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Nobilisitine A and B, two masanane-type alkaloids from *Clivia nobilis*☆

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Abstract

Two masanane-type lactone alkaloids, named nobilisitine A and B, were isolated from Egyptian *Clivia nobilis* and characterized by spectroscopic and chemical methods. Both compounds showed contain the same [2]benzopyrano[3,4-*g*]indole ring system and therefore belong to the same subgroup of Amaryllidaceae alkaloids. In particular, nobilisitine A and B, reported as two new alkaloids, proved to be the 5*β*-hydroxy-3a,11c-*epi*-masan-7-one and the 3-hydroxybutanoyl ester of clivonine (5α-hydroxy-5a-*epi*-masan-7-one), the alkaloid previously extracted from *Clivia miniata* and belonging to the same alkaloid subgroup. Nobilisitine B appears to be an epimer at the acyl side chain of clivatine.

Keywords: Clivia nobilis; Amaryllidaceae; Masanane-type alkaloids; Nobilsiitine A and B; Clivatine epimer

1. Introduction

Clivia miniata and *Clivia nobilis* Regel (Amaryllidaceae) are cultivated in Egypt as ornamental plants for their beautiful flowers. *Clivia* species have been the major source of alkaloids represented by the 3a,4-dihydrolactone[2]benzopyrano[3,4-*g*]indole ring system and containing four chiral centers at the ring junction positions (3a, 5a, 11b and 11c). The further chiral position at C-5 is due to the presence of an oxygen substitute. This class of alkaloids is represented by clivonine which was previously isolated from *C. miniata* (Kobayashi et al., 1980; Jeven et al., 1982; Ali, Ross, El Moghazy, & El Moghazy, 1983) while from *C. nobilis* three alkaloids were isolated and identified, lycorine, clivatine and nobilisine (Jeffs, Mueller, Abou-Donia, Seif El-Din, & Campau, 1988), the latter being a stereochemical variant of the masanane ring system (Jeffs et al., 1988).

In the present work, we describe the isolation and the chemical characterization of two new Amaryllidaceae alkaloids containing the 3a,4-dihydrolactone[2] benzopyrano[3,4-*g*]indole ring system but belonging to different stereochemical classes. They are part of the masanane alkaloid series showing epimerization at both C-3a and C-11c and C-5a.

2. Results and discussion

Two crystalline alkaloids are isolated (for details see Section 3) from the crude $CHCl_3$ extract of *C. nobilis* and named nobilisitine A and B (**1** and **3**, respectively). Preliminary spectroscopic data, indicate that they contain the same [2]benzopyrano[3,4-*g*]indole ring system and therefore should belong to the same subgroup of Amaryllidaceae alkaloids. In fact, the IR, UV, NMR and EI-MS data of the two lactone alkaloids, which recall those of other alkaloids belonging to this subfamily, suggested that they belong to the masanane-type (Hawksworth, Jeffs, Tidd, & Toube, 1965; Ibuka et al., 1966; Jeffs, Hansen, Döpke, & Biernet, 1971; Jeffs, Abou-Donia, Campau, & Staiger, 1985; Jeffs et al., 1988).

Beside the characteristic band of the lactone group the IR spectrum of nobilisitine A (**1**) showed one hydroxy group at 3545 cm^{-1} (Nakanishi & Solomon, 1977), suggesting for **1** the structure of a 5a-hydroxy lactone related

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[1] This institute is part of the 'Istituto Nazionale di Chimica dei Sistemi Biologici'.

