HETEROCYCLES, Vol. 6, No. 11, 1977

THE PARTIAL SYNTHESIS OF STRUCTURAL ANALOGS OF TUBULOSINE

Françoise Sigaut-Titeux, Louisette Le Men-Olivier

and Jean Le Men*

Faculté de Pharmacie, E.R.A. au C.N.R.S. N°319

51, rue Cognacq-Jay, 51096 REIMS CEDEX, FRANCE.

The two couples of title derivatives 4, 5 and 6, 7 were obtained frome the Pictet-Spengler condensation of homoveratrylamine with dihydrocorynantheal 2 and corynantheidal 3, respectively. Their structure and absolute configuration were determined on the basis of their mass and NMR spectra, and of their CD curves.

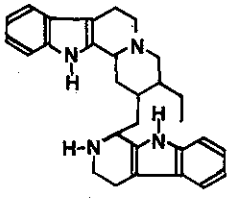
Several alkaloids (1) correspond to each of the three structural types A, B and C, and biogenetically result (2) from the association of a sole monoterpenoïd unit (derived from secologanoside) with two amines (derived from amino-acids) which may be either identical or different.

The present paper describes the partial synthesis of four derivatives of type D, which has not yet been isolated from natural sources.

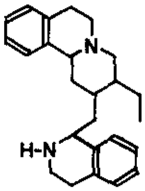
When homoveratrylamine 1 was condensed under modified Pictet-Spengler conditions (3) with dihydrocorynantheal 2 on one hand, and with corynantheidal on the other hand (4), two stereoisomers, $C_{29}H_{37}O_2N_3$ ($M^{+\cdot}$459), were isolated (yield 65 %) and separated by t.l.c. in each case, i.e. 4, 5 and 6, 7 respectively. The UV (λ max., 228, 284, 290 nm) and mass spectra (principal ions at m/e 430, 329, 267, 251, 223, 206, 192 (100%), 184, 176, 169, 144, 124) of these four derivatives were practically identical.

Their NMR spectra all exhibited the uncoupled signals characteristic for two aromatic *para* hydrogens, which indicates the position of cyclisation to the isoquinoline nucleus.

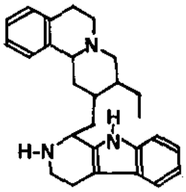
According to literature (5,6) the circular dichroism curves clearly show 5 and 6 to be 17α-H (17S) and 4 and 7 to be 17β-H (17R). These results, when associated with the occurence of strong "Bohlmann's bands" (IR) and with the absence of C(3)-H signals above 4 ppm (NMR) allow determination of all asymmetric centers (including nitrogens) in these four derivatives (7).



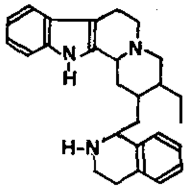
A



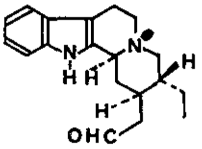
B



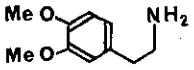
C



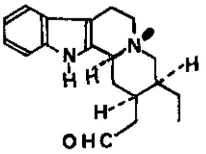
D



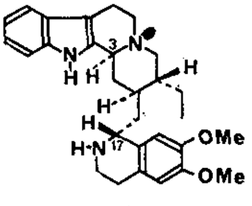
2



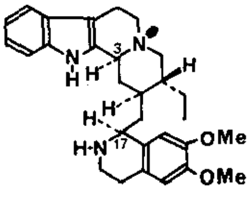
1



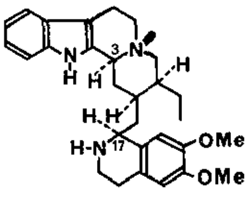
3



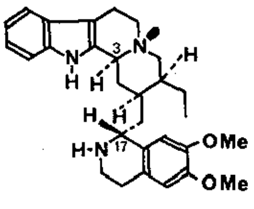
4



5

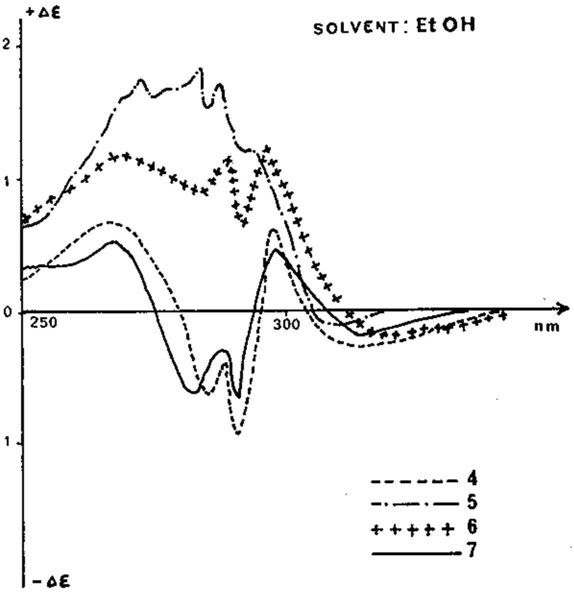


6



7

N°	$(\alpha)_D$ EtOH	I.R. bands νcm^{-1}	N M R (J ppm)					
			Indole N-H	aromatic		OMe	isoquinoline N-H	18 Me
				indole	isoquinoline			
4	+47°	3380 - 2840 2800 - 2740 1620 - 1520	s(1H) 8,78	m(4H) 7,62 à 7	s(1H)6,45 s(1H)6,62	s(3H)3,78 s(3H)3,88	2,05	t(3H) 0,98
5	+29°	3380 - 2840 2800 - 2740 1610 - 1510	s(1H) 8,52	m(4H) 7,70 to7	s(1H)6,58 s(1H)6,64	s(6H) 3,88	2,30	t(3H) 0,94
6	-38°	3390 - 2880 2800 - 2780 1710 - 1620 1520	s(1H) 8,25	m(4H) 7,60to6,95	s(2H) 6,60	s(6H) 3,86	centred on 2,0	t(3H) 0,95
7	-43°	3360 - 2820 2780 - 2740 1700 - 1610 1510	s(1H) 8,58	m(4H) 7,60to6,98	s(1H)6,48 s(1H)6,58	s(3H)3,80 s(3H)3,85	centred on 2,2	t(3H) 0,95



REFERENCES AND FOOTNOTES

1) A - type : isocinchophyllamine, ochrolifuanines, usambarensine ...
B - type : emetine, cephaeline, psychotrine ...
C - type : tubulosines, alangimarckine ...

2) For a recent general review, see : The Alkaloïds Vol. II Specialist Periodical Reports, The Chemical Society Chap. 1 (biosynthesis) 1972.

3) C.S. ZANTAY, L. TÖKE et P. KOLONITZ, *J. Org. Chem., 1966, 81, 1447.*

4) We thank Dr R.Goutarel for a generous gift of corynantheine and corynantheidine.

5) N. KLYNE, R.J. SWAN, N.J. DASTOOR, A.A. GORMAN et H. SCHMID, *Helv.Chemica Acta, 1967, 50, 115.*

6) S. TEITEL, J. O'BRIEN, W. POOL et A. BROSSI, *J. Med. Chem., 1974, 17, 134.*

7) These four derivatives, were obtained by M.C.F. Koch and E.Seguin by Bischler-Napieralski cyclisation, and given by these autours the name pseudo-tubulosines (personal communication of the authors, paper to appear in Comp.Rend.Acad.Sci.,Paris).

Received, 12th July, 1977