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C_1-Derivatives of macrocyclic spermine alkaloids. Verbamedines versus incasines

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Abstract—The isolation, structure elucidation, and synthesis of the macrocyclic spermine alkaloids verbamedine (**3**) and isoverbamedine (**4**) from *Verbascum pseudonobile* Stoj. and Stef. are reported. The synthesis of *N*(13)-formimino-verbacine (**7**) is described. Spectral and chemical evidence is presented to correct the previously published incorrect structures of the incasines A and A′ isolated from *Incarvillea sinensis* LAM. The similarities between the natural C_1-derivatives of verbacine (**1**) and the biochemical one-carbon units transferring tetrahydrofolate cofactors have been observed. © 2002 Published by Elsevier Science Ltd.

Acyl conjugates of the naturally occurring polyamines spermine and spermidine are widely distributed in the living organisms.[1] There contained 1,3-diaminopropane moiety results on some specific chemical properties of these compounds. Due to the 1,3-arrangement of N(1) and N(4), reactions involving six-membered cyclic transition state are facilitated, namely the N(1)↔N(4) acyl migration and its special case the 'zip-reaction',[2] the formation of cyclic aminals (hexahydropyrimidines), cyclic ureas (tetrahydropyrimidin-2-ones) or cyclic amidines (1,4,5,6-tetrahydropyrimidines). These reactions are often unusually smooth when one-carbon (C_1) units are involved (N–CH_2–N′, N–CO–N′, N–CH=N′ etc.) and some of them have been frequently used as protective groups in the syntheses of natural polyamine derivatives.[3,4]

The (*E*)/(*Z*)-isomeric pairs of macrocyclic spermine alkaloids verbacine (**1**)/verballocine (**2**) and their *N*(9),*N*(13)-aminals verbamethine (**5**)/isoverbamethine (**6**) (Scheme 1) are the major alkaloids from *Verbascum pseudonobile* Stoj. and Stef. (Scrophulariaceae).[4–6] Recently, two minor alkaloids, verbamedine (**3**) and isoverbamedine (**4**), were isolated from the same plant.[4f,8] The ESI-MS of both **3** and **4** show quasi-molecular ion $[M+H]^+$ at *m*/*z* 491, which is 28 amu (atomic mass units) higher than those of verbacine (**1**) and verballocine (**2**) ($[M+H]^+$ at *m*/*z* 463), which suggests *N*-formyl derivatives of the (*E*)/(*Z*)-isomers **1** and **2**. The presence of the signals at 8.02 ppm (NC*H*=O) in the ^{1}H NMR and 163.2+162.94 ppm (N*C*H=O) in the ^{13}C NMR spectrum of compound **3** is in agreement with this deduction. The signals of the olefinic protons C(7′)H=C(8′)H are coupled with $J_{AB}=15.3$ Hz in the case of **3** and 12.6 Hz in that of **4**, which indicates their (*E*)/(*Z*)-isomerism. Moreover, by UV-photoisomerisation (254 nm, MeOH) compounds **3** and **4** are mutually convertible. Also, the regioselective *N*-formylation of verbacine (**1**) and verballocine (**2**) with *p*-nitrophenyl formate[9,10] yields quantitatively verbamedine (**3**) and isoverbamedine (**4**), respectively. In addition, with HCHO verbamedine (**3**) yields quantitatively the *N*(5),*N*(9)-methylene bridged derivative **11**,[11] which confirms the *N*(13)-localization of the formyl functionality in the natural and synthetic verbamedine (**3**) and isoverbamedine (**4**). Finally, the chiroptical properties ($[\alpha]_D$) of the synthetic and natural verbamedine (**3**) and isoverbamedine (**4**) are identical. Since the (*S*)-configuration of verbacine (**1**) and verballocine (**2**) is unambiguously established,[4b,4e] the (*S*)-absolute configuration of their derived verbamedine (**3**) and isoverbamedine (**4**) is proven.

