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Jafrine, a novel and labile β-carboline alkaloid from the flowers of *Tagetes patula*☆

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Dedicated to the fond memory of Professor Salim-uz-Zaman Siddiqui FRS (1897–1994), the founder director of H.E.J. Research Institute of Chemistry, University of Karachi

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Abstract—An inherently unstable and structurally novel tetrahydro β-carboline alkaloid, (+) jafrine (**1**) was isolated from the petroleum ether extract of *Tagetes patula* flowers. Its structure and stereochemistry has been determined with the help of spectroscopic analysis and the synthesis of racemate, (±) jafrine starting from available (±) tetrahydroharmine (**2**). The effect of solvent polarity on the ratio of amide rotamers of jafrine during NMR studies is discussed. The transformation of jafrine as well as 4-*N*-acetyl tetrahydroharmine (**3**), into 2-acetyl tryptamine derivatives by auto-oxidation was observed and its detail is presented. This process may be used as a synthetic tool for the preparation of tryptamine derivatives.

1. Introduction

Tagetes patula Linn. (French Marigold) locally known as Jafri, belongs to the family Asteraceae (Compositae). It is a bushy annual, native to Mexico and other warmer parts of America and naturalized elsewhere in the tropics and subtropics. It is a small ornamental garden plant with multiple uses.[1] The flowers are employed for the treatment of jaundice and hepatitis, while the whole plant is used for the treatment of cough and dysentery. The roots and seeds are used as purgative. Moreover, a cardiovascular drug was formed from lyophilized powder of *T. patula*. The volatiles from *T. patula* are highly effective toward both larvae and adult mosquitoes. The roots contain nematocidal polythienyls, including a little terthienyl.[1] Phytochemical investigation on its different parts has resulted in the isolation of various chemical constituents such as thiophenes, flavonoids, benzofurans and carotenoids.[2] The present paper describes the isolation and structure elucidation of a novel β-carboline alkaloid, jafrine (**1**) having a carbon substituent at A ring, from *T. patula*. It is noteworthy that this type of β-carboline is very rare[3,4] and only one such compound had previously been isolated from natural sources.[3]

2. Results and discussion

The petroleum ether extract of red flowers of *T. patula* yielded a tetrahydro β-carboline alkaloid, jafrine through solvent separation followed by preparative thin layer chromatography. The EI mass spectrum of jafrine (yellow gum, $[\alpha]_D^{26}=+19.23$) showed a molecular ion peak at *m/z* 356.2078 consistent with the molecular formula $C_{21}H_{28}N_2O_3$, which was supported by positive ion ($M^+ +1$, *m/z* 357) and negative ion ($M^+ -1$, *m/z* 355) FAB mass spectra. The IR spectrum displayed peaks at 3301 (hydrogen bonded *N*–H, very weak absorption), 3050 (aromatic C–H), 2952, 2855 (aliphatic C–H), 1682 (aromatic ketone), 1662 (tertiary amide carbonyl), 1621, 891 (aromatic ring), 1445 (CH_2), and 1165 (C–O), while its UV spectrum showed maxima at 300, 283, 253, and 210 nm indicating the presence of β-carboline skeleton.[5a,b] The ^{1}H NMR spectrum ($CDCl_3$, Table 1) of jafrine displayed two aromatic proton singlets at δ 7.82 (1H, H-9) and 6.81 (1H, H-12) and a methoxy group singlet at 3.86 (3H, 11-OCH_3) revealing that the A ring of β-carboline has the usual methoxy group at C-11 along with an electron withdrawing substituent at C-10.[5a,c] That this substituent is a caproyl group was shown by a set of resonances of methylene protons at δ 2.98 (H-2′), 1.67 (H-3′), 1.33 (H-4′), and 1.28 (H-5′) and methyl protons at 0.87 (H-6′). Moreover, the ^{1}H NMR data disclosed that C ring of β-carboline is saturated[6] and contained an acetyl group on its nitrogen. The down-field chemical shift of indolic *N*–H showed its intramolecular hydrogen bonding with the carbonyl function at 4-*N*(amide group), as in tetrahydroharmine (**2**) it resonated at δ 7.69 ($CDCl_3$, Table 2), while in 4-*N*-acetyl

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Keywords: tetrahydro β-carbolines; amide; *Z*/*E* rotamers; auto-oxidation.

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Table 1. ^{1}H NMR data (ppm) for jafrine (**1a**+**1b**), in different solvents at 500 MHz; coupling constants (*J*, Hz) are in parentheses

Proton	C_6D_6 (*Z*/*E*; 31.0:1.0)		$CDCl_3$ (*Z*/*E*; 6.0:1.0)		C_3D_6O (*Z*/*E*; 3.0:1.0)		CD_3OD (*Z*/*E*; 3.2:1.0)	
	1a (*Z*)	**1b** (*E*)	**1a** (*Z*)	**1b** (*E*)	**1a** (*Z*)	**1b** (*E*)	**1a** (*Z*)	**1b** (*E*)
1	8.50[a] br.s	8.45[a] br.s	8.88[a] br.s	8.48[a] br.s	10.18[a] br.s	10.15[a] br.s	–	–
3	5.86 q (6.7)	5.03 m	5.73 br.q (6.7)	4.94 br.q (6.6)	5.66 br.q (6.6)	5.12 br.q (6.7)	5.60 br.q (7.0)	5.10 br.q (7.0)
5a	3.11 dd (4.5, 13.5)	5.01 m	3.97 ddd (4.4, 6.3, 13.9)	4.91 m	4.11 ddd (4.4, 6.5, 13.9)	4.84 br.dd (4.4, 12.8)	4.10 ddd (2.0, 6.5, 14.0)	N.O.[b]
5b	2.81 ddd (3.9, 10.8, 13.6)	2.51 m	3.45 ddd (6.2, 9.8, 13.9)	2.92 m	3.46 ddd (5.3, 10.6, 14.0)	2.90 m	3.49 ddd (5.5, 11.0, 14.0)	2.99 m
6	2.20 m	2.15 m	2.76 m	2.72 m	2.77 m	2.77 m	2.74–2.93 m	2.74–2.93 m
9	8.38 s	8.22 s	7.82 s	7.82 s	7.73 s	7.75 s	7.75 s	7.75 s
12	6.65 s	6.46 s	6.81 s	6.76 s	6.98 s	6.99 s	6.92 s	6.93 s
2′	3.20 t (7.4)	3.20 t (7.4)	2.98 t (7.5)	2.98 t (7.5)	2.92 m	2.92 m	2.99 t (7.0)	2.99 t (7.0)
3′	1.94 qn (7.3)	1.94 qn (7.3)	1.67 qn (7.5)	1.67 qn (7.5)	1.64 m	1.64 m	1.65 m	1.65 m
4′	1.40 m	1.40 m	1.33 m	1.33 m	1.31 m	1.31 m	1.32 m	1.32 m
5′	1.30 m	1.30 m	1.28 m	1.28 m	1.27 m	1.27 m	1.27 m	1.27 m
6′	0.87 t (7.1)	0.87 t (7.1)	0.87 t (7.0)	0.87 t (7.0)	0.87 t (7.0)	0.87 t (7.0)	0.88 t (7.0)	0.88 t (7.0)
11-OCH_3	3.44 s	3.44 s	3.86 s	3.81 s	3.90 s	3.90 s	3.90 s	3.90 s
4-$NCOCH_3$	1.73 s	1.82 s	2.22 s	2.14 s	2.14 s	2.13 s	2.21 s	2.16 s
3-CH_3	1.31 d (6.7)	1.38 d (6.7)	1.42 d (6.7)	1.52 d (6.7)	1.41 d (6.7)	1.57 d (6.6)	1.45 d (7.0)	1.57 d (7.0)

[a] Exchangeable with D_2O.
[b] N.O.=Not observed (hidden behind the water peak at δ 4.8).