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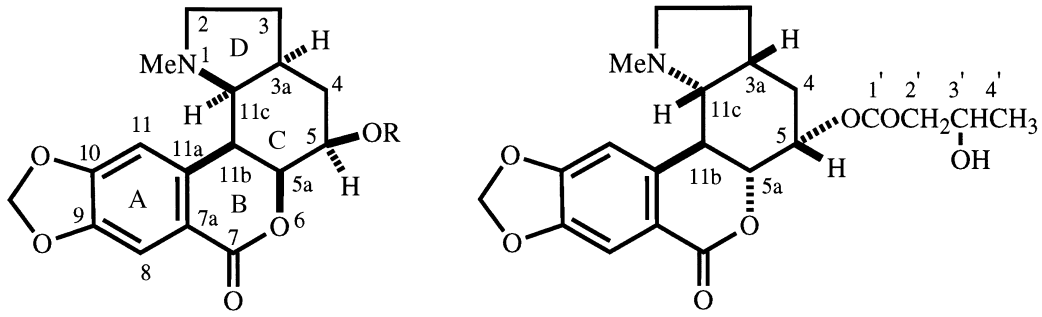

1 R=H **2** R=Ac **3**

Structure 1.

alkaloid. In fact, an examination of the ^{1}H NMR spectrum (Table 1) showed the presence of the two singlets at δ 7.05 and 7.53, assigned to H-11 and H-8 of the benzopyran moiety, in agreement with the downfield effect induced on the latter (H-8) by the lactone group at C-7 in other closely related alkaloids (Hawksworth et al., 1965). The broad and the sharp singlets, typical of the 9,10-methylendioxy and the *N*-methyl groups, resonated at δ 6.05 and 2.24, respectively (Hawksworth et al., 1965; Jeffs et al., 1971; Jeffs et al., 1985, 1988). These structural features were also confirmed by ^{13}C NMR data Table 1. Besides the signals stemming from the carbons of tetra-

Table 1
^{1}H and ^{13}C NMR data of nobilisinine A and B (**1** and **3**, respectively). The chemical shifts are in δ-values (ppm) from TMS[a]

C	**1**			**3**			
	δC	δH	*J* (Hz)	δC	δH	*J* (Hz)	HMBC[c]
2	54.9 t[b]	3.24 ddd	13.6, 8.0, 4.2	53.0 t[b]	3.28 ddd	13.4, 9.0, 5.0	
		2.30 m			2.56 m		
3	30.1 t	2.00 m		30.8 t	2.11 dddd	12.9, 9.0, 4.6, 4.6	
		1.62 m			1.93 m		
3a	34.7 d	2.27 m		32.8 d	2.52 m		
4	33.7 t	2.02 m		28.4 t	2.26 ddd	15.9, 2.8, 2.8	
		1.62 m			1.99 ddd	15.9, 7.1, 4.1	
5	68.6 d	3.96 ddd	9.9, 6.6, 5.0	69.3 d	5.40 ddd	4.1, 4.1, 2.8	2.26, 3.25
5a	81.4 d	4.65 dd	6.6, 5.0	78.5 d	4.21 dd	12.6, 4.1	
7	164.0 s			164.1 s			4.21
7a[e]	137.3 s			139.9 s			3.25, 2.94
8	109.7 d	7.53 s		109.3 d	7.50 s[d]		
9[e]	152.6 s			155.6 s			
10[e]	147.2 s			146.9 s			
11	106.5 d	7.05 s		106.7 d	7.70 s[d]		
11a[e]	118.6 s			118.7 s			
11b	36.6 d	3.34 dd	5.0, 5.0	34.6 d	3.25 dd	12.6, 9.0	2.94
11c	66.6 d	2.67 dd	5.8, 5.0	69.0 d	2.94 dd	9.0, 6.5	3.25
9,10-OCH_2O	102.0 t	6.05 br s		101.9 t	6.05 d	1.4	
					6.04 d	1.4	
N–Me	41.8 q	2.24 s		44.6 q	2.55 s		2.94
C-1′				171.5 s			
C-2′				43.5 t	2.51 d	6.2	
C-3′				64.1 d	4.21 m		
C-4′				23.0 q	1.24 d	6.3	

[a] 2-D ^{1}H, ^{1}H and 2 ^{13}C, ^{1}H NMR experiments delineated the correlations of all protons and the corresponding carbons.
[b] Multiplicities determined by DEPT spectra.
[c] Heteronuclear multiple bond correlation spectrum.
[d] The unusual chemical shift values were attributed in agreement with the value reported for clivonine (Jeffs et al., 1971).
[e] Assigned in agreement with the values reported for the same carbons in structurally close alkaloids (Evidente et al., 1983; Jeffs et al., 1985).

