Pergamon

Tetrahedron Letters 39 (1998) 9689–9692

TETRAHEDRON LETTERS

Studies in the Eburnane Series: a new Dimerization Process

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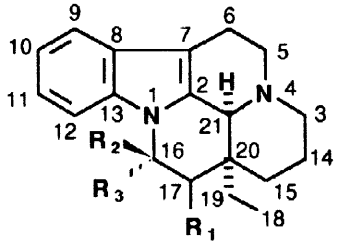
Received 15 September 1998; accepted 29 October 1998

Abstract:
The behaviour of the synthetic (-)-16-(aminomethyl)eburnamenine (prepared from apovincamine) with formaldehyde was studied. Carrying out the reaction in acetic acid led to an original dimer, while in trifluoroacetic acid a 12-functionalized eburnamonine was isolated.

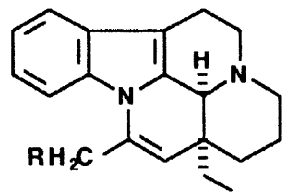
Keywords Alkaloids; indoles; dimers.

In the field of indole alkaloids, several compounds with an eburnane skeleton as vincamine **1**, vinpocetine **2** and eburnamonine **4** are used in medicine for their cerebrovascular activity [1]. In order to build from this skeleton new polycyclic nitrogen systems of pharmacological interest, we tried to introduce through cyclization at C-12 [2] an indolodiazepine structure. It seemed to us that the primary amine **7** could be a good starting compound to achieve this cyclization in fair yield. Two approaches were attempted using the Bischler-Napieralski method or the Pictet-Spengler reaction but neither has proved satisfactory with regard to our initial goal. However, we got some interesting results, especially an original dimerization process of the eburnane skeleton, that we reported below.

The synthesis of 16-(aminomethyl)eburnamenine **7** from apovincamine **3** started with the DIBAL-H reduction (CH_2Cl_2, 2.3 eq, 0°C, 1.5 h) of **3** into **5** (90%) followed by a Mitsunobu reaction with phtalimide [3] (THF, DEAD, $(C_6H_5)_3P$, reflux, 1.5 h) to **6** (74%) then hydrazinolysis of **6** (EtOH, hydrazine hydrate 20 eq, reflux, 1 h) into **7** (100%) [4].



R_1	R_2	R_3	
H	OH	CO_2CH_3	1
double bond		$CO_2C_2H_5$	2
double bond		CO_2CH_3	3
H	O		4



R	
OH	5
phtalimido	6
NH_2	7

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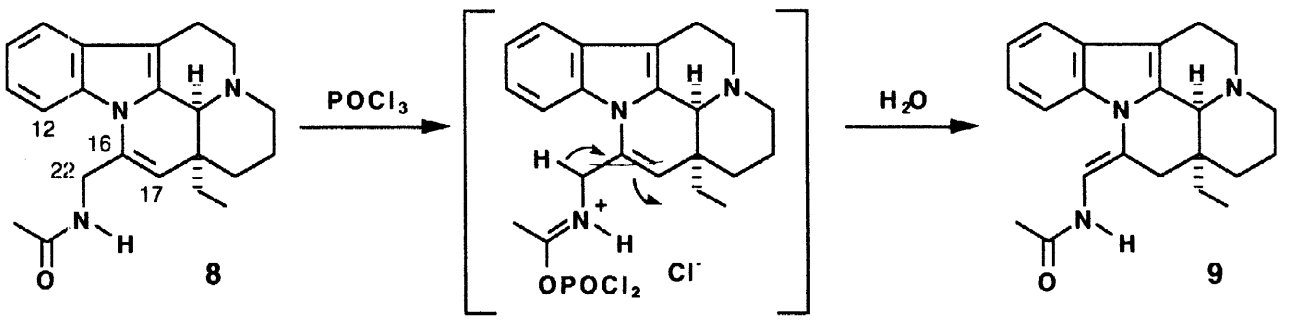
PII: S0040-4039(98)02335-1

Acetylation of **7** into **8** [I.R (CH_2Cl_2) 1640 (amide); same U.V spectrum as **7**] then treatment of **8** with neat $POCl_3$ (r.t.) did not provide any cyclization neither at C-12 nor at C-17. The isolated compound **9** (50%) proved to be the isomeric acetamide resulting from the migration of the 16-17 double bond into exocyclic position [I.R (CH_2Cl_2) 1670 (amide); U.V (EtOH) λ_{max} nm (log ε) 229 (4.27), 232 (4.27), 266 sh (4.16), 274 (4.19), 315 (4.05); ^1H NMR (DMSO-d6, 500 MHz): δ 2.21 and 2.98 (2 d, J = 15 Hz, 2H, H-17), 7.35 (d, J = 9.5 Hz, 1H, H-22), 9.43 (d, J = 9.5 Hz, 1H, NH)]. The *E* configuration of the double bond in **9** was established by the presence of NOE between H-22 and H-12 (δ 7.68 ppm). This isomerization which takes place probably as shown on scheme 1 owing to electron delocalization increase prevents hence a further cyclization (heating the reaction in $POCl_3$ provided a similar result).

