Macrocyclic Spermine Alkaloids from *Verbascum:* Isolation, Structure Elucidation, and Syntheses of the (*E*/*Z*)-Isomeric Pairs (*S*)-Verbasikrine/(*S*)-Isoverbasikrine and (*S*)-Verbamekrine/(*S*)-Isoverbamekrine

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The isolation and structure elucidation of the 17-membered macrocyclic spermine alkaloids (*S*)-verbasikrine (**3**), (*S*)-isoverbasikrine (**6**), (*S*)-verbamekrine (**9**), and (*S*)-isoverbamekrine (**12**) is presented. The syntheses of their racemates are described. The HPLC/APCI-MS analysis of the original total alkaloid extract of *Verbascum pseudonobile* is presented.

Introduction. – The (*E*/*Z*)-isomeric pairs of macrocyclic spermine alkaloids (−)-(*S*)-verbacine (**1**), (−)-(*S*)-verballocine (**4**), (−)-(*S*)-verbasitrine (**2**), and (−)-(*S*)-isoverbasitrine (**5**) and their *N*,*N*′-methylene-bridged derivatives (+)-(*S*)-verbamethine (**7**), (+)-(*S*)-isoverbamethine (**10**), (+)-(*S*)-verbametrine (**8**), and (+)-(*S*)-isoverbametrine (**11**) have been isolated from the leaves of *Verbascum pseudonobile* STOJ. et STEF. (Scrophulariaceae) (*Scheme 1*) [1][2]. Using HPLC/MS techniques, four minor alkaloids were detected in the same plant material, named verbasikrine (**3**), isoverbasikrine (**6**), verbamekrine (**9**), and isoverbamekrine (**12**) (*Scheme 1* and *Figs. 1* and *2*). The further structure elucidation of these alkaloids **3**, **6**, **9**, and **12**, the subject of the present paper, established that they are monomethoxy analogues of **1**, **4**, **7**, and **10**, respectively.

Results and Discussion. – *HPLC/MS Analysis and Structure Elucidation.* The parent total alkaloid extract from the leaves of *V. pseudonobile* contains two main groups of compounds of quite different basicity, which were separated as groups by the reextraction of the aqueous solution of the mixture with $CHCl_3$ at different pH values [2]. From the fraction of the stronger bases, extractable at pH > 9 (*ca.* 90% of the total alkaloid mixture), so far two (*E*/*Z*) pairs of alkaloids have been isolated and structurally elucidated: the secondary amines (−)-(*S*)-verbacine (**1**)/(−)-(*S*)-verballocine (**4**) [1] and (−)-(*S*)-verbasitrine (**2**)/(−)-(*S*)-isoverbasitrine (**5**) [2] (*Scheme 1* and *Fig. 1*). In the fraction of the weaker basic constituents of the alkaloid mixture, extractable at pH ≈ 5 (*ca.* 10% of the total alkaloid extract), the corresponding *N*,*N*′-methylene-bridged derivatives of **1**/**4** and **2**/**5** were detected: the (*E*/*Z*) pairs (+)-(*S*)-verbamethine (**7**)/(+)-(*S*)-isoverbamethine (**10**) [1] and (+)-(*S*)-verbametrine (**8**)/(+)-(*S*)-isoverbametrine (**11**) [2] (*Scheme 1* and *Fig. 2*).

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[1] Part of the Ph. D. thesis of *N. Y.*, University of Zürich, 1999.