substituted aromatic ring, the signals of the lactone, the methylenedioxy and the *N*-methyl groups were observed at the typical δ-values of 164.6, 102.0 and 41.8 ppm, respectively (Jeffs et al., 1985). Moreover, the two oxygenated doublets present at δ 81.4 and 68.6 were accordingly assigned to the oxygenated lactone (C-5a) and hydroxylated (C-5) carbons, respectively (Jeffs et al., 1985). The examination of the COSY(Correlated Spectroscopy) (Bax & Freeman, 1981) and HMQC (Heteronuclear Multiple Quantum Correlation) (Bax, Ikura, Kay, Torchia, & Tschudin, 1990) spectra confirmed these attributions and allowed the assignment of the chemical shifts of all protons and carbons of other three methyne (HC-3a, HC-11b and HC-11c) and three methylene (H_2C-2, H_2C-3 and H_2C-4) groups as reported in Table 1. In addition, the doublet of double doublets of H-5 appeared at δ 3.96 and the constants measured for its coupling with both the protons of CH_2-4 ($J_{4,5}=9.9$ and $J_{4',5}=5.0$ Hz) and H-5a ($J_{5,5a}=6.6$ Hz) allowed assignment of an axial and an equatorial orientation to H-5 and H-5a, respectively. Consequently, the coupling constant of 5.0 Hz between H-5a and H-11b indicated an axial orientation of H-11b and therefore a *cis* B/C ring fusion; furthermore, the coupling of 5.0 Hz between H-11b and H-11c determines an equatorial orientation of H-11c. Finally, the constant of 5.8 Hz measured for the coupling between H-11c and H-3a was consistent with an axial orientation of H-3a and therefore with a *cis* C/D ring fusion. This sterostructure with both *cis* B/C and *cis* C/D ring fusion and the inspection of a Drieding model of **1**, were in agreement with the diagnostic ^{1}H chemical shift value of 2.24 ppm for the *N*-methyl group. This value is very similar to those observed in other related Amaryllidaceae alkaloids containing the 3a,4-dihydrolactone[2]benzopyrano[3,4-*g*]indole ring system and belonging to the same stereochemical class II (Hawksworth et al., 1965; Jeffs et al., 1988). Therefore alkaloid **1** was identified as 5-hydroxy-3a,11c-*epi*-masan-7-one. As suggested by the coupling between H-5 and the two protons of CH_2-4, the C-5 hydroxy group should be equatorial and therefore assume a β-configuration. Consequently, the structure and the relative configuration depicted in **1** could be assigned to nobilisitine A. This structure was supported by EI-MS data. They showed the molecular ion at m/z 317 and a fragmentation peaks at m/z 190 with its daughter ion at m/z 162, which were produced from the parent ion by a mechanism typical of the lactone alkaloids containing the [2]benzopyrano[3,4]indole ring system (Ibuka et al., 1966; Jeffs et al., 1985). Other characteristic ions, produced by the alkaloids of this subgroup by a retro-Diels–Alder cleavage of the C ring, were observed at m/z 126 and 96 (base peak) (Ibuka et al., 1966; Jeffs et al., 1985).

Therefore nobilisitine **1**, may be formulated as 5β-hydroxy-3a,11c-*epi*-masan-7-one, which to the best of our knowledge is the first natural occurring alkaloid of the masanane series showing epimerization at both C-3a and C-11c.

Its structure was confirmed by preparation of the corresponding 5-*O*-acetyl derivative (**2**). The ^{1}H NMR of **2** differed from that of **1** only for the downfield shift ($\delta\Delta$ 1.10) of H-5 resonating as doublet of double doublets at δ 5.06, and for the singlet of the acetyl group present at δ 2.06. Its EI mass spectrum showed the expected molecular ion at m/z 359 which by the alternative loss of CH_2CO, CH_3CO or ACOH generated the ions at m/z 317, 316 and 299, respectively. Moreover, it presented the fragmentation ions typical formed of alkaloids of this subgroup and already observed in **1** (Ibuka et al., 1966; Jeffs et al., 1985).