Table 2. ^{1}H NMR data (ppm) for compounds **2**, **6a**, **6b**, **7a**, **7b**, **8a** and **8b** in $CDCl_3$ at 500 MHz; coupling constants (J, Hz) are in parentheses

Proton	**2**	(*Z*/*E*; 1.0:1.4)		(*Z*/*E*; 5.4:1.0)		(*Z*/*E*; 3.3:1.0)	
		6a (*Z*)	**6b** (*E*)	**7a** (*Z*)	**7b** (*E*)	**8a** (*Z*)	**8b** (*E*)
1	7.69[a] br.s	–	–	8.69[a] br.s	8.36[a] br.s	8.75[a] br.s	N.O.[b]
3	4.13 tq (1.9, 6.7)	6.35 br.q (7.0)	5.68 br.q (6.5)	5.71 br.q (6.6)	4.96 br.q (6.5)	5.75 br.q (6.5)	5.02 m
4	1.64[a] br.s	–	–	–	–	–	–
5a	3.33 ddd (3.5, 5.2, 12.9)	3.93 m	4.88 br.dd (5.5, 13.8)	3.97 ddd (3.7, 5.1, 13.9)	4.92 br.dd (4.9, 13.8)	3.95 m	2.98 m
5b	3.01 ddd (5.0, 9.0, 12.9)	3.50 m	2.99 ddd (5.0, 11.3, 14.7)	3.45 ddd (4.4, 11.7, 13.9)	2.93 ddd (4.3, 11.6, 13.8)	3.51 m	4.99 m
6a	2.71 dddd (1.9, 5.2, 9.0, 15.4)	2.63 m	2.74 m	2.77 m	2.72 m	2.61–2.76 m	2.65 m
6b	2.66 dddd (1.9, 3.5, 5.0, 15.4)	2.63 m	2.74 m	2.77 m	2.72 m	2.61–2.76 m	2.65 m
9	7.32 d (8.5)	7.28 d (8.5)	7.33 d (8.5)	7.93 s	7.93 s	7.56 d (8.5)	7.60 d (8.5)
10	6.74 dd (2.2, 8.5)	6.82 dd (2.0, 8.5)	6.90 dd (2.0, 8.5)	–	–	6.77 d (8.5)	6.78 d (8.5)
12	6.81 d (2.2)	7.35 d (2.5)	7.18 d (2.5)	6.82 s	6.74 s	–	–
11-OCH_3	3.80 s	3.86 s	3.87 s	3.88 s	3.82 s	3.96 s	3.97 s
1-NAC	–	2.74 s	2.77 s	–	–	–	–
4-NAC	–	2.18 s	2.20 s	2.21 s	2.15 s	2.19 s	2.14 s
3-CH_3	1.41 d (6.7)	1.44 d (6.5)	1.51 d (6.0)	1.43 d (7.0)	1.52 d (7.0)	1.46 d (7.0)	1.52 d (7.0)
10- $COCH_3$	–	–	–	2.72 s	2.72 s	–	–
12-$COCH_3$	–	–	–	–	–	2.70 s	2.71 s

[a] Exchangeable with D_2O.
[b] N.O.=Not observed.

Table 3. ^{1}H NMR data (ppm) of **3** (**3a**+**3b**) in $CDCl_3$, C_3D_6O and $CDCl_3$+CD_3OD at 500 MHz; coupling constants (*J*, Hz) are in parentheses

Proton	$CDCl_3$ (*Z*/*E*;4.8:1.0)		C_3D_6O (*Z*/*E*; 2.8:1.0)		$CDCl_3$+CD_3OD (1:1) (*Z*/*E*; 2.6:1.0)	
	3a (*Z*)	**3b** (*E*)	**3a** (*Z*)	**3b** (*E*)	**3a** (*Z*)	**3b** (*E*)
1	7.87[a] br.s	7.68[a] br.s	9.85[a] br.s	9.80[a] br.s	–	–
3	5.71 br.q (6.5)	4.97 br.q (6.5)	5.65 br.q (6.6)	5.09 br.q (6.6)	5.57 br.q (6.7)	4.98 br.q (6.6)
5a	3.97 ddd (3.5, 5.0, 14.0)	4.92 br.dd (5.0, 14.0)	4.07 ddd (1.1, 4.9, 13.7)	4.82 ddd (1.3, 4.8, 12.9)	3.96 ddd (3.4, 6.1, 14.0)	4.80 ddd (3.3, 6.1, 14.0)
5b	3.45 ddd (4.5, 11.5, 14.0)	2.93 ddd (4.5, 11.5, 14.0)	3.44 ddd (4.3, 11.6, 13.7)	2.92 dt (4.4, 12.4, 12.4)	3.44 ddd (6.0, 10.1, 13.9)	2.95 ddd (6.0, 10.1, 13.9)
6a	2.76 m	2.71 m	2.72 m	2.72 m	2.74 m	2.67 m
6b	2.76 m	2.71 m	2.72 m	2.72 m	2.74 m	2.67 m
9	7.32 d (8.5)	7.34 d (8.5)	7.26 d (8.5)	7.28 d (8.5)	7.25 d (8.5)	7.27 d (8.5)
10	6.75 dd (2.0, 8.5)	6.77 dd (2.0, 8.5)	6.66 dd (2.2, 8.5)	6.67 dd (2.2, 8.5)	6.67 dd (2.2, 8.5)	6.68 dd (2.2, 8.5)
12	6.83 d (2.0)	6.82 d (2.0)	6.86 d (2.2)	6.84 d (2.2)	6.83 d (2.2)	6.83 d (2.2)
11-OCH_3	3.82 s	3.84 s	3.76 s	3.76 s	3.78 s	3.78 s
4-NAC	2.19 s	2.18 s	2.12 s	2.12 s	2.16 s	2.16 s
3-CH_3	1.43 d (6.5)	1.54 d (6.5)	1.39 d (6.6)	1.55 d (6.6)	1.41 d (6.7)	1.52 d (6.6)

[a] Exchangeable with D_2O.

Table 4. ^{1}H NMR data (ppm) of **3** (**3a**+**3b**) in CD_3OD, C_5D_5N, and C_2D_6SO at 500 MHz; coupling constants (J, Hz) are in parentheses

Proton	CD_3OD (Z/E; 2.5:1.0)		C_5D_5N (Z/E; 3.4:1.0)		C_2D_6SO (Z/E; 2.8:1.0)	
	3a (Z)	**3b** (E)	**3a** (Z)	**3b** (E)	**3a** (Z)	**3b** (E)
1	–	–	11.72[a] br.s	11.58[a] br.s	10.55[a] br.s	10.50[a] br.s
3	5.60 q (6.5)	5.09 q (6.5)	6.08 br.q (7.0)	5. 13 br.q (7.0)	5.44 q (6.5)	5. 01 br.q (6.5)
5a	4.08 ddd (1.5, 5.0, 14.0)	N.O.[b]	3.88 ddd (1.5, 5.0, 13.5)	5.17 br.dd (5.0, 13.0)	3.95 td (3.0, 3.0, 14.1)	4.58 br.dd (3.1, 11.0)
5b	3.48 ddd (5.0, 11.5, 14.0)	3.02 ddd (6.5, 10.0, 13.0)	3.34 ddd (4.0, 11.5, 13.5)	2.95 br.dt (4.0, 12.0, 12.0)	3.31 td (6.8, 6.8, 14.0)	2.89 dt (3.4, 10.9, 10.9)
6a	2.76 m	2.65 m	2.73 dddd (1.0, 5.0, 11.0, 15.0)	2.80 m	2.63 m	2.63 m
6b	2.76 m	2.65 m	2.67 dddd (1.5, 4.5, 5.0, 15.0)	2.74 m	2.63 m	2.63 m
9	7.24 d (8.5)	7.25 d (8.5)	7.53 d (8.5)	7.52 d (8.5)	7.24 d (8.5)	7.25 d (8.5)
10	6.64 dd (2.0, 8.5)	6.75 dd (2.5, 8.5)	7.04 dd (2.0, 8.5)	7.03 dd (2.0, 8.5)	6.59 dd (2.0, 8.5)	6.60 dd (2.0, 8.5)
12	6.82 d (2.0)	6.83 d (2.5)	7.16 d (2.0)	7.15 d (2.0)	6.82 d (2.0)	6.83 d (2.0)
11-OCH_3	3.78 s	3.78 s	3.73 s	3.72 s	3.68 s	3.68 s
4-NAC	2.20 s	2.16 s	2.17 s	2.14 s	2.07 s	2.08 s
3-CH_3	1.44 d (6.5)	1.57 d (6.5)	1.52 d (7.0)	1.49 d (7.0)	1.31 d (6.5)	1.43 d (6.5)

[a] Exchangeable with D_2O.
[b] N.O.=Not observed (hidden behind the water peak at δ 4.8).