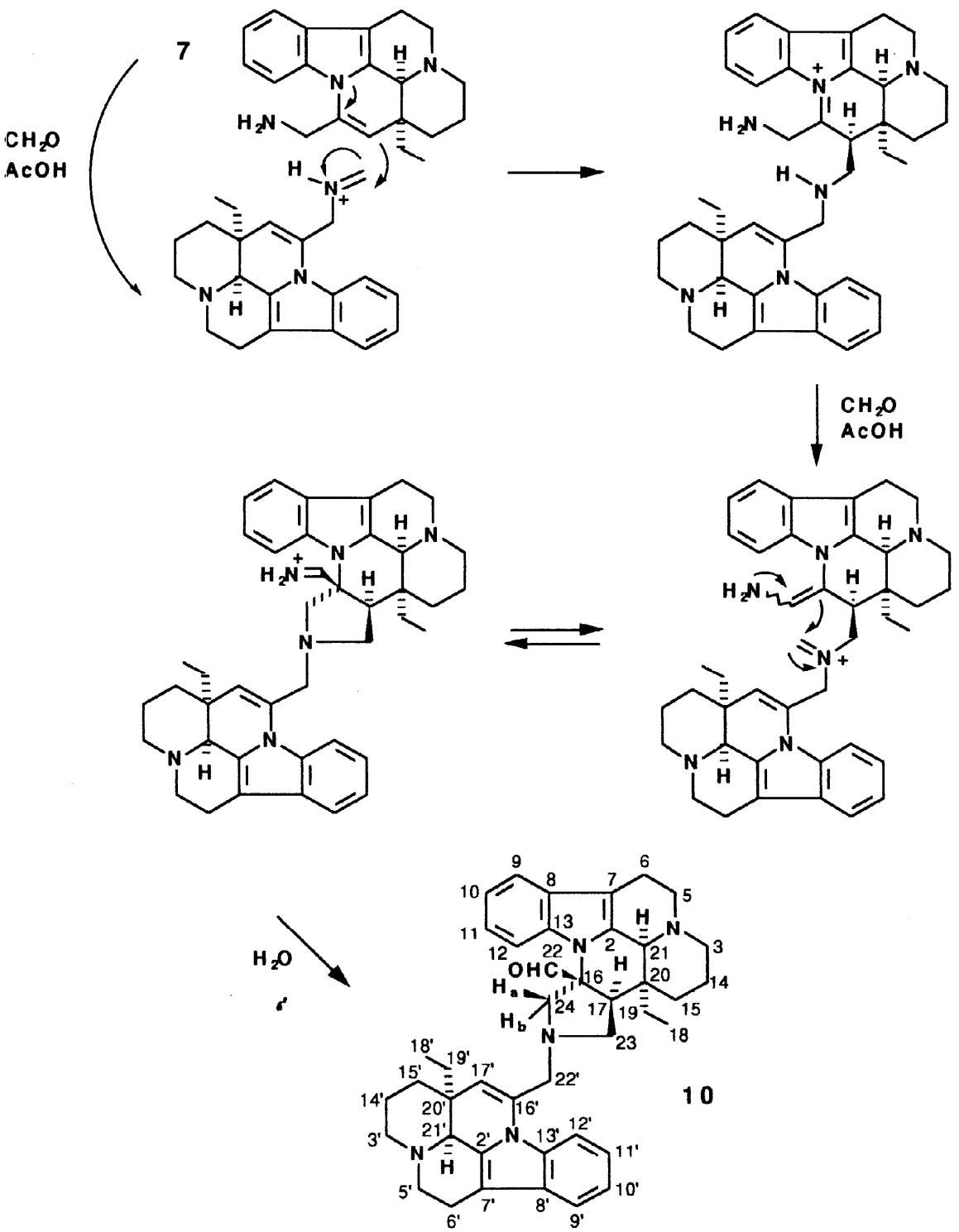


Scheme 1

The Bischler-Napieralski method being in that case unsuccessful, we studied in a second approach the behaviour of **7** with excess formaldehyde under several conditions. Reaction in acetic acid in the presence of aqueous formaldehyde (r.t. 60 h or 75°C 2.5 h) or paraformaldehyde (r.t. 60 h) gave **10** as main compound in 25% (75°C) to 40% (r.t.) respective yields. On the other hand, when the reaction with paraformaldehyde was carried out in trifluoroacetic acid (r.t. 24 h), compound **11** (20%) was isolated as main constituent of a complex mixture, while **10** was not observed.