Scheme 1

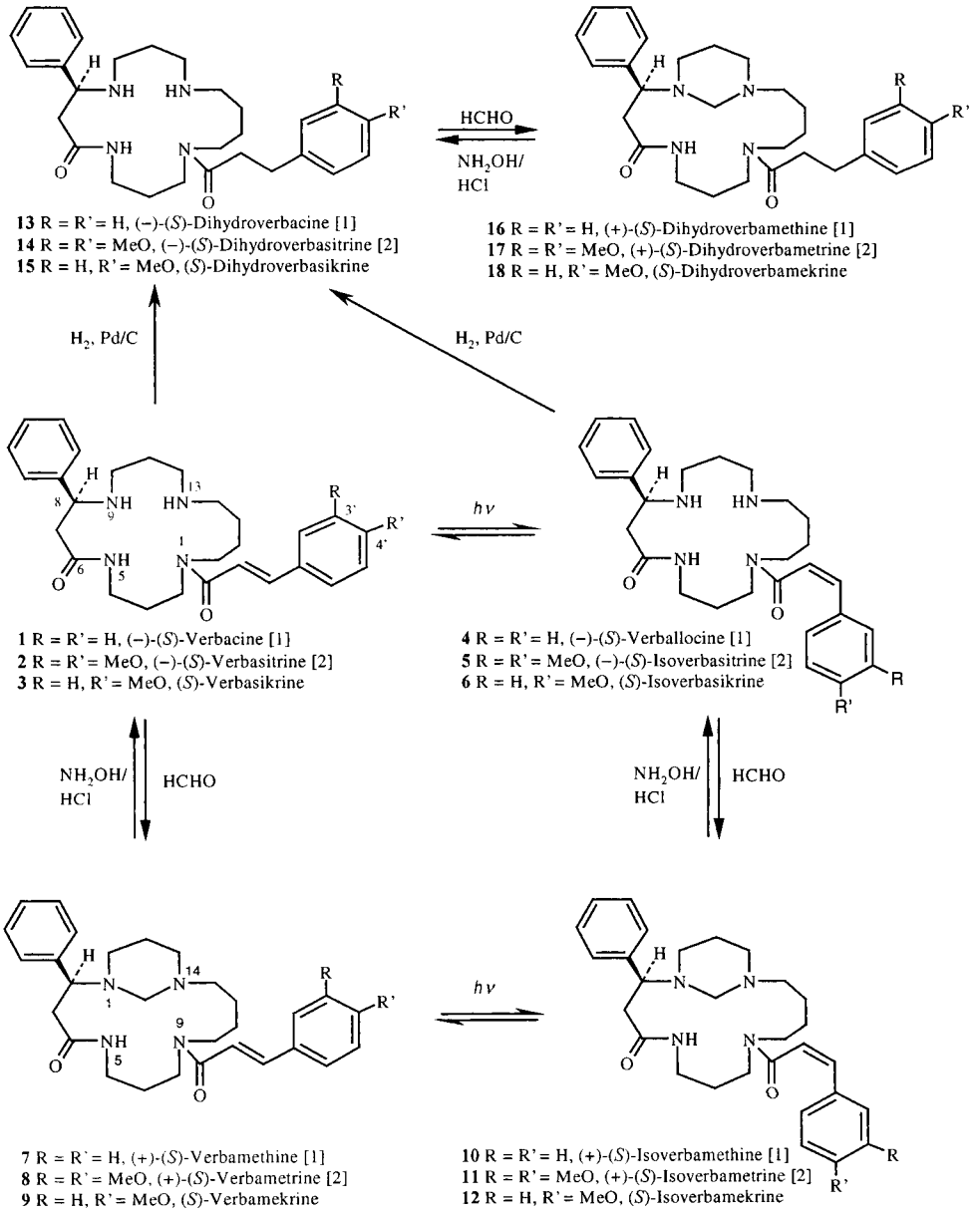


Fig. 1 shows the HPLC separation of the fraction containing the stronger alkaloidal bases with on-line UV (*Fig. 1,a*) and with APCI-MS (atmospheric-pressure chemical-ionization mass spectrometry) detection (*Fig. 1,b–e*; concerning the HPLC/MS technique, see [3]). Beside the chromatographic zones corresponding to the (*E*/*Z*)

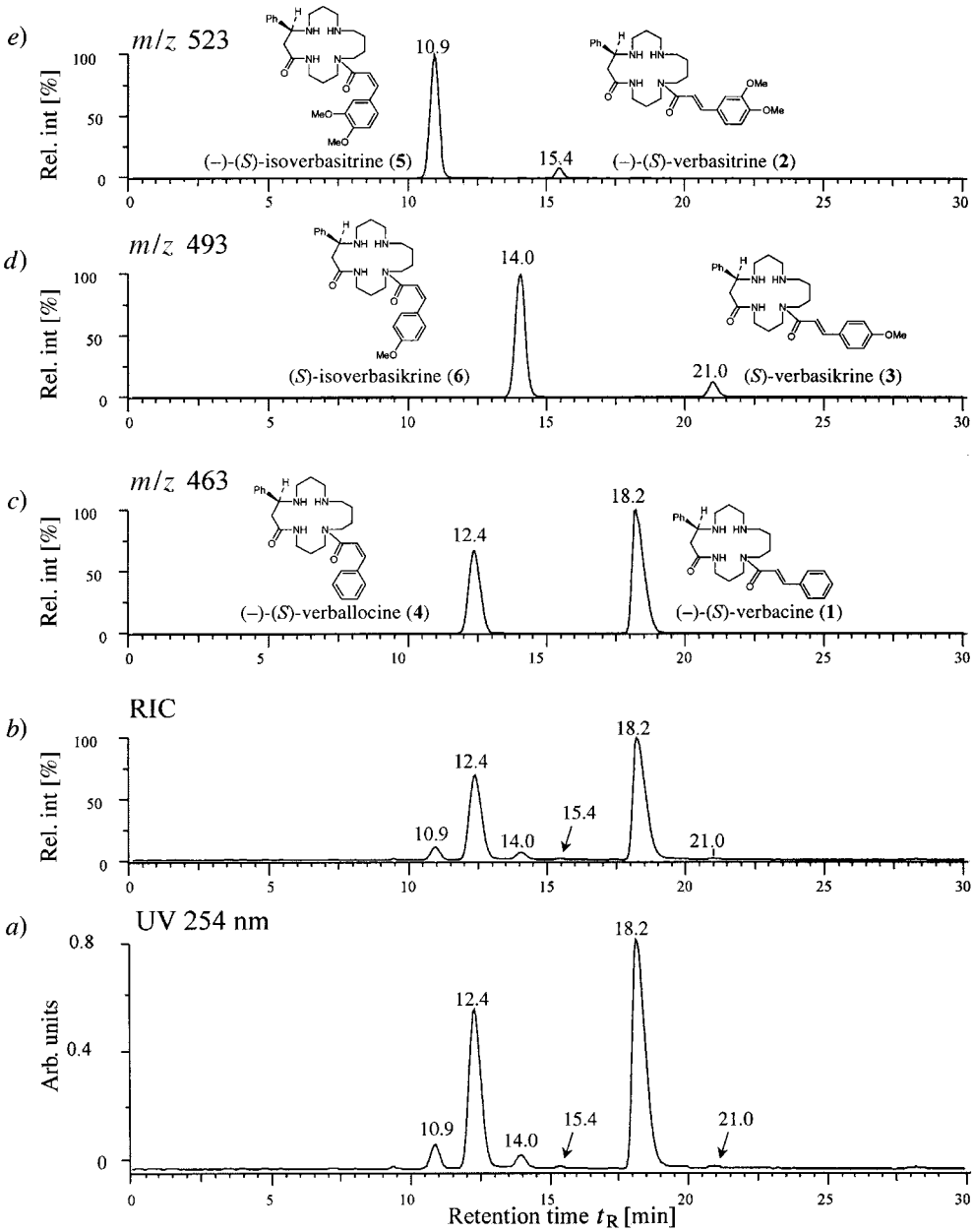


Fig. 1. *HPLC Separation of the group of alkaloids extractable at pH > 9 from* V. pseudonobile *with* a) *on-line UV and* b)–e) *APCI-MS detection*

pairs (–)-(*S*)-verbacine (**1**; (*E*), t_R 18.2 min)/(–)-(*S*)-verballocine (**4**; (*Z*), t_R 12.4 min) ($[M+H]^+$ at *m/z* 463, *Fig. 1,c*) and (–)-(*S*)-verbasitrine (**2**; (*E*), t_R 15.4 min)/(–)-(*S*)-isoverbasitrine (**5**; (*Z*), t_R 10.9 min) ($[M+H]^+$ at *m/z* 523, *Fig. 1,e*), two minor

