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ALKALOIDS FROM *NARCISSUS CONFUSUS**

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Key Word Index—*Narcissus confusus*; Amaryllidaceae; haemanthamine; galanthamine; *N*-formylgalanthamine; pretazettine; two-dimensional NMR spectra.

Abstract—We report the isolation of haemanthamine, galanthamine, pretazettine and the new alkaloid *N*-formylgalanthamine from *Narcissus confusus* plants. Structural determination was carried out by spectroscopic analyses and application of two-dimensional NMR spectroscopy.

INTRODUCTION

The *Narcissus* genus of the Amaryllidaceae is mainly distributed in Europe throughout the Mediterranean region, most of the species being indigenous to the Iberica Peninsula. Our previous reports on the alkaloid series of these plants have established the presence of pseudolycorine and two new acetylated derivatives, together with assoanine and oxoassoanine in *N. assoanus* collected in Montserrat (Barcelona) [2, 3], and the occurrence of homolycorine and 9-*O*-demethylhomolycorine in extracts A and D of *N. confusus* Pugsley [1]. This plant has turned out to be particularly rich in galanthamine (**2**) (0.1% fresh weight of bulbs), the major alkaloid, which has been used in Russia in the treatment of myasthemia gravis, myopathy and diseases of the nervous system [4]. Moreover, a new derivative, *N*-formylgalanthamine (**3**), together with haemanthamine (**1**) and pretazettine (**4**), has been isolated. It should be pointed out that *N*-formyl derivatives of alkaloids are quite uncommon, and this is the first time that a natural *N*-formyl alkaloid has been reported in a member of the Amaryllidaceae.

RESULTS AND DISCUSSION

Compound **1**, $C_{17}H_{19}NO_4$, was identified as haemanthamine on the basis of its physical and spectroscopic data. Thus, its mass spectrum shows the parent peak at *m/z* 301 and fragmentations at *m/z* 227, 225 and 181 [5, 6]. The most important signals of the ^{1}H NMR spectrum recorded in $CDCl_3$ are (i) singlets at δ 3.36 and 5.90 corresponding to a methoxy group and a methylenedioxy group, and at δ 6.48 and 6.84 for the aromatic protons H-7 and H-10, respectively (for the sake of uniformity, the numbering system employed in Ghosal's review [7] is followed), the latter being more deshielded by the nearby double bond [8]; (ii) a doublet at δ 6.40 for H-1 and a double doublet at δ 6.30 for H-2, having coupling constants in agreement for a structure of the haemanthamine series [8]; (iii) two doublets at δ 3.68 and 4.30 for the diastereotopic protons of the C-6 methylene. The chemical shifts observed for **1** are similar to those described for haemanthamine in DMSO-d_6 solution [9].

For unambiguous assignment of the signals of the spectrum (Table 1) a ^{1}H–^{1}H homonuclear correlation experiment (COSY) was recorded. Nonetheless, the large singlet due to the methoxy group masks the signals of correlation in its surroundings (δ 3.0–3.6).

In order to avoid this and to obtain another homonuclear correlated ^{1}H NMR spectrum, but with only those signals and correlations of the protons of the carbon skeleton (without interference of the large singlets of the methoxy and methylendioxy groups), an experiment from the double quantum filtered (DQF) COSY sequence [10, 11] was used.

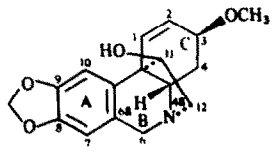
Figure 1 shows the homocorrelated spectrum with

Table 1. ^{1}H NMR (200 MHz) spectral data for haemanthamine (**1**)