By reflux in xylene in the presence of NH_4Cl, verbamedine (**3**) and isoverbamedine (**4**) were transformed into the cyclic amidinium salts **9** and **10**, respectively.[4f] Compounds **9** and **10** are also naturally occurring alkaloids isolated from *Incarvillea sinensis* Lam. (Bignoniaceae), published under the trivial names incasines B′ (**9**) and B (**10**)[7] and from *V. pseudonobile* Stoj. and Stef. as verdoline (**9**) and isoverdoline (**10**).[4d,f]

Keywords: macrocyclic spermine alkaloids; verbacine; *N*-formylation; verbamedines; incasines; tetrahydrofolic acid.

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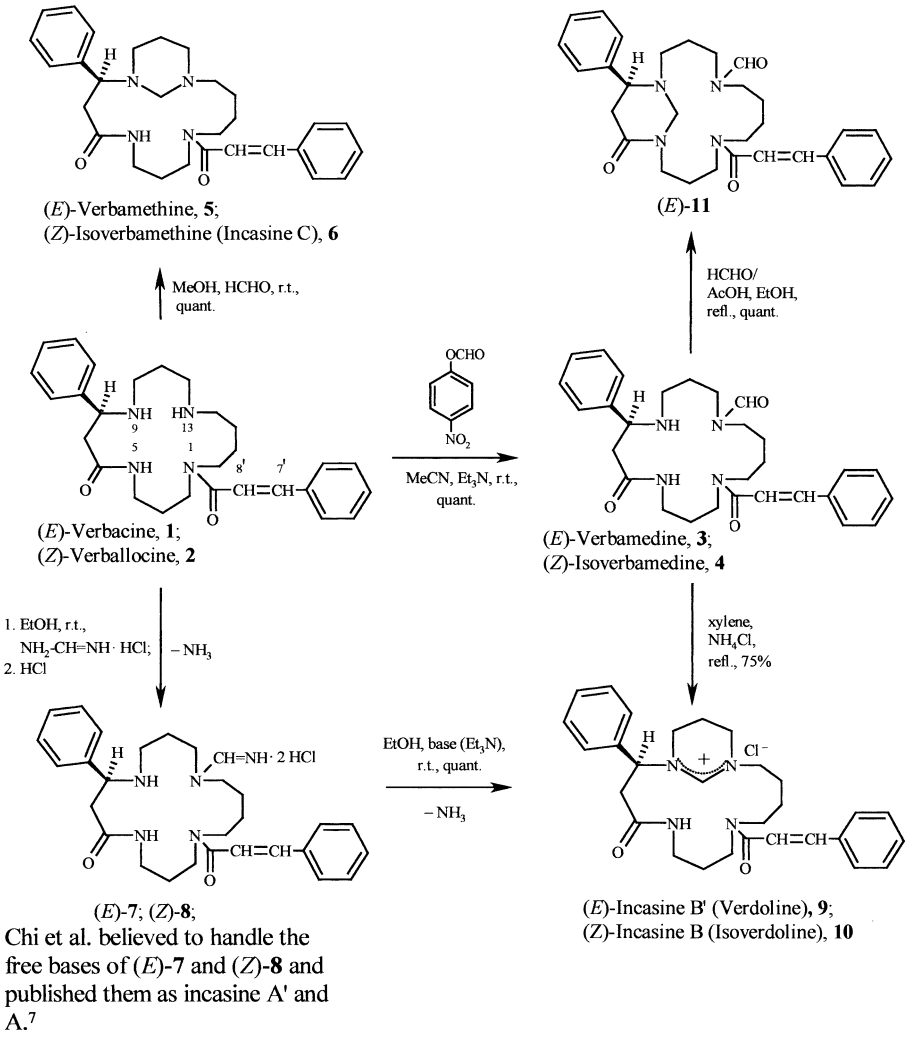

Scheme 1.