Table 5. ^{13}C NMR data (ppm) of **1** (**1a**+**1b**) and **3** (**3a**+**3b**) in $CDCl_3$ and $CDCl_3$+CD_3OD (1:1) respectively at 300 MHz

	(**1**)		(**3**)	
Carbons	*Syn* (**1a**) (*Z*) (major)	*Anti* (**1b**) (*E*) (minor)	*Syn* (**3a**) (*Z*) (major)	*Anti* (**3b**) (*E*) (minor)
2	135.42	133.89	135.31	134.26
3	45.20	49.42	47.05	51.27
5	40.76	35.45	42.39	37.27
6	22.06	21.17	23.33	22.45
7	108.38	110.89	107.64	109.16
8	122.90	N.O.	122.45	123.98
9	120.97	N.O.	119.58	119.86
10	120.78	N.O.	109.95	111.45
11	155.94	N.O.	157.39	157.53
12	93.71	N.O.	96.56	96.04
13	139.53	N.O.	138.53	138.66
1′	203.68	N.O.	–	–
2′	43.77	N.O.	–	–
3′	24.72	N.O.	–	–
4′	31.82	N.O.	–	–
5′	22.82	N.O.	–	–
6′	14.05	N.O.	–	–
14	19.03	20.28	19.94	21.11
15	169.41	171.72	171.48	172.65
16	22.08	21.71	22.81	22.48
17	55.78	N.O.	56.97	56.74

N.O.=Not observed.

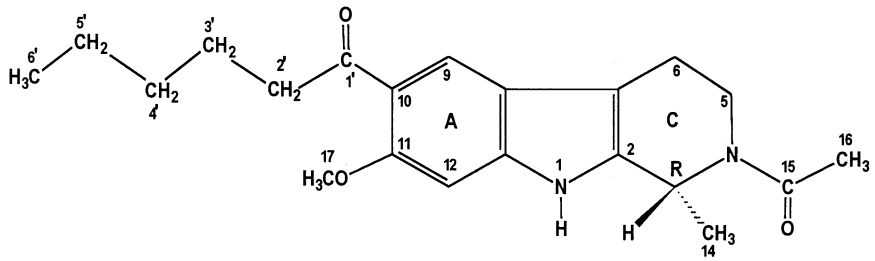
tetrahydroharmine (**3**) (Tables 3 and 4) it shifted down-field to δ 7.87 ($CDCl_3$). The same trend in chemical shifts has been observed for tetrahydroharmane derivatives.[5b] Out of the nine degrees of unsaturation in the molecule, implied by the molecular formula, seven have been accounted for by tetrahydro β-carboline nucleus and two by carbonyl functions. These structural features of jafrine were confirmed through extensive studies of ^{13}C (Broad Band and DEPT, Table 5) and 2D NMR spectra (COSY 45°, HMQC and HMBC). The ^1H ^1H COSY 45° spectrum showed connectivities of both the spin systems of ring C and caproyl moiety, present in the molecule. In the HMBC spectrum, important ^3J bond connectivities were observed for C-2 (135.42) with H-6; C-7 (108.38) with H-5a and H-9; C-8 (122.90) with H-12; C-10 (120.78) with H-12; and C-11 (155.94) with H-9 and H-17. Furthermore, the aromatic carbonyl at δ 203.68 and the amide carbonyl at 169.41 showed ^2J bond correlations with H-2′ and H-16 respectively in the HMBC spectrum.

The CD spectrum of jafrine, showed a positive Cotton effect in the range 217–300 nm, implying *R* configuration (βH, αCH_3) at C-3.[7] Thus, in the light of the above experimental detail the structure of jafrine was determined to be (+)-3α-methyl-4-*N*-acetyl-10-caproyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline (**1**, Fig. 1), which was substantiated by the diagnostic fragment ions (Fig. 2 and Section 3) in the mass spectrum particularly at *m*/*z* 341 (M^+-CH_3); while *m*/*z* 300 arose due to the McLafferty rearrangement of C-10 acyl group and *m*/*z* 285 formed as a result of RDA fragmentation. Tetrahydroharmine may be envisaged as a possible intermediate in the biosynthesis of jafrine.

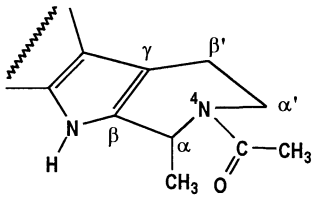
An interesting feature of the ^1H NMR spectrum ($CDCl_3$, Table 1) of **1** is that the compound exists in two forms, **1a** and its isomer **1b**, in 6:1 ratio (Fig. 1), which was inferred by the presence of double signals and their integrals. This is due to the restricted rotation along the C–*N* bond of the amide function, which produced the rotamers *Z* (*syn*) and *E* (*anti*) in **1**.[8,9] It is noteworthy that, cyclic 4-*N* amide of β-carbolines, strictosamide and congeners which could not exist in isomeric forms due to the presence of torsional ring strain, have exactly the same chemical shift values[6,10] for H-3, H-5a and H-5b as observed for rotamer **1b** of **1**.

The ^{13}C NMR spectrum of **1** (Table 5) also showed the *syn*, *anti* rotational isomerism in an excellent manner and gave similar results which have been cited in literature for different types of amides.[9] As reported earlier, carbon nuclei, *cis* to the carbonyl function, become more shielded due to the positive magnetic anisotropy, thus, appear up-field.[9] In the case of **1**, significant ^{13}C chemical shift differences were observed between the *syn* and *anti* rotamers (δ ^{13}C *syn*$-\delta$ ^{13}C *anti*) for C-3 (α), C-5 (α′), C-2 (β), C-6 (β′), C-14 and other carbon nuclei (Fig. 1) nearest to the range of magnetic anisotropy as depicted in Table 6, where the positive and negative values ($\Delta\delta_{s-a}$) showed down-field and up-field shifts respectively for nuclei of *syn* rotamer (**1a**), while in case of ^{13}C nuclei of *anti* rotamer (**1b**) positive and negative values ($\Delta\delta_{s-a}$) described up-field and down-field shifts, respectively. These data supported the structures of **1a** and **1b** as the *Z* (*syn*) rotamer and the *E* (*anti*) rotamer, respectively.

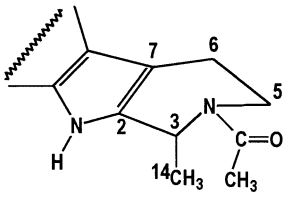
The ^1H NMR chemical shift data of **1** in different solvents have also been obtained, to study the influence of their polarity on *Z*/*E* isomers ratios. Thus, the ^1H NMR spectra (Table 1) of **1** recorded in C_6D_6, $CDCl_3$, C_3D_6O, and CD_3OD, showed the coexistence of both *Z* and *E* isomers in the ratio of 31.0:1.0; 6.0:1.0; 3.0:1.0; and 3.2:1.0, respectively. From the above-mentioned results, it may be inferred that the amount of the *Z* rotamer (with respect to the *E* rotamer) would decrease on increasing solvent polarity. The presence of intramolecular hydrogen bonding between 1-*N*-H and 4-*N*-carbonyl, is responsible for the greater amount of the *Z* isomer (**1a**) over the *E* isomer (**1b**),



1



Syn, Z rotamer (1a)



Anti, *E* rotamer (1b)

Figure 1. Jafrine (**1**) and its *Z* (*syn*) and *E* (*anti*) rotamers.