^{1}H and ^{13}C NMR data (Table 1) indicate that nobililisitine B (**3**) is very similar to **1** and other related alkaloids (Hawksworth et al., 1965; Jeffs et al., 1971, Jeffs et al., 1985, 1988). However, some substantial differences were noted with respect to **1**. The stereochemistry of the B/C and C/D ring fusions should be different. The large typical values of the coupling constants between H-11b with both H-5a ($J_{5a,11b}=12.6$ Hz) and H-11c ($J_{11b,11c}=9.0$ Hz) indicate that the three protons assume an axial orientation and therefore the B/C ring fusion should be *trans*. Furthermore, the values of 6.5 Hz for the coupling of H-11c with H-3a determine an equatorial orientation for the latter proton indicating that the C/D ring fusion should be *cis*. This steric situation has also been observed in the 5a-*epi*-masanane, some 5-substituted 5a-*epi*-masan-7-one (Jeffs et al., 1988) and clivonine, which is the well known 5a-hydroxy-5a-*epi*-masan-7-one previously isolated from *C. miniata* (Jeffs et al., 1971). This relative stereostructure and the inspection of a Drieding model of **3** were consistent with the diagnostic chemical shifts values of the N–Me group appearing at δ 2.55, which is very similar to that of the other alkaloids belonging to the same stereochemical class III (Hawksworth et al., 1965; Jeffs et al., 1988).

Moreover, the very typical values of 4.1 Hz measured for the coupling between the axial H-5a and H-5 suggested for this hydrogen an equatorial *cis*-orientation. Consequently, the oxygenated substituent at C-5 should be axial and therefore assume an α-configuration. On the basis of these considerations and the characteristic chemical shift value of H-5 resonating at δ 5.40, the alkaloid **3** should be a clivonine ester. This hypothesis was confirmed by the examination of its COSY and HMQC spectra, which allowed the assignment of all protons and carbons of the clivonine moiety as well as those of the acyl residue (Table 1), which appeared to be the 3-hydroxybutanoyl. In fact, the ^{1}H NMR spectrum showed the multiplet of the secondary hydroxylated carbon (HC-3′) overlapped with the signal of H-5a, at δ 4.21. The latter proved to be coupled with the protons of the adjacent methylene (H_2C-2′) and methyl (Me-4′) groups, both appearing as a doublet at δ 2.51 and 1.24, respectively.

As expected, the carbonyl ester group (C-1′) resonated, in the ^{13}C NMR spectrum, at the very typical chemical shift values of δ 171.5, and the other carbons of the acyl chain were present at δ 64.1, 43.5 and 23.0 (C-3′, C-2′ and C-4′, respectively) (Breitmaier & Völter, 1987).

These results suggested that the structure of compound **3** is the 3-hydroxybutanoil ester of clivonine, and this is consistent with the correlations observed in the HMBC (Heteronuclear Multiple-Bond Correlation) NMR spectrum Table 1 (Bax & Summers, 1986) and with the IR data. Beside the band typical of the conjugated lactone at 1701 cm^{-1}, the latter spectrum showed typical bands of an ester and an hydroxy group at 1726 and 3585 cm^{-1}, respectively (Nakanishi & Solomon, 1977).