Incasines B′ (verdoline, **9**) and incasine B (isoverdoline, **10**) were also prepared from verbacine (**1**) and verballocine (**2**) and $NH_2CH{=}NH{\cdot}HCl$.[12] Due to the higher sterical accessibility of N(13) the first step of this reaction is the formation of *N*(13)-formimino-verbacine (**7**) and its (*Z*)-isomer (**8**). Further, by intramolecular nucleophilic attack from N(9) to *N*(13)CH=NH compounds **7** and **8** undergo transannular cyclization, via 2-amino-hexahydropyrimidine intermediate and following loss of NH_3, closing the sterically favoured six-membered 1,4,5,6-tetrahydropyrimidinium ring of the resonance stabilized amidinium salts **9** and **10**. This reaction is facilitated under basic conditions and only by the protonation of the benzylic amine N(9)-atom, by addition of HCl to the reaction mixture it was possible to capture the intermediate *N*(13)-formimino-verbacine (**7**) and isolate it as a dihydrochloride. Under basic conditions compound **7**·2HCl rapidly transforms into the cyclic amidinium salt **9** so it was impossible to isolate its free base. Even the dry **7**·2HCl also slowly undergoes spontaneous cyclization. The same reaction ($[M{+}H{-}NH_3]^+$) also takes place during the EI-MS and CI-MS measurements of **7**·2HCl, where the amidinium cation **9** appears at *m*/*z* 473 as a main MS signal and only under the mild ionization conditions of ESI-MS was it possible to detect its quasimolecular ion ($[M{+}H]^+$) at *m*/*z* 490.[12]

Recently, Chi et al.[7] reported the isolation of the free bases of compounds **7** and **8** as natural alkaloids from *I. sinensis* LAM. under the names incasine A′ and A, but the described above inherent high instability of the free base of *N*(13)-formimino-verbacine (**7**) due to its insurmountable tendency for cyclization to the amidinium salt **9** called in question the proposed structures for these alkaloids. Surprisingly we established that the chiroptical ($[\alpha]_D$) and spectral (^1H and ^{13}C NMR) properties of (*S*)-verbamedine (**3**) and (*S*)-isoverbamedine (**4**) are identical to those published for incasines A′ and A, respectively.[7] Thus, we can conclude that the proposed structures **7** and **8** for incasines A′ and A are incorrect[13] and the real alkaloid constituents of *I. sinensis* LAM. are actually (*S*)-verbamedine (**3**) and (*S*)-isoverbamedine (**4**).

It was observed that verbacine (**1**) and its C_1-derivatives **3**, **5**, and **9** are in principle similar to tetrahydrofolic acid (FH_4) and its C_1-derivatives *N*(5),*N*(10)-methylene-FH_4, *N*(5)- and *N*(10)-formyl-FH_4, and *N*(5), *N*(10)-methenyl-FH_4, important intermediates in the biochem-

ical one-carbon units transfer reactions. Full discussion of the interconversion of compounds **1**, **3**, **5**, and **9** and their naturally occurring derivatives is to be published.[4f]