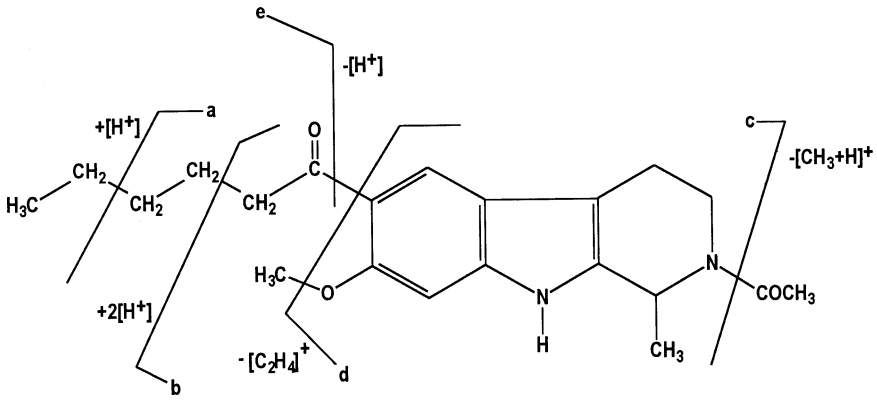


Figure 2. Mass fragmentation pattern in **1**.

Table 6. ^{13}C NMR chemical shift differences ($\Delta\delta_{s-a}$) of *syn* (*Z*) and *anti* (*E*) rotamers of compounds **1** and **3** in $CDCl_3$ and $CDCl_3+CD_3OD$, respectively

Carbons	$\Delta\delta_{s-a}=\delta$ ^{13}C *syn* $-\delta$ ^{13}C *anti*	
	(**1**)	(**3**)
2β	+1.5270	+1.0570
3α	−4.2204	−4.2228
5α′	+5.3121	+5.1250
6β′	+0.8922	+0.8787
7γ	−2.5065	−1.5120
8	–	−1.5240
9	–	−0.2800
10	–	−1.4950
11	–	−0.1420
12	–	+0.5191
13	–	−0.1320
14	−1.2446	−1.1680
15	−2.3090	−1.1660
16	+0.3758	+0.3290
17	–	+0.2273

although the possible existence of steric hindrance between the 4-*N*-carbonyl and the methyl group at C-3 (as shown by its Drieding model) would destabilize it. When the solvent polarity (from benzene to methanol) increases, the possibility of intermolecular hydrogen bonding between solute and solvent molecules also increases, with the increase in the amount of the *E* rotamer (**1b**) and decrease of the *Z* rotamer (**1a**), here the absence of intramolecular hydrogen bonding in **1**, steric interaction plays its part.

This phenomenon of *Z*/*E* isomerism was also observed in other 4-*N*-acetyl β-carboline derivatives, which were studied for the confirmation of structural features of jafrine (**1**). Thus, 4-*N*-acetyl tetrahydroharmine (**3**), which was obtained from the acetylation of available tetrahydroharmine (**2**) showed coexistence of *Z*/*E* rotamers. The ^1H NMR spectrum of **3** (Table 3) in $CDCl_3$, exhibited exactly the same chemical shift values and multiplicities for ring C protons as observed in case of **1**. Here also the *E* rotamer, which is more stable than the *Z* rotamer with respect to steric interactions, exists in high ratio in more polar protic solvents as well as in polar aprotic solvents (Tables 3 and 4). The ^{13}C NMR spectrum of **3** (Table 5) also showed the presence of *Z* (*syn*) and *E* (*anti*) rotamers, and the positive and negative values ($\Delta\delta_{s-a}$) were similar to those observed for **1** (Table 6).

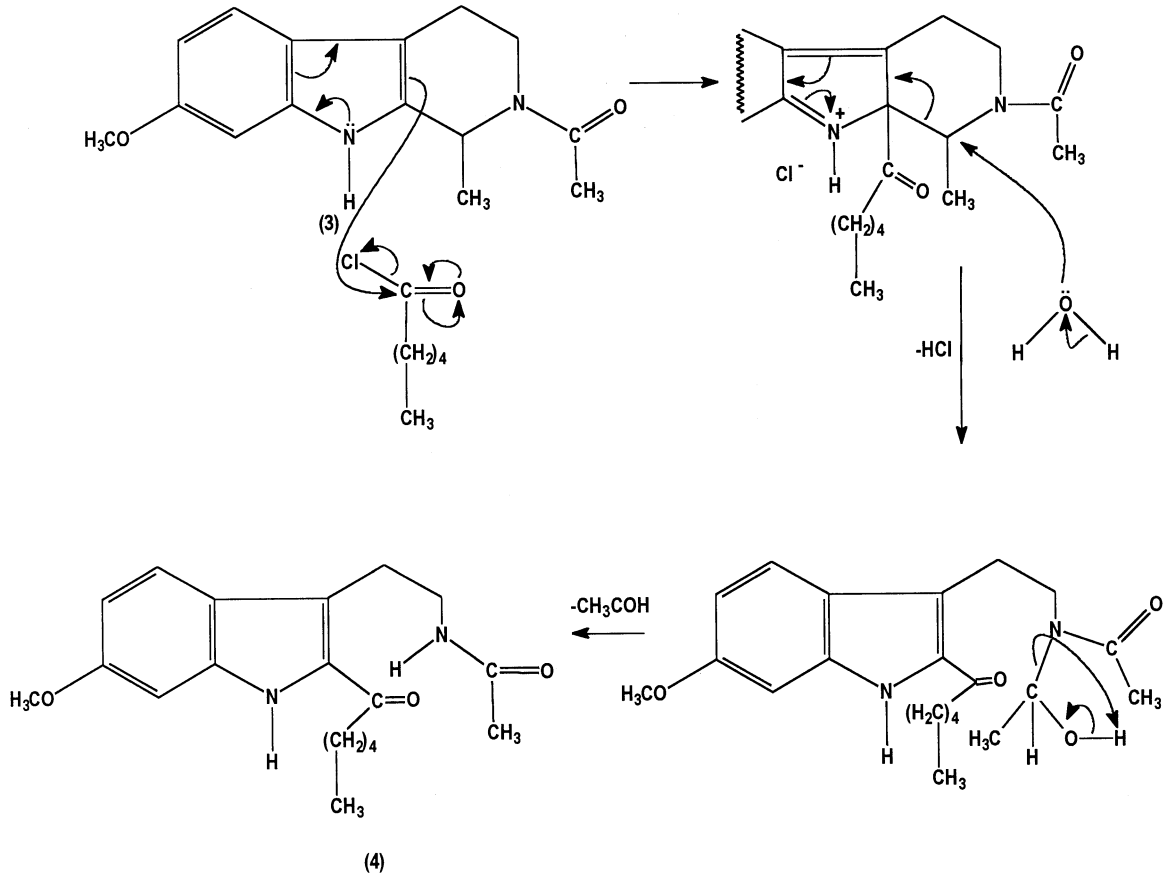
The impact of the steric factor is nicely shown by compound **6**, which is the 1-*N*,4-*N*-diacetylated derivative, obtained through Friedel Crafts acetylation of **3**. The HR EIMS of **6** showed molecular ion peak at *m*/*z* 300.1454 ($C_{17}H_{20}N_2O_3$). The IR spectrum exhibited a strong peak at 1691 cm^{-1} for the carbonyl group (1-*N*-acetyl and 4-*N*-acetyl) and no absorbance for *N*–H. The ^1H NMR spectrum ($CDCl_3$, Table 2), also contained no resonance for indolic *N*–H. Instead it revealed that indolic *N*–H has been replaced by an acetyl group, as it has a down-field value for an *N*-acetyl signal at δ 2.74. Other ^1H NMR spectral features are same as those of **3**, except for H-12 (7.35, d, *J*=2.5 Hz) and H-3 (6.35, br.q, *J*=7.0 Hz), which appeared further down-field due to the presence of 1-*N*-acetyl group. Thus the structure of **6** was elucidated as 3-methyl-1-*N*,4-*N*-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline, which exists in *Z* and *E* forms in a ratio of 1.0:1.4, respectively. In this case the steric contribution allowed the *E* rotamer to be the major one. Here the indolic nitrogen has an acetyl group, so the intramolecular hydrogen bonding with 4-*N*-carbonyl was not possible, and the steric factor controls the ratio of *Z*/*E* forms.