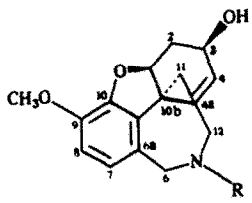
Assignment	δ($CDCl_3$)
H-1	6.40 *d* (10.1)*
H-2	6.30 *dd* (10.1, 4.8)
H-3	3.88 *m* (4.8, 3.6, 1.9, 1.6)
H_α-4	2.12 *ddd* (13.5, 13.4, 3.6)
H_β-4	2.06 *ddd* (13.5, 6.1, 1.9)
H-4a	3.32 *dd* (13.4, 6.1)
H_α-6	4.30 *d* (16.8)
H_β-6	3.68 *d* (16.8)
H-7	6.48 *s*
H-10	6.84 *s*
H-11	3.98 *dddd* (6.6, 3.5, 1.1)
H_{exo}-12	3.39 *dd* (14.0, 6.6)
H_{endo}-12	3.19 *dd* (14.0, 3.5)
OCH_2O	5.90 *s*
OCH_3	3.36 *s*

*Values in parentheses are coupling constants in Hz.

*Part 4 in the series "*Narcissus* Alkaloids". For Part 3, see ref. [1].



1



2 R = CH_3
3 R = CHO

DQF in absolute value representation. Thus, correlation of H-3 with either the vinylic proton H-2 or H-4 is observed and H-10 (δ 6.84) exhibits a correlation with either H-1 or H-7, whilst the latter also correlates with both protons of the C-6 position. This agrees with former observations on the weak splitting of this aromatic proton [8]. The assignment of the C-12 protons is evidenced by their correlation with H-11. The neatness of this zone of the spectrum, once the signal of the methoxy group has been removed, shows the great value of this technique.