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References

1. Bienz, S.; Detterbeck, R.; Ensch, C.; Guggisberg, A.; Häusermann, U.; Meisterhans, C.; Wendt, B.; Werner, C.; Hesse, M. In *Putrescine*, *Spermine*, *Spermidine*, *and Related Polyamine Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2002, 58, in press.
2. Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, New York, 1991.
3. (a) McManis, J. S.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 2041; (b) Chantrapromma, K.; McManis, J. S.; Ganem, B. *Tetrahedron Lett.* **1980**, *21*, 2605; (c) Chantrapromma, K.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 23; (d) Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290.
4. (a) Drandarov, K. *Tetrahedron Lett.* **1995**, *36*, 617; (b) Drandarov, K.; Guggisberg, A.; Linden, A.; Hesse, M. *Helv. Chim. Acta* **1998**, *81*, 1773; (c) Youhnovski, N.; Drandarov, K.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1999**, *82*, 1185; (d) Guggisberg, A.; Drandarov, K.; Hesse, M. *Helv. Chim. Acta* **2000**, *83*, 3035; (e) Drandarov, K.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 979; (f) Drandarov, K.; Zikmundová, M.; Youhnovski, N.; Hesse, M. *Helv. Chim. Acta* **2002**, submitted.
5. Compounds **5** and **6** were understood earlier as artificial condensation products of verbacine (**1**) and verballocine (**2**) with HCHO from the solvents used as extractants.[4a] Later their natural origin was established.[4d,f]
6. Recently, isoverbamethine (**6**) was republished with the wrong (*R*)-configuration under the trivial name incasine C by Chi et al.[7] We have unambiguously established its (*S*)-configuration.[4b,4e]
7. Chi, Y.-M.; Hashimoto, F.; Yan, W.-M.; Nohara, T. *Tetrahedron Lett.* **1997**, *38*, 2713.
8. *Isolation of (−)-(S)-verbamedine (**3**) and (−)-(S)-isoverbamedine (**4**).* The total alkaloid extract from *V. pseudonobile* Stoj. and Stef. (prepared according to Ref. 4a) was dissolved in $CHCl_3$. The solution was washed with diluted aq. AcOH and H_2O, dried (Na_2SO_4) and evaporated. The residue was separated by CC (alumina, consecutively elution with AcOEt and AcOEt/EtOH, 9:1). Compounds **3** and **4** were additionally purified by PTLC (silica gel, AcOEt/MeOH, 8:2). Data for (−)-(*S*)-verbamedine (**3**): colorless glass-like solid. TLC (silica gel, AcOEt/MeOH, 8:2): R_f 0.2. $[\alpha]_D = -31$ ($c = 1.57$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, mixture of conformers): 8.02 (*s*, NCHO); 7.72, 7.73 (2*d*, $J = 15.3$ Hz, C(7′)H); 7.57–7.48 (*m*, 2 arom. H); 7.46 (br. *t*, 0.5H, C(6)NHC); 7.42–7.17 (*m*, 8 arom. H); 7.09 (br. *t*, C(6)NHC); 6.83, 6.84 (2*d*, $J = 15.3$ Hz, C(8′)H); 4.1–3.9 (*m*, PhCHN); 3.7–3.1 (*m*, 10NCH); 2.66–2.3 (*m*, 4H); 2.1–1.51 (*m*, 4CCH_2C). ^{13}C NMR: 171.96, 171.73 (C(6)=O); 166.77, 166.49 (C(9′)=O); 163.19, 162.94 (NCHO); 143.31, 143.08, 142.75 (C(7′)); 135.13 (C(1′)); 129.84, 128.89, 128.78, 128.58, 127.87, 127.62, 127.48, 126.52, 126.44, 126.27 (arom. C); 117.34, 117.06 (C(7′)); 59.57 (PhCN); 49.14, 48.81, 48.62, 47.23, 46.70, 46.19, 45.91, 44.99, 44.67, 44.22, 44.06, 43.81, 43.23, 42.48, 42.12, 37.43, 37.27, 36.61, 30.88, 30.25, 29.68, 29.31, 28.73, 27.16, 26.37, 