Finally the structure of **1** was confirmed by the synthesis of its racemate, (±) jafrine, which was carried out in two steps

Table 7. NMR data (ppm) of **4**, **5** and **9** in $CDCl_3$ at 500 MHz

Position	4 δ_H	5 δ_H	9 δ_H	9 δ_C
1	8.81 br.s[a]	8.82 br.s[a]	9.04 br.s[a]	–
2	–	–	–	136.73[b]
3	–	–	–	123.92[b]
3a	–	–	–	126.50[b]
4	7.54 d (9.0)	7.54 d (9.0)	8.01 s	124.21
5	6.82 dd (2.0, 9.0)	6.81 dd (2.5, 9.0)	–	125.11[b]
6	–	–	–	154.69
7	6.74 d (2.0)	6.75 d (2.0)	6.77 s	92.80
7a	–	–	–	138.52[b]
1′	3.28 t (6.5)	3.28 t (7.0)	3.28 t (6.5)	22.46
2′	3.55 q (6.5)[c]	3.54 q (6.5)[c]	3.51 q (6.5)[c]	40.57
3′	5.91 br.t (6.5)[a]	5.83 br.t (6.5)[a]	5.89 br.t (6.7)[a]	–
1″	–	–	–	202.46
2″	2.90 t (7.0)	–	2.99 t (7.5)	43.63
3″	1.61 m	–	1.68 m	24.79
4″	1.32 m	–	1.32 m	31.82
5″	1.24 m	–	1.26 m	22.57
6″	0.86 t (7.0)	–	0.86 t (6.5)	13.97
2-CO	–	–	–	196.72
2-$COCH_3$	–	2.61 s	2.66 s	24.55
6-OCH_3	3.84 s	3.84 s	3.91 s	55.70
3′-CO	–	–	–	171.92
3′-$COCH_3$	1.89 s	1.90 s	1.93 s	22.59

[a] Disappeared on shaking with D_2O.
[b] Assignments may be reversed.
[c] On D_2O shake converted into triplet (*J*=6.5 Hz).



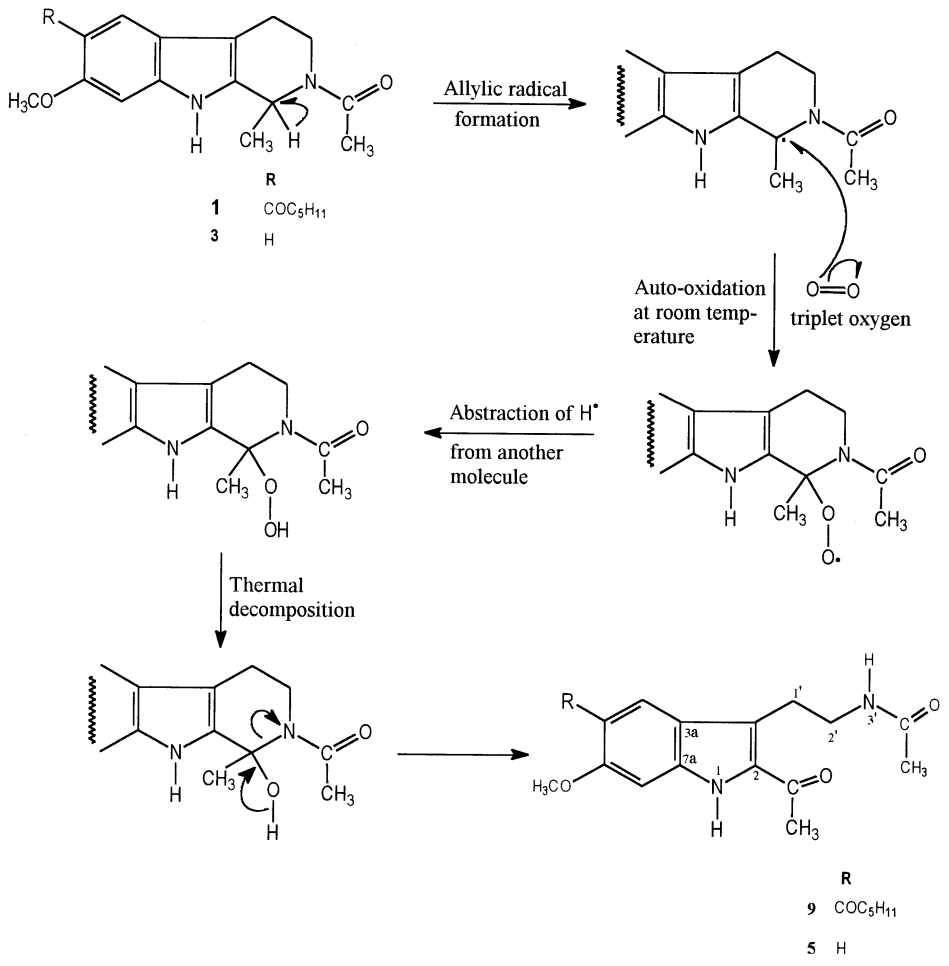
Scheme 1. Possible mechanism for the formation of **4** from **3**.

starting from an authentic sample of (±)-3,4,5,6-tetrahydroharmine (**2**). In the first step, **2** was treated with acetic anhydride to give (±)-4-*N*-acetyl tetrahydroharmine (**3**) regioselectively. In the second and last step, **3** was subjected to Friedel Crafts acylation with hexanoyl chloride in the presence of a catalytic amount of a Lewis acid. The R_f value and also the spectral data (UV, IR, ^{1}H NMR, EIMS) of synthetic (±)-**1** and natural (+)-**1** were found to be identical. A very low yield of synthetic (±)-**1** was obtained due to the competition of the formation of two degraded compounds (**4** and **5**) (2-acetyl tryptamine derivatives), having interesting chemistry to explain, along with other minor products.

The HR EIMS of **4** gave the molecular formula $C_{19}H_{26}N_2O_3$ (330.1934), while its IR spectrum showed *N*–H absorption at 3351 cm^{-1} along with the carbonyl peak at 1683 for 2- and 3′-carbonyl groups. The ^{1}H NMR spectrum ($CDCl_3$, Table 7) of **4** showed the same resonance patterns for ring A protons, as that of **3**, however, H-4, H-5 and 1-*N*-H appeared further down-field due to the presence of the caproyl group in the indolic chromophore at C-2. The shifts at δ 3.28, 3.55, 5.91 and 1.89 showed ring C cleaved moiety at C-3. Thus the structure of **4** was elucidated as 3-(2-acetamidoethyl)-2-caproyl-6-methoxyindole.

The spectral data of **5** determined its structure as 3-(2-acetamidoethyl)-2-acetyl-6-methoxyindole.[11] The possible mechanism for the formation of compound **4** is depicted in Scheme 1 which is supported by the reported mechanism of C-3 epimerization of reserpine in acidic media as well as acid prompted substitution reaction at C-2 of tetrahydro β-carboline.[12] The formation of compound **5** may be rationalized by the auto-oxidation[13] of **3** during the Friedel Crafts reaction (Scheme 2).