Nonetheless, confirmation of the relative configuration

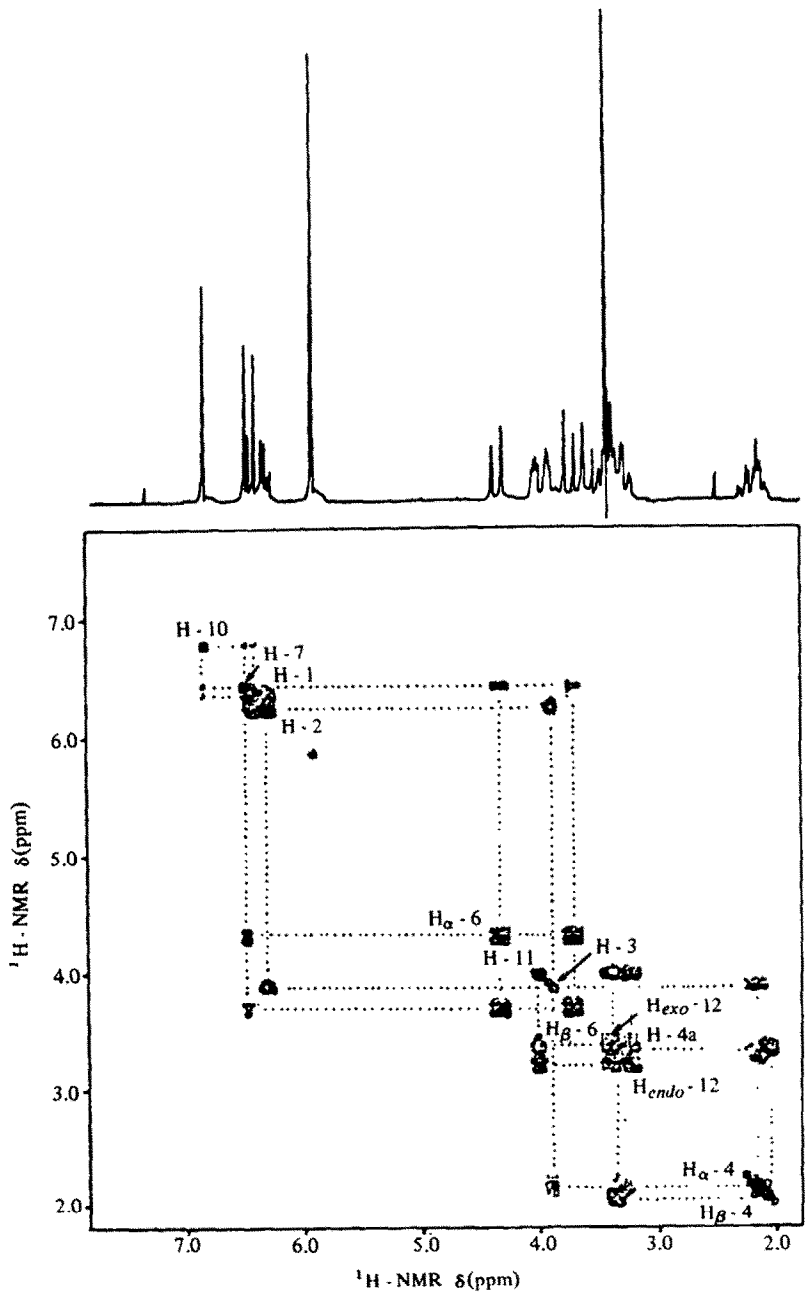


Fig. 1. Homonuclear correlated ^{1}H NMR spectrum (200 MHz) with DQF of haemanthamine (1) in $CDCl_3$.

of H-3 and H-11, as well as of the disposition of the ethylidene bridge C-11/C-12 (distinction between the haemanthamine and the crinine series) has been achieved by means of the 2D NOE technique (Fig. 2). Thus, H_α-6 (δ4.30) shows a NOE effect with *endo* H-12 (δ3.19) (the *exo* H-12 is at lower field due to its *cis* disposition with the nitrogen lone pair). In turn, H_β-6 (δ3.68) is close to H-4a, which confirms the *trans* disposition for rings B and C. Moreover, the existence of a NOE effect between H-11 and pseudo-axial H-4 (δ2.12) implies a *syn* position of the C-11 hydroxyl with respect to the aromatic ring, and the half-chair conformation for ring C.

The ^{13}C NMR spectrum of **1** agrees with previous literature [12], with variations not exceeding ± 0.7 ppm.

Compound **2**, $C_{17}H_{21}NO_3$, was identified as galanthamine on the basis of its physical and spectroscopic data [12, 13]. Surprisingly enough, although it is a widespread Amaryllidaceae alkaloid, its mass spectrum and ^1H NMR spectrum do not seem to be available in previous literature [7, 14, 15]. The latter exhibits (i) an AB system at δ6.78 and 6.74 corresponding to the two *ortho* aromatic protons H-7 and H-8; (ii) a *dd* and *ddd* at δ6.21 and 6.10 for the olefinic protons H-4a and H-4; (iii) two singlets at δ3.95 and 2.52 due to the *O*-methyl and *N*-methyl protons, respectively; and (iv) two doublets at δ4.21 and 3.79, the latter with a small 1 Hz splitting, for the methylene protons adjacent to the aromatic ring and the amine group. Complete assignment of all the other signals and exact measurement of the coupling constants were performed according to the proton selective decoupling experiments. Thus, irradiation of H-1 induces simplification of the doublet of doublets (*dd*) at δ2.12 due to H_α-2 to a doublet, the *ddt* at δ2.80 due to H_β-2 to a *dt* and the *dd* at δ6.21 due to H-4a which loses the long-range splitting of *ca* 1 Hz. Irradiation of H-3 affected both H-4 (δ6.10 *br d*) and the β-proton of the C-2 position (δ2.80, *ddd*). Irradiation of H_α-12 simplified the signals due to H_α-6 (δ3.79, *d*), H_α-11 (δ2.20, *dd*) and H_β-11 (δ1.69, *dd*).