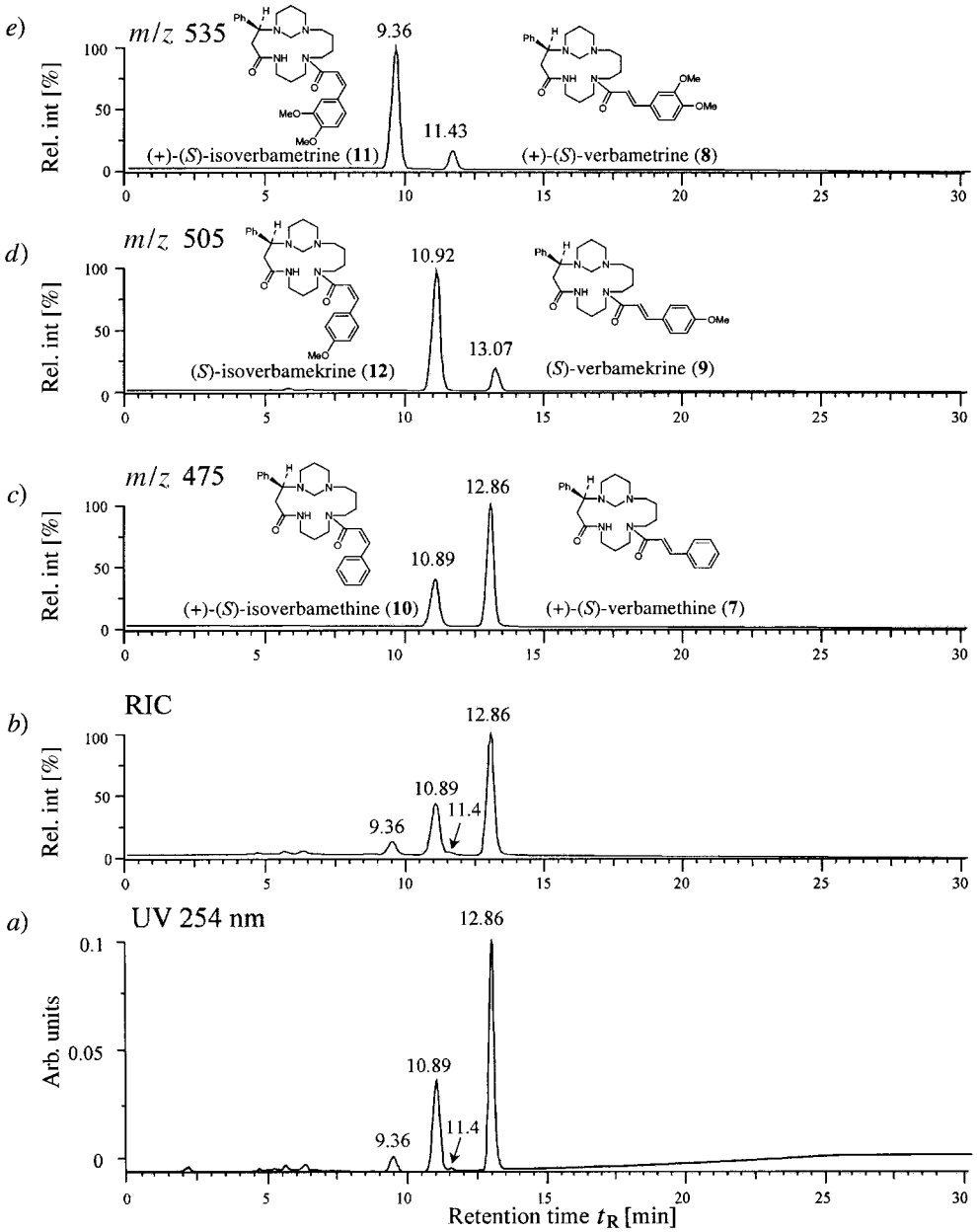


Fig. 2. *HPLC Separation of the group of alkaloids extractable at pH ≈ 5 from* V. pseudonobile *with* a) *on-line UV and* b)–e) *APCI-MS detection*

alkaloids were detected having the same molecular mass (quasi molecular-ion peak $[M+H]^+$ at *m/z* 493, *Fig. 1,d*) but different t_R and UV absorption spectra, which suggested another (*E*/*Z*) pair of alkaloids. These compounds were named verbasikrine

(**3**; t_R 21.0 min; *ca.* 0.3% of the total alkaloid extract) and isoverbasikrine (**6**; t_R 14.0 min; *ca.* 2.4%).

The fact that the quasi molecular ion peak $[M+H]^+$ at *m/z* 493 (*Fig. 1,d*) of verbasikrine (**3**) and isoverbasikrine (**6**) is 30 amu (atomic mass units) higher than those of (−)-(*S*)-verbacine (**1**) and (−)-(*S*)-verballocine (**4**) (*Fig. 1,c*) and 30 amu lower than those of the 3,4-dimethoxycinnamoyl derivatives (−)-(*S*)-verbasitrine (**2**) and (−)-(*S*)-isoverbasitrine (**5**) (*Fig. 1,e*) suggested that **3** and **6** are monomethoxy derivatives of **1** and **4**. Isoverbasikrine (**6**) was isolated in a minute amount (2 mg) by prep. HPLC from the original plant extract (see *Exper. Part*), and the structures of **3** and **6** were established by spectroscopic means.