Furthermore, from the key intermediate **3**, employing Friedel Crafts conditions, the synthesis of a new β-carboline alkaloid **7** has also been accomplished, which, possesses an acetyl group at C-10 in place of the caproyl moiety of **1**. Here, 1-*N*,4-*N*-diacetylated β-carboline (**6**) as described above, 4-*N*,12-diacetylated β-carboline (**8**) and ring C cleaved, auto-oxidized product (**5**) were also obtained. The HR EIMS of compound **7** gave the molecular formula $C_{17}H_{20}N_2O_3$ (300.1461). Its UV and IR spectra were similar to those of **1**. The ^{1}H NMR spectrum ($CDCl_3$, Table 2) revealed that it has an acetyl group (δ 2.72, 3H, s) at C-10 of indole instead of a caproyl moiety in case of **1**, rest of the resonance patterns were same as those of **1**. Consequently the structure of **7** was elucidated as 3-methyl-4-*N*,10-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline, which exists in *Z* and *E* forms (**7a**, **7b**) in a ratio of 5.4:1.0, respectively, as revealed by the ^{1}H NMR integral. The molecular formula of compound **8** was identical to that of **7** ($C_{17}H_{20}N_2O_3$, HR EIMS, 300.1465). Its spectral data (UV, IR, Mass, ^{1}H NMR) reflected that it was a regioisomer of **7** and elucidated its structure as 3-methyl-4-*N*,12-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline. The ^{1}H NMR spectrum of **8** showed *Z*/*E* rotational isomerism in a ratio of 3.3:1.0, respectively (Table 2). Of the compounds (**4**–**8**)



Scheme 2. Plausible mechanism for auto-oxidation of **1** to **9** and **3** to **5**.

discussed above, only compound **5** is known in the literature as a synthetic product[11] while **4**, **6**–**8** are new chemical entities.

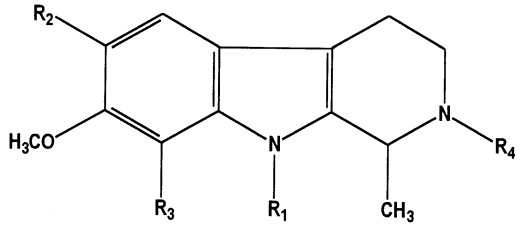
In the series of indole alkaloids, derivatives of simple β-carbolines are naturally less abundant, especially alkaloids having substitution of an acyl group at 1-*N* or 4-*N*.[3,4] Jafrine (**1**) is the first β-carboline alkaloid to have been found thus far in the genus Tagetes, though the presence of indole in the leaf oil of *T. erecta* has been reported in literature.[14] Furthermore, it is also the first instance of isolation of a β-carboline from nature bearing a long chain carbonyl function in the A ring. The isolation of a β-carboline having a carbon substituent in the A ring has only once been reported, however, there are many reports of isolation of β-carbolines possessing a carbon substituents at ring C.[3,4] It is important to note that there are examples of naturally occurring carbazole alkaloids having carbon substituents both at ring A and C.[4]

During the ^{1}H NMR studies on the *Z*/*E* rotational isomerism of compound **1**, it was observed that **1** has transformed into another compound jafrinine (**9**), which is more polar than **1** as indicated by TLC. The EIMS spectrum of **9** showed the M^+ peak at *m*/*z* 372 (HR EIMS, 372.2033, $C_{21}H_{28}N_2O_4$). The ^{13}C NMR spectrum (Table 7) is in agreement with the molecular formula deduced from the HR EIMS accounting for all 21 carbons. Its ^{1}H NMR spectrum (Table 7) showed the structural similarity with **1**, except for ring C protons, at δ 3.28 (t, J=7.0 Hz, 2H), 3.51 (q, J=7.0 Hz, 2H), 5.89 (br.t, J=6.7 Hz, 1H), 1.93 (s, 3H) and 2.66 (s, 3H) ascribed to H-1′, H-2′, H-3′, 3′-$COCH_3$ and 2-$COCH_3$, respectively. These data indicated the presence of an acetyl group at C-2 and a cleaved ring C in **9**. Furthermore, the chemical shift values of the other protons (H-9, H-12, 11-OCH_3) especially the indolic *N*–H which shifted down-field (δ 9.04, br.s) as compared to **1**, reaffirmed the presence of an electron withdrawing group at C-2. The ^{13}C NMR spectra also resembled that of **1**, except for changes due to the opening of ring C and additional substitution of an acetyl group at C-2 of indole. Thus its structure was elucidated as 3-(2-acetamidoethyl)-2-acetyl-5-caproyl-6-methoxy indole, which is hitherto unreported in the literature. It is interesting to note that this transformed product (**9**) is structurally similar to the synthetic compounds **4**, and **5**, which were produced in the Friedel Crafts acylation of **3**. Furthermore, compound **5** was also formed from **3** by auto-oxidation without providing Friedel Crafts reaction condition.

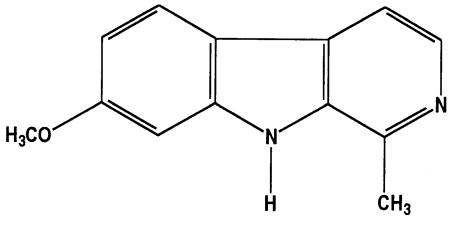
The transformation of compound **1** into **9**, and **3** into **5**, at room temperature, suggested that these compounds are inherently unstable at the C-3 position, which is due to the presence of an amide group at 4-*N*. In the ^{1}H NMR spectra of **1** and **3**, the down-field signal of H-3 at δ 5.73 and 5.71,

respectively, also showed its instability and propensity for radical formation. As reported in the literature[13] the weakly bonded protons (C–H) for example those adjacent to double bond and carbonyl group can form radicals, thus auto-oxidation with triplet molecular oxygen takes place. It may be suggested that the auto-oxidation of **1** and **3** (Scheme 2), progress through the radical formation at C-3 which reacted with molecular oxygen of air to form their respective C-3 peroxide derivatives. The peroxides collapsed to C-3 hydroxy compounds and then converted into ring C cleaved products **9** and **5** respectively. From the step by step ^{1}H NMR analysis of **1** and **3** it has been observed that the auto-oxidation process of **1** was faster than **3**. This might be due to the presence of caproyl group at C-10 of indolic moiety in **1**, which also increases the instability of H-3 (decrease in the bond energy of 3-C–H) and its ease towards auto-oxidation. This process of auto-oxidation of 4-*N*-acetyl tetrahydro β-carbolines can be developed into a synthetic methodology for obtaining tryptamine derivatives, which possess important biological activities.[3,4]

It is interesting to note that during these studies, the decomposition of teterahydroharmine (**2**) was also observed in chloroform solution of the ^{1}H NMR sample, which gave after fifteen days exclusively 3,4,5,6-tetradehydro derivative (harmine, **10**, see Section 3)[5c] probably through a radical mechanism. The same type of conversion has been witnessed previously in case of reserpine when its chloroform solution transformed into the 3,4,5,6-tetradehydro reserpine.[15]



	R_1	R_2	R_3	R_4
2	H	H	H	H
6	$COCH_3$	H	H	H
7	H	$COCH_3$	H	$COCH_3$
8	H	H	$COCH_3$	$COCH_3$



Harmine (10)

These observations are in agreement with the fact that alkaloids are unstable compounds towards their extraction, isolation and analysis procedures, where conditions such as pH, heat, light and organic solvents, all play important role in artifact formation.[15,16]

3. Experimental

3.1. General

Optical rotation was measured with Schmidt & Haansch Polartronic-D while CD spectrum was recorded on JASCO spectrophotopolarimeter J-600. UV (in MeOH) and IR (in $CHCl_3$) spectrum was run on Hitachi-U-3200 and JASCO-A-302 spectrophotometers, respectively. The EI, FAB positive, FAB negative and HREI mass spectra were recorded on Finnigan MAT-112, and JMS HX-110 spectrometers. The ^{1}H NMR spectra were recorded in C_6D_6, $CDCl_3$, C_3D_6O, CD_3OD, C_5D_5N and C_2D_6SO at room temperature (30°C) using Bruker Aspect AM-500 spectrometer operating at 500 MHz, with spectra referenced to residual protiodeuterio solvent signals. While ^{13}C NMR spectra (Broad Band and DEPT) were run on a Bruker Aspect AM-300 and AM-400 operating at 75 and 100 MHz, respectively. The chemical shifts are in ppm (δ) and coupling constants (J) are in Hz. The ^{13}C NMR spectral assignments have been made partly through DEPT and HMQC spectra and partly through comparison with the reported values of similar compounds.[5,6,17] The purity of compounds was checked on silica gel GF_{254} coated plates.