The structure assigned to nobilisitine B was confirmed by mass spectra data. In fact, the EI-MS spectrum showed the intense molecular ion at *m/z* 403, which by the consecutive loss of the methyl and H_2O from the acyl side chain produced the ions at *m/z* 388 and 370. By alternative fragmentation mechanisms, the molecular ion by loss of the 3-hydroxybutanoyl, the corresponding ketene or the carboxy residue generated the significant ions at *m/z* 316, 317 and 300, respectively. The same spectrum showed, as previously observed for **1**, the ion at *m/z* 162 which is produced from ion at *m/z* 317 by a fragmentation mechanism typical of the lactone alkaloids containing the [2]benzopyrano[3,4-*g*]indole ring system. Moreover, the characteristic ions produced from the alkaloids of this subgroup by a retro-Diels–Alder cleavage of the C ring, were also observed at *m/z*, 126 and 96 (base peak) (Hawksworth et al., 1965; Ali et al., 1983). Finally, its FAB-MS showed the pseudomolecular ion at *m/z* 404, which by loss of the carboxybutanoyl residue produced the ion at *m/z* 301.

Nobilitisine B (**3**) may be thus formulated as the 3-hydroxybutanoyl ester of clivonine. Furthermore, spectroscopic data of **3** were very similar to the partial data reported for clivatine (Kobayashi et al., 1980), except for the ^1H chemical shifts of H-11c and CH_2-2′ protons. Clivatine is an alkaloid of the same subgroup previously isolated from *C. miniata* Regel (Kobayashi et al., 1980) and *C. nobilis* (Jeffs et al., 1988), and had been already described by Döpke (1977) as an ester of clivonine and the β-hydroxybutyric acid. However, the significant downfield shift ($\Delta\delta$ 0.31) measured for the CH_2-2′ by comparison of the ^1H NMR data of **3** with those reported in the partial spectroscopic data of clivatine (Kobayashi et al., 1980) suggested that nobilisitine B might be a stereoisomer of clivatine epimeric at C-3′. This structure was strongly supported by the marked difference observed in the melting point measured for **3** (205–207°C) compared to those (159–161 and 167–168°C) reported for clivatine (Kobayashi et al., 1980; Jeffs et al., 1988).

In conclusion, this paper reports the isolation and the chemical characterization of two new Amaryllidaceae alkaloids containing both the 3a,4-dihydrolactone[2]benzopyrano[3,4-*g*] indole ring system but belong to a different stereochemical class. In particular, nobilisitine A is the first naturally occurring alkaloid of masanane series showing epimerization both at C-3a and C-11c while, to the best of our knowledge, nobilisitine B is an unusual 3-hydroxybutanoyl ester of clivonine epimer at C-3′ of clivatine.

3. Experimental

3.1. General

Mps uncorr.; UV and IR: MeOH and KBr, respectively. ^1H and ^{13}C NMR: 500, 300 and 250 and 125, 100 or 75 MHz, respectively on Bruker in $CDCl_3$, using the same solvent as internal standard. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) spectra (Breitmaier & Völter, 1987). DEPT, COSY, HMQC and HMBC experiments were performed using Bruker microprograms. EI-MS: 70 eV; FAB-MS: glycerol–thioglycerol using Cs as bombarding gas. Analytical and preparative TLC: silica gel (Merck, Kieselgel, 60 F_{254}, 0.25 and 0.50 mm, respectively) plates; the spots were visualized by exposure to I_2, UV radiation or Dragendorff's spray reagent. CC: silica gel (Merck, Kieselgel 0.063–0.2 mm). Solvent systems: (a) $CHCl_3$–MeOH (9:1), (b) $CHCl_3$–MeOH (85:15), (c) $CHCl_3$–EtOAc–MeOH (2:2:1).

3.2. Plant materials

C. nobilis was collected in May 1997 from flowering plants, cultivated in Alexandria, Egypt. The plant was kindly identified by Professor Nabil El Hadidy (Faculty of Science, Cairo University, Egypt). A voucher sample is deposited in the Department of Pharmacognosy, Faculty of Pharmacy, Alexandria.