The ESI-MS fragmentation pattern of **6** is similar to those of (−)-(*S*)-verbacine (**1**), (−)-(*S*)-verballocine (**4**), (−)-(*S*)-verbasitrine (**2**), and (−)-(*S*)-isoverbasitrine (**5**) [1][2]. The fragment ion at *m/z* 333, arising by cleavage of the acyl moiety at N(1), corresponds to the protonated 17-membered macrocyclic ring, common to all of these alkaloids (*Scheme 1*). This and the presence of a fragment ion at *m/z* 161 (base peak) indicate the localization of the additional substitution at the peripheral acyl substituent of **6** and supports the suggestion for a monomethoxycinnamoyl residue. The ^{1}H-NMR spectrum (600 MHz, (D_6)DMSO, 350 K) of **6** confirms the presence of one aromatic MeO group (*s* at 3.78 ppm). The *AA'BB'* spin system with *d*s at 7.38 ($J=8.6$ Hz, H−C(2′) and H−C(6′)) and 6.91 ppm ($J=8.6$ Hz, H−C(3′) and H−C(5′)) establishes the 4-position of the MeO substitution on its peripheral acyl group. The presence of the *d*s at 6.54 (H−C(7′)) and 6.05 ppm (H−C(8′)) with $J=12.7$ Hz indicates the (*Z*)-configuration of the 4-methoxycinnamoyl residue, in accordance with the UV absorption at λ_{max} 268 nm.

The quasi molecular-ion peak $[M+H]^+$ of **3** at *m/z* 493 (*Fig. 1,d*) and its UV absorption at λ_{max} 307 nm establish that **3** is the (*E*)-counterpart of **6**.

The (*E*)/(*Z*)-relationship of verbasikrine (**3**) and isoverbasikrine (**6**) was confirmed by their mutual photochemical conversion. Thus, short-time exposure of the (*E*)-isomer **3** in MeOH solution to light of 365 nm caused an almost quantitatively conversion to the (*Z*)-isomer **6**. On the other hand, irradiation of **6** in MeOH at 254 nm resulted in a mixture **3**/**6**.

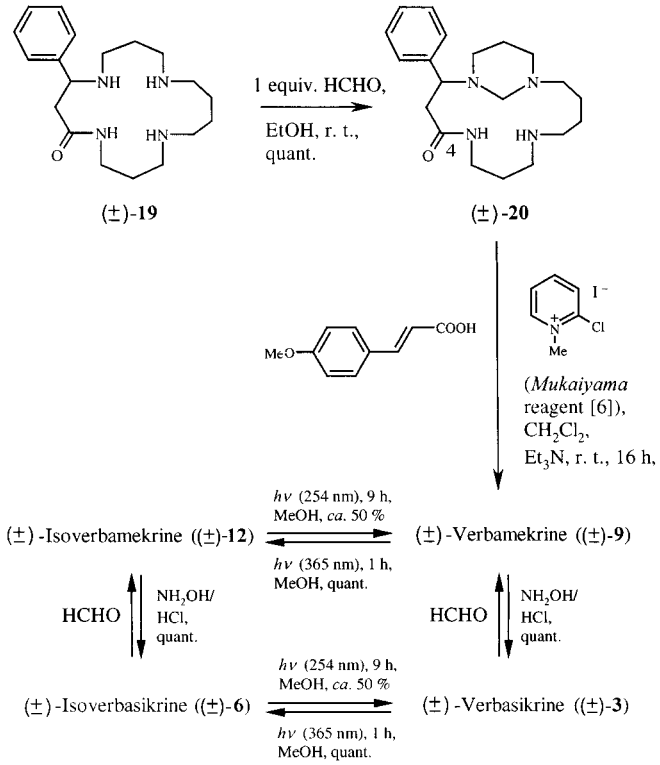
Verbasikrine (**3**) and isoverbasikrine (**6**) reacted quantitatively with HCHO, giving the bicyclic aminals **9** and **12**. This result indicates a similar molecular constitution of **3** and **6** as those of their analogues **1** and **2**, and **4** and **5**, respectively, with localization of the methoxycinnamoyl residue at the N(1) atom (*Scheme 1*). The (*E*/*Z*) pair **9**/**12** of the cyclic aminals (both with $[M+H]^+$ at *m/z* 505) were detected also by HPLC/MS analysis in the group of the weaker basic constituents of the total alkaloid mixture (*Fig. 2,d*). These compounds were named verbamekrine (**9**; t_R 13.07 min; *ca.* 0.03% of the total alkaloid mixture) and isoverbamekrine (**12**; t_R 10.92 min; *ca.* 0.2%), respectively. By mild acid hydrolysis in the presence of NH_2OH, according to [1], **9** and **12** were converted quantitatively to **3** and **6**, respectively (*Schemes 1* and *2*).

The presented structural conclusions for the (*E*/*Z*) pairs verbasikrine (**3**)/isoverbasikrine (**6**) and verbamekrine (**9**)/isoverbamekrine (**12**) were further supported by a total synthesis of their racemates (see below).