3.2. Plant material

The red flowers of *T. patula* were collected in the month of April 1998 from Karachi University campus. A voucher sample (KUH GH No. 67280) is preserved in the Botany department, Karachi University, Karachi, Pakistan.

3.3. Extraction and isolation

The fresh, undried, and uncrushed red flowers (600 g) of *T. patula* were extracted with petroleum ether (2.0 L×3) at room temperature, and solvent of combined extracts was evaporated under reduced pressure, yielding an oily residue (3.20 g). This was dissolved in water (15 ml) to give a whitish suspension which was decanted affording a water insoluble (JFP, 3.14 g) and soluble fractions, the latter was extracted with chloroform. The chloroform phase after drying on sodium sulfate anhydrous, and evaporation of solvent furnished 35.40 mg residue, which was subjected to preparative thin layer chromatography (Kiesel gel_{254}, petroleum ether/ethyl acetate, 2:8) furnishing jafrine (**1**) (21.4 mg) showing a single spot on tlc (R_f=0.46, petroleum ether/ethyl acetate, 2:8).

3.3.1. 3α-Methyl-4-*N*-acetyl-10-caproyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline, (jafrine) (1). Yellow gum, $[\alpha]_D^{26}$=+19.23 (*c* 0.10, $CHCl_3$); CD ($CHCl_3$, 29.0°C), λ_{max} ($\Delta\varepsilon$): 385 (+0.6), 367 (+1.5), 353 (+0.8), 340 (+1.6), 329 (−0.2), 317 (+1.8), 305 (−0.1), 292 (+1.4), 256 (+0.5), and 217 (+0.4); EIMS *m/z* (%) 356 (M^+, 89),

341 (100), 327 (17), 313 (19), 300 (33), 299 (88), 297 (25), 286 (18), 285 (85), 241 (14), 227 (19), 226 (11), 214 (27), 213 (15), 184 (10), 170 (12), 156 (10), and 55 (6); HR EIMS *m/z* 356.2078 (M^+, calculated for $C_{21}H_{28}N_2O_3$, 356.2099), 341.1907 (M^+-CH_3, $C_{20}H_{25}N_2O_3$), 328.1844 (a, $C_{19}H_{24}N_2O_3$), 301.1511 (b, $C_{17}H_{21}N_2O_3$), 297.1599 (c, $C_{18}H_{21}N_2O_2$), 214.0784 (d, $C_{12}H_{10}N_2O_2$), 98.0801 (e, $C_6H_{10}O$). For ^1H and ^{13}C NMR data, see Tables 1, 5, and 6.

3.3.2. (±)-3-Methyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline (2). Light pink amorphous powder, UV (MeOH) λ_{max}: 294, 278, 217, and 199 nm; IR ($CHCl_3$) ν_{max}: 3491, 2952, 2855, 1630, 1451, 1282 and 1163 cm^{-1}; EIMS *m/z* (%) 216 (M^+, 54), 201 (100), 187 (15), 186 (13), 172 (15), and 100 (6); HR EIMS *m/z* 216.1259 (M^+, calculated for $C_{13}H_{16}N_2O$, 216.1262). For ^1H NMR data, see Table 2.

3.3.3. Acetylation of (±)-tetrahydroharmine (2). Tetrahydroharmine (**2**) (2 g, 9.2 mmol) was dissolved in 2.0 ml (2.1 mmol) acetic anhydride at room temperature to readily give compound (±)-4-*N*-acetyl-tetrahydroharmine **3** (2.34 g) as colorless needles; (methanol/benzene; 1:1); mp 198–200°C; UV (MeOH) λ_{max}: 276, 266, 242, 229, 203 nm; IR ($CHCl_3$) ν_{max}: 3305, 3051, 2953, 2852, 1661, 1621, 1430, and 1162 cm^{-1}; EIMS *m/z* (%) 258 (M^+, 84), 244 (16), 243 (96), 215 (12), 201 (100), 199 (11), 186 (45), 172 (13), and 129 (12); HR EIMS *m/z* 258.1369 (M^+, calculated for $C_{15}H_{18}N_2O_2$, 258.1368), 243.1135 (M^+-15, $C_{14}H_{15}N_2O_2$). For ^1H and ^{13}C NMR data see Tables 3–6.

3.4. Synthesis of (±)-1 from (±)-3 through Friedel Crafts acylation (hexanoylation)

Hexanoyl chloride (6 ml, 43 mmol) and catalytic amount of aluminium chloride were added to a solution of (±)-4-*N*-acetyl tetrahydroharmine (**3**) (82 mg, 0.3 mmol) in nitrobenzene (5 ml) and the reaction mixture was kept at room temperature for 48 h and then filtered to separate aluminium chloride. The filtrate was subjected to preparative thin layer chromatography (PTLC, silica gel GF_{254}, petroleum ether/ethyl acetate, 2:8) affording (±)-**1** (9.52 mg) along with **4** (26.2 mg), **5** (11.4 mg) and other minor products. All spectral data of (±) jafrine (**1**) including UV, IR, EIMS and ^1H NMR, are same as those of (+) jafrine (**1**).

3.4.1. 3-(2-Acetamidoethyl)-2-caproyl-6-methoxyindole (4). Light brown gum, UV (MeOH) λ_{max}: 332, 283, 261, 254, 226, 216 and 203 nm; IR ($CHCl_3$) ν_{max}: 3351, 3105, 2952, 2851, 1683, 1621, 1452, and 1185 cm^{-1}; EIMS *m/z* (%): 330 (M^+, 32) 271 (100), 258 (25), 243 (24), 231 (16), 215 (50), 188 (42), and 169 (31); HR EIMS *m/z* 330.1934 (M^+, calculated for $C_{19}H_{26}N_2O_3$, 330.1943). For ^1H NMR data see Table 7.

3.4.2. 3-(2-Acetamidoethyl)-2-acetyl-6-methoxyindole (5). Light brown amorphous powder, UV (MeOH) λ_{max}: 331, 280, 262, 255, and 218 nm; IR ($CHCl_3$) ν_{max}: 3353, 3101, 2902, 1681, 1625, 1447, 1191, and 1116 cm^{-1}; EIMS *m/z* (%): 274 (M^+, 52), 215 (100), 202 (45), 188 (20), 160 (13), 149 (19), and 71 (27); HR EIMS *m/z* 274.1301 (M^+, calculated for $C_{15}H_{18}N_2O_3$, 274.1317), 215.0943 [$M^+-(HNCOCH_3+H^+)$, $C_{13}H_{13}NO_2$], 202.0856 ($C_{12}H_{12}NO_2$). For ^1H NMR data see Table 7.

3.5. Friedel Crafts acetylation of compound 3

A catalytic amount of aluminium chloride was added into a solution of **3** (1 g, 3.8 mmol) in acetic anhydride (1 ml, 10 mmol) and kept at room temperature for 48 h. After separation of aluminium chloride the resulting reaction mixture was subjected to PTLC (silica gel GF_{254}, petroleum ether/ethyl acetate, 2:8) furnishing compounds **6** (15.3 mg), **8** (4.2 mg), **7** (10.3 mg), and **5** (32.4 mg) in increasing order of polarity.

3.5.1. (±)-3-Methyl-1-*N*,4-*N*-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline (6). White amorphous powder, UV (MeOH) λ_{max}: 293, 282, 222, 210, and 202 nm; IR ($CHCl_3$) ν_{max}: 2953, 2854, 1691, 1620, 1425, 1302, and 1151 cm^{-1}; HR EIMS *m/z* (%) 300.1454 (M^+, calculated for $C_{17}H_{20}N_2O_3$, 300.1473, 94), 285.1258 (M^+-15, $C_{16}H_{17}N_2O_3$, 97) 243.1125 [$M^+-(COCH_3-CH_2)$, $C_{14}H_{15}N_2O_2$, 100], and 201.1029 ($C_{12}H_{13}N_2O$, 69). For ^1H NMR data see Table 2.