3.3. Extraction and purification of the alkaloids

Freshly chopped whole plant (8 kg) was exhaustively extracted with 95% EtOH by percolation. The combined extracts were concentrated under red. pres. and then defatted with petrol, acidified with 5% tartaric acid to pH 2, filtered and then washed with Et_2O. The acidic aqueous phase was rendered alkaline with NaOH solution to pH 10, and extracted successively with $CHCl_3$, EtOAc and *n*-BuOH. The $CHCl_3$ extracts were combined, washed with H_2O and dried (Na_2SO_4), then concentrated to a small volume, at this stage lycorine was precipitated (2 g). The crude alkaloidal residue (5 g) left after removal of the solvent was fractionated over a silica gel column. Elution achieved using $CHCl_3$–MeOH mixtures of increasing polarity until pure MeOH was used. Fractions (100 ml each) were collected and monitored by TLC

(solvent systems a and b). Chromatographic separation resulted in the isolation of nobilisitine A, B and lycorine. Fractions eluted with 3% MeOH in $CHCl_3$ resulted in the isolation of nobilisitine B (35 mg) as colorless needles from MeOH. Fractions eluted with 4% MeoH in $CHCl_3$ were further purified by CC on silica gel eluted with 2% MeOH in $CHCl_3$ and then by preparative TLC using the solvent system A to give colorless clusters of nobilisitine A (300 mg).

3.4. Nobilisitine A (*1*)

Mp 186–187°; UVλ_{max} nm (log ε): 305 (3.71), 265 (3.67) and 232 (4.28); IR ν_{max} cm^{-1}: 3545 (OH), 1712 (C═O, lactone); ^1H and ^{13}C NMR: Table 1; EI-MS *m/z*: (rel. int.): 317 $[M]^+$ (78), 300 $[M–OH]^+$ (1), 190 $[M–H_2–C_7H_{11}NO]^+$ (6.3), 162 $[M–H_2–C_7H_{11}NO–CO]^+$ (16), 126 (22) $[C_7H_{12}NO]^+$, 96 $[C_6H_{10}N]^+$ (100).

3.5. 5-O-*Acetylnobilisitine A* (*2*)

Nobilitine A (**2**, 2 mg) was acetylated with pyridine and Ac_2O at room temperature overnight. The reaction was stopped by addition of MeOH and the mixture was dried by a N_2 stream. The residue was purified by preparative TLC (eluent C) to afford 5-*O*-acetylnobilisitine A (**3**, 1.8 mg) as pure oil: ^1H NMR differed from that of nobilisitine A only for the following signals, δ: 5.06 (^1H, ddd, $J=10.0$, 6.7 and 4.9 Hz, H-5), 2.06 (3H, s, MeCO); EI-MS *m/z*: (rel. int): 359 $[M]^+$ (61), 317 $[M–CH_2CO]^+$ (3.7), 316 $[M–CH_3CO]^+$ (22), 299 $[M–AcOH]^+$ (14), 190 $[M–CH_2CO–H_2–C_7H_{11}NO]^+$ (4), 162 $[M–CH_2CO–H_2–C_7H_{11}NO–CO]^+$ (15), 126 $[C_7H_{12}NO]^+$ (38), 96 $[C_6H_{10}N]^+$ (100).

3.6. Nobilisitine B (*3*)

Mp 205–207°; UVλ_{max} nm (log ε): 305 (3.65), 266 (3.66) and 232 (4.21); IR ν_{max} cm^{-1}: 3585 (OH), 1726 (C═O, ester), 1701 (C═O, lactone); ^1H and ^{13}C NMR: Table 1; EI-MS (rel. int.): *m/z*: 403 $[M]^+$ (62), 388 $[M–Me]^+$ (7), 370 $[M–Me–H_2O]^+$ (2), 359 $[M–CH_3CHO]^+$ (5), 317 $[M–CO═CHCH(OH)CH_3]^+$ (9) 316 $[M–COCH_2CH(OH)CH_3]^+$ (33), 300 $[M–OCOCH_2CH(OH)CH_3]^+$ (25), 162 $[M–CO═CHCH(OH)CH_3–H_2–C_7H_{11}NO]^+$ (11), 126 $[C_7H_{12}NO]^+$ (37), 96 $[C_6H_{10}N]^+$ (100); FAB-MS *m/z* (rel. int.): 404 $[MH]^+$ (100), 301 $[MH–OCOCH_2CH(OH)CH_3]^+$ (36).

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