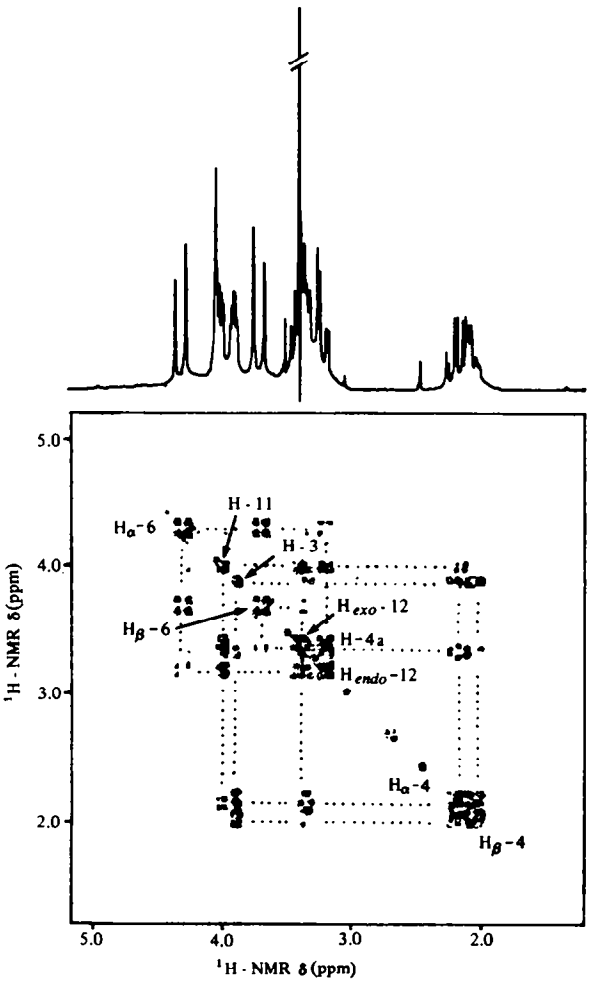


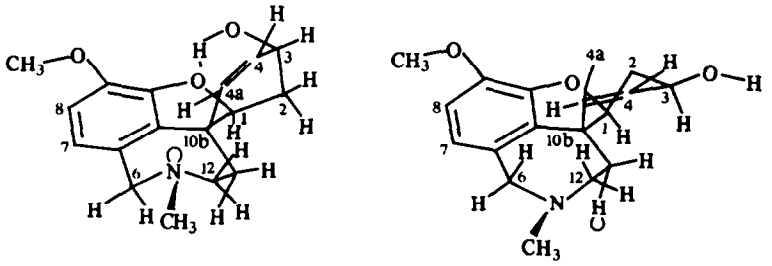
Fig. 2. 2D NOE spectrum of haemanthamine (**1**) in $CDCl_3$.

Ring B can adopt two conformations, being the amino group either *syn* or *anti* with respect to the C-10b–C-4a bond (Fig. 3). Examination of the Dreiding model of the *anti*-conformation reveals that the axial protons of positions C-6 and C-12 should show a strong NOE effect with the olefinic proton H-4a. In order to study the conformation of this ring and to confirm the foregoing assignments (Table 2) a 2D NOE experiment was performed. It revealed spatial proximity between H-8 and the *O*-methyl group, and between H-1 and H_α-11. Nonetheless, there was no NOE effect between H-4a and H_β-6 or H_β-12, which implies a *syn*-conformation for ring B. Further evidence for this was afforded by the existence of a NOE effect between H_α-6 and H_α-11. Moreover, in this conformation, the nitrogen lone pair is directly affecting H-4a (for the methyl group must be equatorial), which stands for its shift at lower fields with respect to H-4.

On the other hand, ring C adopts a conformation in which the β-hydroxyl group is axial, so that a hydrogen bond can be established between the latter and the heterocyclic oxygen atom. This conformation is further supported by measurement of the dihedral angles of vicinal hydrogens in the Dreiding model (which agree with the coupling constants measured for H-3 and H_α-2), and the coplanarity of H-1 with H-4a, and of H_β-2 with H-4, which show long-range couplings in a *W*-mechanism (1 and 1.4 Hz, respectively).

Compound **3**, $C_{17}H_{19}NO_4$, exhibited an IR spectrum similar to that of galanthamine, except for the presence of a carbonyl group at 1650 cm^{-1}. The ^1H NMR spectrum was consistent with a galanthamine-type structure, although no signal assignable to a *N*-methyl group was present. The spectrum exhibited (i) two doublets at δ6.76 and 6.60, due to the *ortho* aromatic protons, H-8 and H-7, (ii) a *dd* and *ddd* at δ5.88 and 6.00, respectively, assigned to H-4a and H-4; (iii) two singlets at δ8.02 and 8.07 characteristic of the two rotamers *Z* and *E* resulting from hindered rotation of a *N*-formyl group; (iv) two doublets at δ5.10 and 4.80 for rotamers *Z* and *E* of H_β-6, respectively (the *peri* carbonyl group causes a downfield shift of the signal [16]) and two multiplets at δ3.82 and 3.15 for rotamers *E* and *Z* of H_α-12, respectively, which confirm the position of the formyl group. The rest of the spectrum was in agreement with the galanthamine skeleton; thus the structure of *N*-formylgalanthamine is proposed for compound **3** (Fig. 4).