3.5.2. (±)-3-Methyl-4-*N*,10-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline (7). Yellowish brown amorphous powder, UV (MeOH) λ_{max}: 299, 285, 251, 212, and 203 nm; IR ($CHCl_3$) ν_{max}: 3305, 3042, 2952, 2849, 1680, 1663, 1619, 1451, and 1162 cm^{-1}; EIMS *m/z* (%) 300 (M^+, 91) 285 (100), 243 (87), 203 (15), 201 (32), 160 (14), and 97 (13); HR EIMS *m/z* (%) 300.1461 (M^+, calculated for $C_{17}H_{20}N_2O_3$, 300.1473). For ^1H NMR data see Table 2.

3.5.3. (±)-3-Methyl-4-*N*,12-diacetyl-11-methoxy-3,4,5,6-tetrahydro-β-carboline (8). Yellowish brown amorphous powder, UV (MeOH) λ_{max}: 298, 285, 252, 212, and 203 nm; IR ($CHCl_3$) ν_{max}: 3310, 3039, 2951, 2852, 1682, 1664, 1621, 1449, and 1162 cm^{-1}; EIMS *m/z* (%) 300 (M^+, 95), 285 (100), 243 (89) and 201 (42); HR EIMS *m/z* (%) 300.1465 (M^+, calculated for $C_{17}H_{20}N_2O_3$, 300.1473). For ^1H NMR data see Table 2.

3.5.4. 3-(2-Acetamidoethyl)-2-acetyl-5-caproyl-6-methoxyindole (9). Light brown gum, UV (MeOH) λ_{max}: 332, 282, 261, 253, and 221 nm; IR ($CHCl_3$) ν_{max}: 3361, 3104, 2951, 2857, 1679, 1621, 1451, and 1189 cm^{-1}; EIMS *m/z* (%): 372 (M^+, 37), 357 (29), 341 (79), 339 (17), 330 (59), 316 (13), 297 (35), 285 (68), 274 (44), 242 (55), 239 (100), 231 (15), 216 (34), and 204 (32); HR EIMS *m/z* 372.2033 (M^+, calculated for $C_{21}H_{28}N_2O_4$, 372.2049). For ^1H and ^{13}C NMR data see Table 7.

3.5.5. Harmine (10). Light yellow powder, UV (MeOH) λ_{max}: 345, 327, 301, 272, 240, 219 nm; IR ($CHCl_3$) ν_{max}: 3071, 2923, 1623, 1568, 1447, 1280, 1160, 1023 and 814 cm^{-1}; EIMS *m/z* (%): 212 (M^+, 100), 197 (20), 189 (75), 176 (73), 174 (42), 169 (31), 162 (50) and 150 (35); HR EIMS *m/z* 212.0974 (M^+, calculated for $C_{13}H_{12}N_2O$, 212.0949); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.17 (1H, br. s, H-1), 8.28 (1H, d, J=5.5 Hz, H-5), 7.69 (1H, d, J=5.5 Hz, H-6), 7.94 (1H, d, J=8.5 Hz, H-9), 6.88 (1H, dd, J=2.0, 8.5 Hz, H-10), 6.95 (1H, d, J=2.0 Hz, H-12), 2.77 (3H, s, H-3-Me) and 3.93 (3H, s, H-11-OMe).

References

1. (a) Manjunath, B. L. *Raw Material*; *The Wealth of India*, Vol. 10; CSIR: New Delhi, 1969 pp 109–112. (b) Fakim, A. G.; Gueho, J.; Bissoondoyal, M. S. *Int. J. Pharmacog.* **1997**, *35*, 237–254. (c) Grigorescu, E.; Segal, B.; Pavelescu, M.; Stanciu, V.; Dorneanu, V.; Stanescu, U.; Ionescu, A. Rom. Ro 90, 722 (C1. A61 K31/70), 10 Dec 1986, Appl. 114, 983, 23 Aug 1984, 3 pp.; *Chem. Abstr.* **1987**, *107*, 223318p. (d) Wells, C.; Bertsch, W.; Perich, M. *Chromatographia* **1993**, *35*, 109–115. (e) Vasudevan, P.; Kashyap, S.; Sharma, S. *Biores. Technol.* **1997**, *62*, 29–35.
2. (a) Kagan, J. *Progress in the Chemistry of Organic Natural Products*; Zechmeister, L., Ed.; 1991; Vol. 56, pp 87–169. (b) Ivancheva, S.; Zdravkova, M. *Fitoterapia* **1993**, *64*, 555 and references cited therein. (c) Menelaou, M. A.; Fronczek, F. R.; Hjortso, M. A.; Morrison, A. F.; Foroozesh, M.; Thibodeaux, T. M.; Flores, H. E.; Fischer, N. H. *Spectrosc. Lett.* **1991**, *24*, 1405–1413. (d) Karrer, P.; Jucker, E.; Steinlin, K. *Helv. Chim. Acta* **1947**, *30*, 531–535.
3. Allen, J. R. F.; Holmstedt, B. R. *Phytochemistry* **1980**, *19*, 1573–1582.
4. Husson, H. P. In *Simple Indole Alkaloids including* β-*Carbolines and Carbazoles*, Brossi, A., Ed.; *The Alkaloids*; Academic/Harcourt Brace Javanovich: Orlando, 1985; Vol. 26, pp 1–51.
5. (a) Siddiqui, S.; Khan, O. Y.; Faizi, S.; Siddiqui, B. S. *Heterocycles* **1988**, *27*, 1401–1410. (b) Ayer, W. A.; Browne, L. M. *Can. J. Chem.* **1970**, *48*, 1980–1984. (c) Siddiqui, S.; Khan, O. Y.; Faizi, S.; Siddiqui, B. S. *Heterocycles* **1989**, *29*, 521–527.
6. Abreu, P.; Pereira, A. *Nat. Prod. Lett.* **2001**, *15*, 43–48.
7. (a) Tsuda, M.; Watanabe, D.; Kobayashi, J. *Heterocycles* **1999**, *50*, 485–488. (b) Stockigt, J.; Zenk, M. H. *J. Chem. Soc., Chem. Commun.* **1977**, 646–648.
8. (a) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849–858. (b) Fischer, G. *Chem. Soc. Rev.* **2000**, *29*, 119–127.
9. Wilson, N. K.; Stothers, J. B. In *Stereochemical Aspects of* ^{13}C *NMR Spectroscopy*, Eliel, E. L., Ed.; *Topics in Stereochemistry*; Wiley: New York, 1974; Vol. 8, pp 1–158.
10. Lukáts, Á. P.; Kocsis, Á.; Szabó, L. F.; Podányi, B. *J. Nat. Prod.* **1999**, *62*, 1492–1499.
11. Rahman, A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 736–738.
12. (a) Siddiqui, S.; Begum, S.; Siddiqui, B. S. *Pakistan J. Sci. Ind. Res.* **1983**, *26*, 53–58. (b) Gaskell, A. J.; Joule, J. A. *Tetrahedron* **1967**, *23*, 4053–4063.
13. (a) Solomons, T. W. G. *Radical Reactions, and Conjugated Unsaturated Systems*; *Organic Chemistry*, Wiley: New York, 1996 pp 366–414 and 496–533. (b) Gilbert, A.; Baggott, J. *Photo-Oxygenation Reactions*; *Essentials of Molecular Photochemistry*, Oxford Blackwell Scientific: London, 1991 pp 501–525.
14. Machado, M. I. L.; Silva, M. G. V.; Matos, F. J. A.; Craveiro, A. A.; Alencar, J. W. *J. Essent. Oil Res.* **1994**, *6*, 203–205.
15. Svendsen, A. B.; Verpoorte, R. *Chromatography of Alkaloids*; Elsevier: Amsterdam, 1983 pp 51–58.
16. Lounasmaa, M.; Hanhinen, P. *J. Nat. Prod.* **2000**, *63*, 1456–1460.
17. Morales-Ríso, M. S.; Espiñeira, J.; Joseph-Nathan, P. *Magn. Reson. Chem.* **1987**, *25*, 377–395.