25.13, 24.91 (CH_2). ESI-MS: 491 ($[M+H]^+$). Data for (−)-(*S*)-isoverbamedine (**4**): colorless glass-like solid. TLC (silica gel, AcOEt/MeOH, 8:2): R_f 0.18. $[\alpha]_D = -18$ ($c = 0.9$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, mixture of conformers): 8.02, 7.96, 7.92 (3*s*, NCHO); 7.43–7.17 (*m*, 10 arom. H+C(6)NHC); 6.65, 6.64, 6.63 (3*d*, $J = 12.6$ Hz, C(7′)H); 6.08, 6.05, 6.04 (3*d*, $J = 12.6$ Hz, C(8′)H); 4.07–3.85 (*m*, PhCHN); 3.69–3.05 (*m*, 10NCH); 2.65–2.28 (*m*, 4H); 2.02–1.24 (*m*, 4CCH_2C). ESI-MS: 491 ($[M+H]^+$).
9. Martinez, J.; Laur, J. *Synthesis* **1982**, *11*, 979.
10. *Synthesis of compounds **3** and **4**.* A mixture of 103 mg (*S*)-**1** (or (*S*)-**2**), 45 mg *p*-nitrophenyl formate[9] and 0.25 ml Et_3N in 3 ml MeCN was stirred 1 h at rt, then diluted with $CHCl_3$, washed several times with aq. NH_3 and H_2O, dried (Na_2SO_4) and evaporated to yield (*S*)-**3** (or (*S*)-**4**) quantitatively.
11. Compound (+)-(*S*)-**11**. A mixture of 60 mg (*S*)-**3**, 1.5 ml 37% aq. HCHO, 1.5 ml AcOH and 3 ml MeOH was refluxed for 1 h then evaporated. The residue was dissolved in $CHCl_3$, washed with diluted aq. NH_3 and H_2O, dried (Na_2SO_4) and evaporated to yield 60 mg (95%) of (*E*)-**11** as a colorless glass-like solid. TLC (silica gel, AcOEt/MeOH, 8:2): R_f 0.33. $[\alpha]_D = +27$ ($c = 2.37$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, mixture of conformers): 8.02 (*s*, 0.6H, NCHO); 7.99 (*s*, 0.4H, NCHO); 7.71 (*d*, $J = 15.3$ Hz, C(7′)H); 7.6–7.46 (*m*, 2 arom. H); 7.46–7.25 (*m*, 8 arom. H); 6.85, 6.79 (2*d*, $J = 15.8$ Hz, C(8′)H); 4.18–4.05 (*m*, PhCHN); 4.05–3.07 (*m*, 10H); 2.87–2.27 (*m*, 4H); 2.06–1.5 (*m*, 8H). EI-MS: 502 (70, $[M]^{+\bullet}$); 371 (70, $[M-C_6H_5-CH=CH-CO]^+$); 131 (100, $[C_6H_5-CH=CH-CO]^+$).
12. *(+)-(S)-N(13)-Formimino-verbacine* (*Incasine A′*, **7**). A mixture of 100 mg (*S*)-verbacine (**1**)[4a] and 40 mg $NH_2CH=NH\cdot HCl$ in 1.5 ml EtOH was stirred for 1 h and than acidified with a few drops 32% aq. HCl. The mixture was introduced into a silica gel column and eluted consecutively with $CHCl_3$, $CHCl_3$/MeOH (9:1) and $CHCl_3$/MeOH (8:2) to yield 58 mg (48%) of **7**·2HCl as a colorless solid. TLC (silica gel, $CHCl_3$/MeOH, 8:2): **7**·2HCl R_f 0.1; **1**·2HCl R_f 0.27; **9**·Cl^- R_f 0.39. $[\alpha]_D = +10$ ($c = 3.1$, MeOH). ^{1}H NMR (MeOH-d_4, mixture of conformers): 8.03 (*s*, NCH=N); 7.69–7.56 (*m*, 4 arom. H+C(7′)H); 7.52–7.38 (*m*, 6 arom. H); 7.12, 7.11, 7.10 (3*d*, $J = 15.5$ Hz, C(8′)H); 3.86–3.54 (*m*, 7H); 3.52–3.33 (*m*, 2H); 3.29–2.74 (*m*, 5H); 2.38–1.69 (*m*, 8H). ESI-MS: 490 ($[M+H]^+$). CI-MS (NH_3 as reactant gas): 473 ($[M+H-NH_3]^+$).
13. Obviously, the incorrect structures **7** and **8** for incasines A′ and A are the result of a mistaken elemental analysis, giving $C_{29}H_{39}N_5O_2$ for **7** and **8** (corresponding to molecular mass 489)[7] instead of $C_{29}H_{38}N_4O_3$ (corresponding to compounds **3** and **4** with molecular mass 490) and the registered signal at m/z 490 in the EI-MS of incasines A and A′ should not be interpreted as a quasimolecular ion $[M+H]^+$ (as in Ref. 7) but as a molecular radical cation $[M]^{+\bullet}$.