The mass spectrum showed the molecular ion peak at *m/z* 301; other significant peaks at *m/z* 243, 230 and 115, similar to those of galanthamine, and two stronger peaks at *m/z* 225 and 211. The peak at *m/z* 272 $[M-29]^+$ must be due to the loss of the formyl group. The UV spectrum



(a) *syn* · Conformation of ring B, axial hydroxyl group

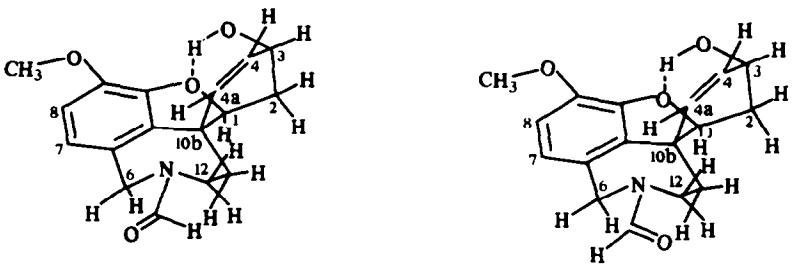
(b) *anti* · Conformation of ring B, equatorial hydroxyl group

Fig. 3. Possible conformations of ring B in galanthamine. (a) *syn*-Conformation of ring B, axial hydroxyl group. (b) *anti*-Conformation of ring B, equatorial hydroxyl group.

Table 2. ^{1}H NMR (200 MHz, $CDCl_3$) spectral data for galanthamine (**2**) and *N*-formylgalanthamine (**3**)

Assignment	**2**	**3**
H-1	4.73 *m* ($W_{1/2}$ = 7.0)	4.50 *m* ($W_{1/2}$ = 7.4)
H_α-2	2.12 *ddd* (15.7, 5.0, 2.5)*	1.95 *ddd* (15.7, 5.1, 2.5)
H_β-2	2.80 *ddt* (15.7, 3.7, 1.4)	2.61 *ddt* (15.7, 3.4, 1.0)
H-3	4.25 *m*†	4.07 *m* (5.1, 4.8, 1.0)
H-4	6.10 *ddd* (10.3, 4.5, 1.4)	6.00 *ddd* (9.8, 4.8, 1.0)
H-4a	6.21 *dd* (10.3, 1.0)	5.88 *dd* (9.8, 1.0)
H_α-6	3.79 *dd* (15.2, 1.0)	3.94 *dd* (15.2, 1.0)
H_β-6	4.21 *d* (15.2)	4.80 *d* (15.2) rot. *E*
		5.10 *d* (15.2) rot. *Z*
H-7	6.74 *d* (8.2)	6.60 *d* (8.2)
H-8	6.78 *d* (8.2)	6.76 *d* (8.2)
H_α-11	2.20 *ddd* (13.5, 12.2, 3.5)	1.71 *ddd* (13.3, 12.0, 4.3)
H_β-11	1.69 *ddd* (13.5, 3.5, 2.2)	1.81 *ddd* (13.3, 2.5, 2.3)
H_α-12	3.16 *dt* (14.4, 3.5)‡	3.82 *ddd* (15.3, 4.3, 2.5)‡ rot. *E*
		3.15 *ddd* (14.3, 8.9, 6.1) rot. *Z*
H_β-12	3.39 *ddd* (14.4, 12.2, 2.1)	3.61 *ddd* (14.3, 12.0, 2.3)
OMe	3.95 *s*	3.84 *s*
NMe	2.52 *s*	—
NCHO	—	8.02 *s*
		8.07 *s*

*Values in parentheses are coupling constants in Hz.
†Signal masked by the doublet at δ4.21.
‡With a further weak splitting of *ca* 1 Hz.