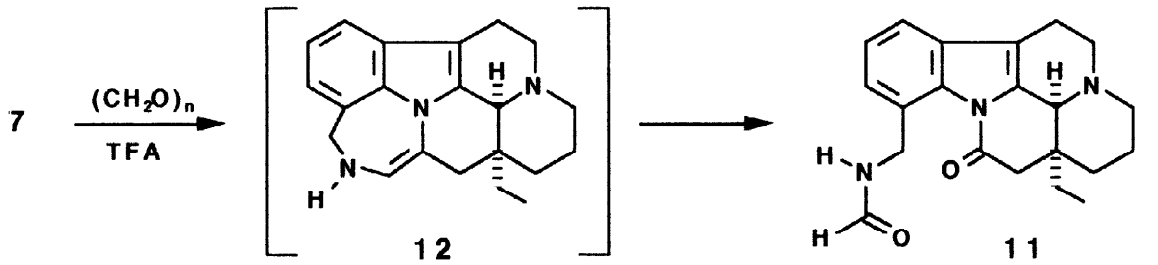
Compound **10** [$(\alpha)_D$ = -27 (c = 0.3, $CHCl_3$)] displayed a dimeric structure with an odd number of nitrogens (HRMS calcd for $C_{42}H_{49}N_5O$ 639.3937, found 639.3932). Its UV spectrum [(EtOH) λ_{max} nm (log ε) 229 (4.58), 260 (4.25), 285 (3.92), 294 (3.90), 303 (3.87), 315 (3.85)] was indicative of the addition of two chromophores, the starting one and an indole chromophore. Two observed fragments at *m/z* 347 and 292 in the EIMS and detailed homo- and heteronuclear NMR expefiments led us to assign the structure **10** [5]. HMBC experiments (especially long range couplings observed between H-22' and the three carbons C-23, C-24 and C-17') allowed to determine the linking between both moieties. In other respects, the position of the formyl group on the indole chromophore was deduced from significant NOE observed between H-12 and the aldehyde proton and one of the H-24 protons. Furthermore, relative stereochemistry at C-16 and C-17 was inferred from NOESY experiments: significant NOE's were observed between H-17 on one hand and H-19, H-21 and H-24b on the other hand and between the aldehyde proton and H-24a. When the reaction was carried out in acetic acid with paraformaldehyde-d_2, the tetradeuterated analog of **10** was isolated. Comparison of its ^1H NMR spectrum with that of **10** fixed the four deuterium atoms at C-23 and C-24. Therefore the aldehyde function of **10** is derived from the aminomethyl group of **7** and the dimerization is thought to proceed according to the mechanism depicted in scheme 2 [6].

Compound **11** showed in the HRMS a molecular ion at m/z 351.1939 (351.1947 calcd for $C_{21}H_{25}N_3O_2$). The IR spectrum displayed two strong absorptions at 1675 and 1705 cm^{-1} consistent with two carbonyl groups and a NH band between 3280 and 3420 cm^{-1}. The UV spectrum [(EtOH) λ_{max} nm (log ε) 245 (4.09), 268 (3.83), 300 (3.28), 306 (3.28)] was indicative of a chromophore very similar to that of eburnamonine **4**.



Scheme 2

These observations enabled us to assign the structure **11** which was fully confirmed by NMR experiments [7]. Compound **11** probably results (scheme 3) from the expected Pictet-Spengler reaction at C-12, migration of the 16-17 double bond then oxidative cleavage of the electron rich double bond of the indolodiazepine intermediate **12**. This surprisingly easy oxidation [8] is supposed to take place during the work up of the reaction since similar results were observed when the reaction was carried out under nitrogen.



Scheme 3

Though failing in its initial goal to access to new indolodiazepine derivatives, this study allowed isolation of: a) a new dimer structure with an original junction between the two halves compared with eburnane-eburnane dimers already described [9]; b) a new C-12 functionalized analog of the therapeutically used eburnamonine **4** .