Syntheses. The macrocyclic alkaloid (±)-verbacine (**1**) has been synthesized recently by two independent methods [4][5]. Both methods led to the 17-membered macrocyclic compound (±)-**19** ((±)-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one) as an intermediate. According to [5], from (±)-**19** and formaldehyde, the corresponding *N*,*N*′-methylene-bridged derivative (±)-**20** ((±)-2-phenyl-1,5,9,14-tetraazabicy-

clo[12.3.1]octadecan-4-one) was prepared (*Scheme 2*). By further *N*-acylation with (*E*)-4-methoxycinnamic acid according to *Mukaiyama*'s procedure [6], (±)-verbamekrine ((±)-**9**) was obtained from (±)-**20** in excellent yield. The mild acid hydrolysis of the latter, in the presence of NH_2OH, gave (±)-verbasikrine ((±)-**3**). By (*E*) → (*Z*)-photoisomerization, (±)-verbamekrine ((±)-**9**) was converted to (±)-isoverbamekrine ((±)-**12**), which was finally hydrolyzed, in the presence of NH_2OH, to give (±)-isoverbasikrine ((±)-**6**) (*Scheme 2*). The synthetically prepared ((±)-**6** was spectroscopically (UV, NMR, MS) and chromatographically identical with the natural compound and the synthetically prepared (±)-**3**), (±)-**9**, and (±)-**12** were spectroscopically (UV and MS) and chromatographically identical with the corresponding natural alkaloids.

Scheme 2



The (*E*/*Z*)-pairs of the dimethoxycinnamoyl derivatives, *i.e.*, (±)-verbasitrine ((±)-**2**)/(±)-isoverbasitrine ((±)-**5**) and (±)-verbametrine ((±)-(**8**)/(±)-isoverbametrine ((±)-(**11**) were synthesized recently by a similar procedure [2].

Absolute Configuration. The chiroptical properties of the present class of macrolactam spermine alkaloids (*Scheme 1*) were discussed in details in [7]. The CD spectra of the naturally derived dihydroverbasikrine (**15**) and dihydroverbamekrine (**18**), prepared by catalytic hydrogenation of (*S*)-isoverbasikrine (**6**) and further condensa-

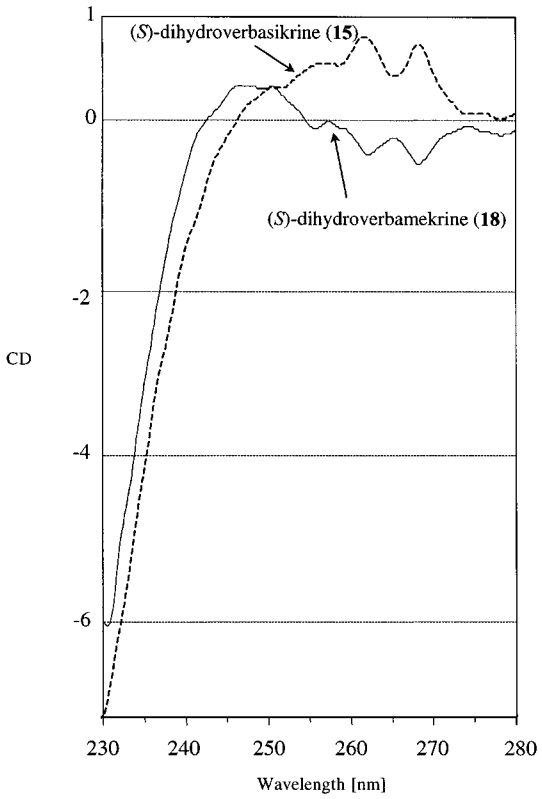


Fig. 3. *CD Curves of* (S)*-dihydroverbasikrine* (**15**) *and* (S)*-dihydroverbamekrine* (**18**)

tion with HCHO (see *Scheme 1* and *Exper. Part*), are shown in *Fig. 3*. They are similar to those of (−)-(*S*)-dihydroverbacine (**13**) [7] and (−)-(*S*)-dihydroverbasitrine (**14**) [2] and (+)-(*S*)-dihydroverbamethine (**16**) [7] and (+)-(*S*)-dihydroverbametrine (**17**) [2], respectively. Thus, the (*S*)-chirality of **15**, its bridged derivative **18**, and their unsaturated natural analogue **6** is unambiguously established. Scarcity of material prevented the registration of CD curves of the corresponding dihydro derivatives of verbasikrine (**3**), verbamekrine (**9**), and isoverbamekrine (**12**). Since the (*S*)-isomers of the compounds (±)-**19** and (±)-**20** (*Scheme 2*), named (−)-(*S*)-protoverbine (**19**) and (+)-(*S*)-protomethine (**20**), are precursors in the biogenesis of the present class of alkaloids (*Scheme 1*) [8], the (*S*)-configuration of verbasikrine (**3**), verbamekrine (**9**), and isoverbamekrine (**12**) is evident. Unfortunately, the isolated amount of the natural (*S*)-isoverbasikrine (**6**) was not sufficient for the registration of its $[\alpha]_D$ value.

We thank the *Swiss National Science Foundation* for generous financial support. *K.D.* thanks the *Prof. Dr. Hans E. Schmid Foundation*, University of Zurich.

Experimental Part

General. TLC: *Merck* precoated plates, silica gel *60* F_{254}; detection by *Schlittler*'s (potassium iodoplatinate) [9] and *Dragendorff*'s (No. D 156a in [10]) reagents; for more details about the TLC behavior of the (*E/Z*)-