(a) *Z* · rotamer

(b) *E* · rotamer

Fig. 4. Possible rotamers of *N*-formylgalanthamine. (a) *Z*-rotamer. (b) *E*-rotamer.

showed a strong absorption at 220 nm. These data, together with those of the ^{13}C NMR spectrum, confirm the proposed structure. In the latter, the *N*-formyl group appears at δ162.7 and 162.1, most of the other signals corresponding to the galanthamine skeleton also duplicated for rotamers *Z* and *E*, especially C-6 and C-12, which are the closest to the formyl group. The assignment of the signals corresponding to each rotamer is based on the evidence that the *peri* disposition of the carbonyl group shields the adjacent carbon atoms [17, 18]. Thus, δ39.1 of C-12 belongs to the *Z*-rotamer, whilst δ35.7 belongs to the *E*-rotamer (Table 3).

EXPERIMENTAL

All mps are uncorr. EIMS were recorded at 70 eV. NMR spectra were recorded on a Varian XL spectrometer working at 200 and 50.3 MHz, for hydrogen and carbon, respectively. Chemical shifts are in ppm. The ^1H–^1H homonuclear correlation expt (COSY) was performed using the standard sequence [19] and transients were accumulated for 256 values of the evolution period, with a spectral width of 1226 Hz in both dimensions. The time between transients was 1.5 sec, and the acquisition time was 0.208 sec. A 512 × 512 point data matrix was measured with pseudoecho [20] data for improved peak definition and triangular folding for improved sensitivity. For the ^1H–^1H homonuclear correlation expt using the double quantum filtered (DQF) COSY sequence [10, 11], 64 transients were accumulated for 512 values of the evolution period, with a spectral width of 1266 Hz in both dimensions. The time between transients was 5 sec and the acquisition time was 0.208 sec. A 512 × 512 data matrix was used with pseudo-echo data processing [20] for improved peak definition and triangular folding for improved sensitivity. In the 2D NOE expts, the samples were degassed by a N_2 stream, and were performed using the standard sequence [21]. The mixing time was 0.150 msec, and 32 transients were accumulated for 256 values of the evolution period with a spectral width of 1315 Hz in both dimensions, and a delay of 2 sec was employed. A 512 × 512 data matrix was used with pseudo-echo and triangular folding.

Table 3. ^{13}C NMR (50.6 MHz) spectral data for *N*-formylgalanthamine (3)

Assignment	δ($CDCl_3$–CD_3OD)
C-1	88.7 *d*
	87.9 *d*
C-2	29.8 *t*
C-3	61.4 *d*
C-4	128.0 *d*
	128.2 *d*
C-4a	125.8 *d*
	126.2 *d*
C-6	41.0 *t*, rot. *Z*
	52.8 *t*, rot. *E*
C-6a	127.4 *s*
C-7	119.9 *d*
	121.6 *d*
C-8	111.4 *d*
C-9	146.2 *s*
	146.5 *s*
C-10	144.3 *s*
	144.5 *s*
C-10a	131.8 *s*
	131.9 *s*
C-10b	48.0 *s*
	48.1 *s*
C-11	46.6 *t*
	46.7 *t*
C-12	35.7 *t*, rot. *E*
	39.1 *t*, rot. *Z*
OMe	55.8 *q*
NCHO	162.1 *d*
	162.7 *d*

Plant material. N. confusus was collected in Béjar (Salamanca) in March 1985 during the flowering period. The species was authenticated by Dr. Javier Fernández Casas of the Botanic Institute of Madrid, and a voucher specimen is deposited in the herbarium of the Department of Botany, Faculty of Pharmacy, University of Barcelona.