Acknowledgements: The authors would like to thank the J.P. Volland's laboratory (IdRS), especially P.-H. Lambert for mass spectra measurements

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1. For a general review on the eburnane alkaloids, see: Lounasmaa M, Tolvanen A. In *The Alkaloids*; Cordell G.A. Ed; Academic Press, San Diego 1992; vol. 42 pp 1-116.
2. Numbering system proposed by Le Men J, Taylor W.I. *Experientia* 1965; 21: 508-510.
3. Mitsunobu O. *Synthesis* 1981; 1-28 and ref 22a and 22b.
4. Selected data for compounds **6** and **7**. **6**: CIMS *m/z* 438 $(M+1)^+$; I.R (CH_2Cl_2) 1770 and 1710 (imide); ^1H NMR ($CDCl_3$, 200 MHz): δ 4.15 (s, 1H, H-21), 4.66 (s, 1H, H-17), 5.03 and 5.18 (2d, *J* = 15 Hz, 2H, CH_2N-), 7.1-7.9 (m, 8H, aromatics); **7**: $[(\alpha)_D$ = -74 (c = 0.65, $CHCl_3)]$; EIMS *m/z* (% rel. int.) 307 (46) (M^+), 278 (100), 237 (75); U.V (EtOH) λ_{max} nm (log ε) 226 (4.17), 258 (4.43), 291 sh (3.70), 304 (3.83), 313 (3.86); I.R (CH_2Cl_2) 3400-3100 (NH_2); ^1H NMR ($CDCl_3$, 200 MHz): δ 3.80 and 4.12 (2 br d, *J* = 15 Hz, 2H, CH_2N-), 4.12 (s, 1H, H-21), 4.95 (s, 1H, H-17), 6.95-7.45 (m, 4H, aromatics).
5. NMR data of **10**: ^1H NMR ($CDCl_3$, 500 MHz): δ 0.78 (H-15), 0.85 (H-18), 0.97 (H-18'), 1.10 (H-15'), 1.28 (H-14 and H-19), 1.31 (H-15), 1.38 (H-14' and H-15'), 1.64 (H-19'), 1.71 (H-14 and H-14'), 1.93 (H-19'), 2.40 (H-6'), 2.42 (H-3'), 2.43 (H-6), 2.50 (H-19), 2.57 (H-3'), 2.64 (H-3), 2.80 (H-17), 2.91 (H-6 and H-6'), 2.98 (H-23), 3.09 (H-23), 3.13 (H-5, H-5' and H-24b), 3.25 (H-5), 3.30 (H-5'), 3.56 (H-22'), 3.68 (H-24a), 3.80 (H-22'), 3.85 (H-21), 3.98 (H-21'), 4.95 (H-17'), 6.93 (H-12), 6.97 (H-11'), 7.03 (H-10'), 7.11 (H-10 and H-11), 7.35 (H-9'), 7.37 (H-12'), 7.48 (H-9), 9.85 (CHO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.5 (C-18), 13.2 (C-18'), 20.6 (C-6), 20.9 (C-6'), 25.0 (C-14 and C-14'), 29.8 (C-19), 31.4 (C-15), 31.9 (C-19'), 34.4 (C-15'), 49.0 (C-3'), 49.5 (C-3), 55.5 (C-5 and C-5'), 56.0 (C-17), 57.0 (C-23), 60.3 (C-21'), 60.5 (C-22'), 61.2 (C-21), 65.7 (C-24), 113.9 (C-12), 116.9 (C-12'), 122.2 (C-9'), 123.1 (C-9), 123.9 (C-10'), 124.2 (C-10), 125.2 (C-11), 125.6 (C-11'), 205.3 (C-22).
6. The authors are grateful to Professor J. Lévy for suggestion of this mechanism.
7. ^1H NMR data of **11** ($CDCl_3$, 500 MHz): δ 0.95 (H-18), 1.01 (H-15), 1.43 (H-14), 1.54 (H-15), 1.70 (H-19), 1.78 (H-14), 2.05 (H-19), 2.47 (H-3 and H-6), 2.60 (H-17), 2.64 (H-3), 2.77 (H-17), 2.91 (H-6), 3.23 and 3.34 (H-5), 4.04 (H-21), 4.54 and 5.03 (CH_2NH), 6.88 (NH), 7.29 (H-9), 7.35 (H-10), 7.51 (H-11), 8.20 (CHO).
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