) and 20.38 ppm (CH_3CO); ms: m/z 276 (^{37}Cl, M^+, 3), 274 (^{35}Cl, M^+, 10), 234 (33), 232 (100), 207 (3), 197 (5), 165 (3),140 (3), 114 (2).

Anal. Calcd. for $C_{14}H_{11}N_2O_2Cl$: C, 61.21; H, 4.04; N, 10.20; O, 11.65; Cl, 12.80. Found: C, 61.22; H, 4.04; N, 10.21; Cl, 12.79.

6,8-Dichloro-7-acetylharmol (**5c**).

Compound **5c** was obtained as trace in the chlorination of compound **5** in solution (see Table I, method (ii)). ^1H nmr (dimethylsulfoxide-d_6): δ 11.78 (s, 1 H, NH), 8.26 (d, 1H, 3-H, J = 5.2 Hz), 8.50 (s, 1H, 5-H), 7.97 (d, 1H, 4-H, J = 5.2 Hz), 2.85 (s, 3H, CH_3) and 2.43 (s, 3H, CH_3CO); ms: m/z 310 (^{37}Cl, M^+, 3), 308 (^{35}Cl, M^+, 10), 268 (70), 266 (100), 231 (8).

General Procedure for the Chlorination Reaction of β-Carbolines (**1-5**) in Solid State with *N*-Chlorosuccinimide (NCS) (Table I, method (iii)).

The substrate (~1.0 g) and freshly powdered NCS (1:1.2 molar equivalents) were mixed very gently in a mortar, at room temperature. Aliquots were taken at different reaction times, dissolved in ethanol and the fresh solution was immediately monitored: (a) by tlc

as usual and (b) by gas chromatography (gc), and the products obtained were characterized by comparison of its R_f (tlc) and t_R (gc) with authentic samples whose spectroscopic data are described above. The percentage conversion of β-carbolines and the products yields are shown in Table I. Then the reaction mixture was separated by flash column chromatography (silica gel – hexane – ethyl acetate and ethyl acetate – ethanol mixtures as eluent). All the products obtained were characterized by ^{1}H-nmr and ms.

During the chlorination of nor-harmane and additional monochloro-nor-harmane derivative **1d** was obtained as trace (Table I, β-carboline **1**, method (iii)). It showed a t_R of 5.68 min, different than those of 6-chloro-nor-harmane (**1a**, 7.75 min), 8-chloro-nor-harmane (**1b**, 5.76 min) and 6,8-dichloro-nor-harmane (**1c**, 8.14 min). ms: m/z 204 (^{37}Cl, M$^+$, 33), 202 (^{35}Cl, M$^+$, 100), 174 (3), 167 (85), 139 (38), 113 (18), 101 (20).

During the chlorination of harmane and additional monochloro-harmane derivative **2d** was obtained as trace (Table I, β-carboline **2**, method (iii)). It showed a t_R of 4.55 min, different than those of 6-chloro-harmane (**2a**, 4.29 min), 8-chloro-harmane (**2b**, 3.18 min) and 6,8-dichloro-harmane (**2c**, 4.05 min); ms: m/z 218 (^{37}Cl, M$^+$, 33), 216 (^{35}Cl, M$^+$, 100), 188 (7), 181 (30), 179 (10), 154 (25), 140 (2).

Either grinding of the mixture or monitoring the reaction for a longer time did not result in a paste, because of high melting point reactants and products were involved.

Calculations.

The ground-state geometry and heat of formation, static charge distribution for predicting chemical reactivity of β-carbolines **1** - **5** and chloro-β-carbolines were calculated by using the semiempirical parametrized PM3 and AM1 methods as implemented in version of the HyperChem program [20], which has proven to be effective in studies on molecular containing heteroatoms, compared with other methods such as MINDO/3 or MNDO.

Acknowledgment.

Partial financial support from UBA and CONICET is gratefully acknowledged. Authors are also grateful to Dr. H. Nonami (College of Agriculture, Ehime University, Japan) for HyperChem Suite for professionals release 7.01 program and Lic Laura B. Talarico for her technical help. R. Erra-Balsells is research member of CONICET.

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