isomeric pairs of macrocyclic spermine alkaloids, their dihydro derivatives, and simpler cinnamamides, see [11]. CC: Alumina *N* (act. 1) *ICN Biomedicals.* Anal. HPLC: *Waters 626* LC system, *Waters-996* photodiode array detector, and *Waters-600S* controller with *Millenium* chromatography manager *2010 v.2.15* (*Waters Corp.*) and *Rheodine* rotary valve *7725i* with a 5-µl loop. Prep. HPLC: *Perkin-Elmer* Series *1* LC pump; *Perkin-Elmer-LC-55-13* spectrophotometric detector. HPLC/APCI-MS: triple-stage quadrupole instrument *Finnigan TSQ 700*, equipped with a *Finnigan* atmospheric-pressure chemical-ionization ion source; UV absorption data from the current on-line HPLC-UV detection (λ in nm). CD Spectra: *JASCO-J-715* spectropolarimeter, 1-cm quartz cell, at r. t. in EtOH, between 230 and 280 nm; λ (molar ellipticity ($[\Theta]$) in nm. IR: *Perkin-Elmer 297*, film, in cm^{-1}. NMR: *Bruker ARX-300* or *AMX-600* (^1H) and *Bruker ARX-300* (75 MHz) or *AMX-600* (150 MHz; ^{13}C); chemical shifts δ in ppm rel. to $SiMe_4$ as internal standard; $CDCl_3$, at r. t., unless otherwise stated. ESI-MS: *Finnigan-TSQ-700* mass spectrometer, equipped with a *Finnigan* electrospray ionization (ESI) ion source.

Plant Material. Air-dried leaves of *Verbascum pseudonobile*, cultivated and collected in summer in south-west Bulgaria, were used. For the extraction procedures, see [1][2].

Extractive Group Separation of the Secondary Amines **1**–**6** *from Their Aminals* **7**–**12**. Compounds **1**–**6**, being quite stronger bases than **7**–**12**, were separated as groups by extraction from an aq. soln. at different pH values. The $CHCl_3$ soln. of the total alkaloid mixture was extracted with 3% aq. H_3PO_4 soln. and the pH of the acidic aq. extract adjusted to 5 with dil. aq. NaOH soln. and extracted with $CHCl_3$. The cyclic aminals **7**–**12** passed to the org. solvent (extract *A*). The aq. layer containing **1**–**6** was alkalinized with NaOH and extracted with $CHCl_3$ (extract *B*). *Fig. 1* and *2* show the HPLC/MS analysis of the residues after the evaporation of the extracts *A* and *B*.

Anal. HPLC. Alkaloids extractable at pH > 9 (**1**–**6**, *Fig. 1*): *ET-250/4-Nucleosil-100-5-C_8* column (*Macherey-Nagel*); flow rate 0.6 ml/min, mobile phase MeCN/H_2O 27.5 : 72.5 containing 0.1% of CF_3COOH. Alkaloids extractable at pH ≈ 5 (**7**–**12**, *Fig. 2*): *ET-250/4-Nucleosil-100-5-C_8* column (*Macherey-Nagel*); injection volume 2 µl in concentrations of 1–2 mg/ml; flow rate 0.6 ml/min; mobile phase H_2O/MeCN/0.4% aq. Et_3N soln. with the following gradient: 0.0 min (3 : 6 : 1) → 5.0 min (3 : 6 : 1) → 20.0 min (1 : 8 : 1). HPLC/MS: APCI-MS, pos. mode, vaporizer temp. 440–450°, corona voltage 4.5–5 kV, heated-capillary temp. 200–220°, sheath gas N_2 with a pressure of 60 p.s.i., conversion dynode −15 kV.

Prep. HPLC: VP-250/21-Nucleosil-100-7-C_8 column (7 µm, 250 × 21 mm; *Macherey-Nagel*); flow rate 20 ml/min, mobile phase MeCN/H_2O 27.5 : 72.5 containing 0.1% of CF_3COOH; detection at 254 nm.

Photoisomerization. The photoisomerizations were performed in a quartz cell, with a standard TLC UV-detection lamp *Camag* at 254 or 365 nm placed 10 cm above the cuvette, no filter.

*(±)-1-[(*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (=*(±)-Verbasikrine*, (±)-**3**). A mixture of (±)-verbamekrine ((±)-**9**; 35 mg) and NH_2OH (50 mg) in 1% aq. HCl soln. (3 ml) was heated at 60° for 1 h [1], alkalinized with 25% aq. NH_3 soln., and extracted with $CHCl_3$. The org. extract was washed with H_2O, dried (Na_2SO_4), and evaporated: (±)-**3** (almost quant.). Colorless glass-like solid. UV: max. 307, min. 243. TLC (silica gel, $CHCl_3$/MeOH/25% aq. NH_3 soln. 8 : 2 : 0.2): R_f 0.28. IR: 1645*s* (C=O, amide I), 1600*s* (C=C), 1540*m* (CONH, amide II), 1512*s*, 1250*s*. ^1H-NMR (conformer mixture): 8.35 (br. *t*, 0.5 H, CONH···N); 7.66 (*d*, *J* = 15, C*H*=CHCO); 7.48 (*d*, *J* = 8.5, H–C(2′), H–C(6′)); 7.4 (br. *t*, 0.5 H, CONH); 7.35–7.15 (*m*, 5 arom. CH); 6.9 (*d*, *J* = 8.3, H–C(3′); H–C(5′)); 6.73, 6.7 (2*d*, *J* = 15, CH=C*H*CO); 3.97 (*m*, PhC*H*N); 3.84 (*s*, arom. MeO); 3.75–2.9 (*m*, 6 H); 2.85–2.1 (*m*, 10 H); 2.0–1.4 (*m*, 8 H). ^{13}C-NMR (conformer mixture): 171.2, 167.0 (2 C=O), 142.8, 142.5, 139.4, 129.4, 128.5, 127.9, 127.2, 126.6, 126.3, 115.1, 114.2 (C=C); 59.7 (Ph*C*N); 55.3 (arom. MeO), 49.5, 48.8, 48.3, 46.5, 43.8, 37.5, 36.5, 30.4, 29.5, 28.6, 28.5, 28.2, 26.7 (CH_2). ESI-MS: 493 ($[M+H^+]$).