Alkaloid isolation. The fresh plant material was treated as previously described [1]. The 22.42 g constituting extract C from the bulbs was treated several times with boiling hexane, yielding white crystals on cooling. Recrystallization of this material from Me_2CO afforded compound **2** (2898 mg). The rest of the extract was filtered through 600 g of neutral alumina. Fractions I and II were obtained by elution with $CHCl_3$–Et_2O (1:1), and fractions III and IV by eluting with $CHCl_3$–EtOAc (1:1).

Fraction II afforded more compound **2** (2102 mg, from Me_2CO) and the remaining material (4.70 g) was rechromatographed by CC on 120 g neutral alumina. Elution with $CHCl_3$ afforded compound **4**, which yielded 300 mg of white needles after crystallization with MeOH. Fraction III was rechromatographed on a silica gel column (120 g). Elution with $CHCl_3$–EtOH (97:3) yielded compound **3** (78 mg, from MeOH). More compound **2** (1200 mg, from Me_2CO) was obtained by eluting with $CHCl_3$–EtOH (9:1). Fraction IV was treated with C_6H_6. The soluble material afforded more compound **3** (20 mg) and the insoluble material crystallized from MeOH, yielding 700 mg compound **1**.

Haemanthamine (**1**). Mp 195–198° (lit. 195–197° [22], 203° [10]); IR ν_{max}^{KBr} cm^{-1}: 3400–2960, 1470, 1320, 1225, 1025; UV λ_{max}^{EtOH} nm (log ε): 212 (4.05), 242 (3.10), 296 (3.48); MS *m/z* (rel. int.): 301 $[M]^+$ (65), 269 (41), 257 (48), 227 (100), 225 (96), 224 (65), 181 (96), 115 (52), 45 (89); ^{13}C NMR ($CDCl_3$–CD_3OD) in agreement with lit. [10].

Galanthamine (**2**). $C_{17}H_{21}NO_3$ (Found: C, 70.88; H, 7.32; N, 4.88. $C_{17}H_{21}NO_3$ requires: C, 70.61; H, 7.42; N, 4.90%). Mp 124–126° (lit. 127–129° [23], 130–131° [12]); IR ν_{max}^{KBr} cm^{-1}: 3270, 1625, 1510, 1440, 1280, 1040; UV λ_{max}^{EtOH} nm (log ε): 218 (4.22), 2.86 (3.32); MS *m/z* (rel. int.): 287 $[M]^+$ (100), 286 (98), 244 (53), 230 (33), 216 (97), 174 (90), 44 (83); ^{13}C NMR ($CDCl_3$) in agreement with lit. [11].

2-*Hydrochloride*. Mp 247–249° (lit. 254–255° [13]); ^1H NMR ($CDCl_3$–CD_3OD): δ2.71 (3H, *s*, NMe), 3.88 (3H, *s*, OMe), 4.21 (1H, *d*, H_β-6), 4.74 (1H, *d*, H_α-6), 6.11 (2H, *br s*, H-4 and H-4a), 6.85 (1H, *br s*, H-8), 7.64 (1H, *br s*, H-7).

N-*Formylgalanthamine* (**3**). $C_{17}H_{19}NO_4$ (Found: C, 67.65; H, 6.56; N, 4.56. $C_{17}H_{19}NO_4$ requires: C, 67.77; H, 6.31; N, 4.65%). Mp 190–192°; IR ν_{max}^{KBr} cm^{-1}: 3470, 1650, 1500, 1425, 1270, 1055; UV λ_{max}^{EtOH} nm (log ε): 220 (3.37), 288 (2.53); MS *m/z* (rel. int.): 301 $[M]^+$ (100), 272 (1), 243 (8), 230 (12), 225 (24), 211 (24), 128 (14), 115 (19).

Pretazettine (**4**). Direct comparison (IR, co-TLC) with a reference sample established that they were identical. ^1H NMR ($CDCl_3$) in agreement with lit. [24].

Tazettine. A soln of **4** in 0.1 M NaOH was allowed to stand at room temp. for 24 hr [25], giving tazettine, mp 195–198° (lit. 210°

[13]); ^{1}H NMR ($CDCl_3$–CD_3OD) in agreement with lit. [24]; ^{13}C NMR ($CDCl_3$–CD_3OD) in agreement with lit. [12].

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