*(8*S*)-1-[(*Z*)-3-(4-Methoxyphenyl)prop-2-enoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (=*(*S*)-Isoverbasikrine*; **6**). The mixture **1**–**6** (extract *B*, see above) was separated by prep. HPLC. The eluate corresponding to (*S*)-isoverbasikrine (**6**; see *Fig. 1*, *a* and *d*) was lyophilized and the residue dissolved in $CHCl_3$/MeOH 1 : 1 and purified by CC (alumina (2 g), $CHCl_3$/MeOH/25% aq. NH_3 soln. 8 : 2 : 0.2). UV: max. 268; min. 243. ^1H-NMR (600 MHz, (D_6)DMSO, 350 K): 7.9–7.8 (*m*, 0.5 H, CONH···N); 7.6–7.5 (*m*, 0.5 H, CONH); 7.5–7.2 (*m*, 7 arom. CH, incl. *d* at 7.38, *J* = 8.6, H–C(2′), H–C(6′)); 6.91 (*d*, *J* = 8.6, H–C(3′), H–C(5′)); 6.54 (*d*, *J* = 12.7, C*H*=CHCO); 6.05 (*d*, *J* = 12.6, CH=C*H*CO); 4.4–4.0 (br. *m*, PhC*H*N); 3.78 (*s*, MeO); 3.25–2.8 (*m*, 16 H); 2.0–1.4 (*m*, 8 H). ESI-MS/MS (−28 eV): 493 (40, $[M+H]^+$), 374 (35), 333 (15, $[M+H-MeOC_6H_4CH=CHC{\equiv}O]^+$), 275 (15), 214 (55), 161 (100, $[MeOC_6H_4CH=CHC{\equiv}O]^+$).

(±)-Isoverbasikrine ((±)-**6**). A mixture of 45 mg (±)-isoverbamekrine ((±)-**12**; 45 mg) and NH_2OH (50 mg) in 1% aq. HCl soln. (3 ml) was heated at 60° for 1 h [1], alkalinized with 25% aq. NH_3 soln., and extracted with $CHCl_3$. The org. extract was washed with H_2O, dried (Na_2SO_4), and evaporated: (±)-**6** (almost quant.). Colorless glass-like solid. TLC (silica gel, $CHCl_3$/MeOH/25% aq. NH_3 soln. 8 : 2 : 0.2): R_f 0.35. IR:

1660*s*, 1640*s* (C=O, amide I), 1610*s* (CH=CH), 1550*m* (C=O, amide II), 1510*s*, 1255*s*. ^{1}H-NMR[2]) (conformer mixture): 8.2 (br. *t*, 0.5 H, CONH···N); 7.6 (br. *t*, 0.5 H, CONH); 7.45–7.15 (*m*, 7 arom. H, incl. H–C(2′), H–C(6′)); 6.83, 6.82 (2*d*, *J* = 8.8, H–C(3′), H–C(5′)); 6.55 (*d*, *J* = 12.6, C*H*=CHCO); 5.95, 5.93 (2*d*, CH=C*H*CO); 4.01–3.97 (*m*, 0.5 H, PhC*H*N); 3.9–3.81 (*m*, 0.5 H, PhC*H*N); 3.8, 3.79 (2*s*, arom. MeO); 3.7–2.9 (*m*, 6 H, CH_2N); 2.8–2.35 (*m*, 8 H); 1.95–1.3 (*m*, 8 H). ^{13}C-NMR (conformer mixture): 171.6/171.4, 169.3 (2 C=O); 159.6, 142.7/142.5, 132.8/132.7, 129.9, 128.7/128.6, 128.1, 127.3/127.2, 126.5/126.3, 121.5/121.4, 113.8 (CH=CH); 59.6 (Ph*C*N); 55.2 (arom. MeO); 49.5, 48.6, 48.5, 48.3, 47.1, 46.3, 45.7, 45.5, 43.9, 43.7, 43.2, 37.2, 36.5, 29.5, 29.2, 29.0, 28.2, 26.8, 26.4, 26.3, 24.7 (CH_2). ESI-MS: 493 ($[M+H]^+$).

*(±)-9-[(*E*)-3-(4-Methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (=*(±)-Verbamekrine;* (±)-**9**). To a suspension of 2-chloro-1-methylpyridinium iodide (51 mg, 0.2 mmol) [6] and (*E*)-4-methoxycinnamic acid (30 mg, 0.17 mmol) in CH_2Cl_2 (2 ml) and Et_3N (0.1 ml), a soln. of (±)-**20** (58 mg, 0.17 mmol; prepared from (±)-**19** and HCHO according to [2][5]) in CH_2Cl_2 (2 ml) was added dropwise under Ar. The mixture was stirred at r.t. for 16 h, then washed with 10% aq. K_2CO_3 soln., and evaporated. The residue was purified by CC (alumina, AcOEt/MeOH 9:1): (±)-**9** (77 mg, 90%). Colorless glass-like solid, indistinguishable from the natural **9** by HPLC/MS. IR: 1660*s* (C=O, amide I), 1600*s* (C=C), 1540*m* (C=O, amide II), 1510*s*, 1250*s*. ^{1}H-NMR: 9.53, 9.33 (2 br. *s*, CONH···N); 7.68, 7.67 (2*d*, *J* = 15, C*H*=CHCO); 7.48 (*d*, *J* = 8.6, H–C(2′), H–C(6′)); 7.4–7.2 (*m*, 3 arom. H); 7.1 (*d*, *J* = 7, 2 arom. H); 6.9 (*d*, *J* = 8.3, H–C(3′), H–C(5′)); 6.7, 6.68 (2*d*, *J* = 15, CH=C*H*CO); 4.02 (br. *d*, PhC*H*N); 3.8 (*s*, MeO); 3.8–2.5 (*m*, 10 H); 2.5–1.4 (*m*, 14 H). ^{13}C-NMR: 166.1, 160.7 (2 C=O); 142.2, 141.9, 135.8, 129.2, 128.2, 127.9, 114.9, 114.8, 114.1 (C=C); 64.0 (Ph*C*N); 55.3 (arom. MeO); 53.6, 50.8, 47.1, 45.7, 37.5, 36.4, 29.5, 27.2, 25.3, 21.5, 21.2 (CH_2). ESI-MS/MS (–28 eV): 505 (25, $[M+H]^+$), 360 (15), 188 (15), 161 ($[(MeO)C_6H_4CH{=}CHC{\equiv}O]^+$, 100).

*(±)-9-[(*Z*)-3-(4-Methoxyphenyl)prop-2-enoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (=*(±)-Isoverbamekrine;* (±)-**12**). A $1 \cdot 10^{-3}$M MeOH soln. of (±)-**9** was irradiated 2 h at 365 nm under Ar. TLC (silica gel, AcOEt/MeOH 8:2; R_f 0.6 ((±)-**9**), 0.5 ((±)-**12**) showed almost quant. (*E*) → (*Z*) conversion. (±)-**12**: Colorless glass-like solid. IR: 1660*s*, 1640*s* (C=O), amide I), 1610*s* (CH=CH), 1540*m* (C=O, amide II), 1510*s*, 1255*s*. ^{1}H-NMR (conformer mixture): 9.35 (br. *s*, CONH···N); 7.45–7.25 (*m*, 5 arom. H, incl. H–C(2′), H–C(6′)); 7.1–7.07 (*m*, 2 arom. H); 6.8, 6.83 (2*d*, *J* = 8.7, H–C(3′), H–C(5′)); 6.53 (*d*, *J* = 12.7, C*H*=CHCO); 5.95, 5.94 (2*d*, *J* = 12.6, CH=C*H*CO); 3.98 (br. *t*, PhC*H*N); 3.81, 3.8 (2*s*, arom. MeO); 3.85–2.5 (*m*, 11 H); 2.5–1.25 (*m*, 13 H). ^{13}C-NMR: 168.7, 159.6 (2 C=O), 135.8, 132.8, 129.9, 128.2, 128.1, 127.9, 127.8, 121.0, 113.7 (C=C); 64.0 (Ph*C*N); 55.18 (arom. MeO), 47.57, 44.0, 37.5, 36.4, 25.7, 21.5, 21.1 (CH_2). ESI-MS: 505 ($[M+H]^+$).

*(8*S*)-1-[3-(4-Methoxyphenyl)propanoyl]-8-phenyl-1,5,9,13-tetraazacycloheptadecan-6-one* (=*(*S*)-Dihydroverbasikrine,* **15**). (*S*)-Isoverbasikrine (**6**; 1.5 mg) was hydrogenated with H_2 over 10% Pd/C at r.t. for 6.5 h: **15** (quant.; by ESI-MS). CD (*c* = 0.015%, EtOH): 230 (–6.1), 246 (±0), 250 (max., +0.3), 252 (min., +0.32), 256 (max., +0.56), 259 (min., +0.55), 262 (max., +0.84), 265 (min., +0.43), 268 (max., +0.77), 274 (±0). ESI-MS: 595 ($[M+H]^+$).

*(2*S*)-9-[3-(4-Methoxyphenyl)propanoyl]-2-phenyl-1,5,9,14-tetraazabicyclo[12.3.1]octadecan-4-one* (=*(*S*)-Dihydroverbamekrine;* **18**). To the EtOH soln. of (*S*)-dihydroverbasikrine (**15**; *ca.* 1.5 mg), a molar excess of 40% aq. HCHO soln. was added. After several min, the mixture was evaporated: **18** (quant.; by ESI-MS). CD (*c* = 0.015%, EtOH): 230 (–5.1), 242 (±0), 244 (sh, +0.12), 247 (sh, +0.35), 256 (max., –0.1), 257 (min., ±0), 262 (max., –0.36), 265 (min., –0.18), 268 (max. –0.45), 274 (±0). ESI-MS: 507 ($[M+H]^+$).

REFERENCES

[1] K. Drandarov, *Tetrahedron Lett.* **1995**, *36*, 617.

[2] K. Drandarov, A. Guggisberg, M. Hesse, *Helv. Chim. Acta* **1999**, *82*, 229.

[3] N. Youhnovski, L. Bigler, Ch. Werner, M. Hesse, *Helv. Chim. Acta* **1998**, *81*, 1654.

[4] K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 1569; K. Ishihara, Y. Kuroki, N. Hanaki, S. Ohara, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221.

[5] A. Guggisberg, M. Hesse, in, 'The Alkaloids', Ed. G. A. Cordell, Academic Press, New York, 1998, Vol. 50, p. 219.

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[2]) The ^{1}H-NMR spectrum (600 MHz, (D_6)DMSO, 350 K) of the synthetic (±)-isoverbasikrine ((±)-**6**) is superimposable with that of the natural (*S*)-isoverbasikrine (**6**).

[6] E. Bald, K. Saigo, T. Mukaiyama, *Chem. Lett*. **1975**, 1163.
[7] K. Drandarov, A. Guggisberg, M. Hesse, *Helv. Chim. Acta* **1998**, *81*, 1773.
[8] K. Drandarov, A. Guggisberg, M. Hesse, in preparation.
[9] E. Schlittler, J. Hohl, *Helv. Chim. Acta* **1951**, *35*, 29.
[10] 'Handbuch der Papierchromatographie', Eds. I. M. Hais and K. Macek, 2nd edn., G. Fischer, Jena, 1963, Vol. I, p. 932.
[11] K. Drandarov, I. M. Hais, *J. Chromatogr.*, *A* **1996**, *724*, 416.

Received April 26, 1999