Tetrahedron Letters,Vol.28,No.16,pp 1773-1776,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A BIOMIMETIC ENTRY IN THE HEXACYCLIC TUBOXENIN RING SYSTEM METHYLENE-INDOLINES, INDOLENINES AND INDOLENINIUMS, XXII (1)

Georgette HUGEL[1], Janine COSSY[2], Jean LEVY[1]

1 Laboratoire de Transformations et Synthèse, UA/CNRS N°492, Faculté de Pharmacie, 51 rue Cognacq-Jay, 51096 REIMS CEDEX, FRANCE
2 Laboratoire de Photochimie, UA/CNRS N°459, Faculté des Sciences, Moulin de la Housse, 51062 REIMS CEDEX, FRANCE

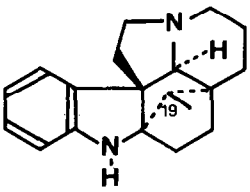
Summary : indolenine 9 was reacted with Na in THF to yield tuboxenine 1a, 19-épi tuboxenine 1b, indoline 10 and the two indoles 13 and 14.

The hexacyclic skeleton of the indole alkaloids tuboxenine 1a (2) and vindolinine 2(3) (Table) which includes four adjacent five-membered rings had not been synthesized until now. It obviously arises in the plant from pentacyclic *aspidosperma* precursors such as 9 (→ 1) and 4 (→ 2), and the supplementary 2-19 bond is likely to originate from a radical process.

In view of testing the synthetic utility of this scheme, vindolinine 2 and dihydro-vindolinine 3 were transformed along Langlois' procedure (4) into the pentacyclic esters 4 and 5 which were further saponified and decarboxylated to 7 and 9, respectively. For comparison purposes indolenine 11 was similarly obtained from tabersonine 6.

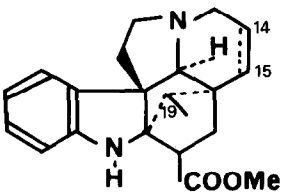
Photochemical attempts of cyclizations of indolenines 7 and 9 proved to be unsuccessful: irradiation of 7 following Mariano's conditions (5) (MeCN,$HClO_4$,254 nm, 2h) resulted only in a very sluggish reduction (2%) to indoline 8. Extension of the photochemical cyclization of δ,ε-vinyl ketones (6) to δ,ε-unsaturated imines was next explored. Here again, irradiation of 9 (MeCN,Et_3N,254nm,2h) yielded indoline 10 (30%), which was identified with the $LiAlH_4$ reduction product of 9.

Metal promoted ion-radical formation was more gratifying. Refluxing indolenine 9 (35mg) in dry THF (15ml)(8) admixed with c.a. 250 mg Na for 2.5 hours under argon atmosphere allowed recovery of 9 (1-2 mg), isolation of indoline 10 (3mg) and of three new compounds : the seco-6,7 indolic derivative 13 (9) (6.5mg,19%), its de-ethyl derivative 14 (10) (4mg,11%) and a product (10mg,29%) which proved to be tuboxenine 1a containing a very slight amount (c.a.1%,NMR) of 19-epi-tuboxenine 1b (11). Both alkaloids were separated carefully by tlc. Tuboxenine 1a (12) was identified by its NMR (1) and mass (1) spectra, its rotation : $(\alpha)_D$ +4°,$CHCl_3$,c=0.08(lit(1)+5°) and its picrate mp 160-5°C (Reichert)(lit(1),163-6°C).



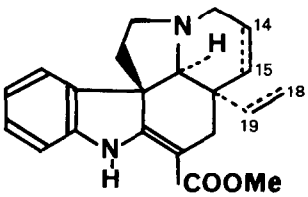
1a tuboxénine

1b 19-épi tuboxénine

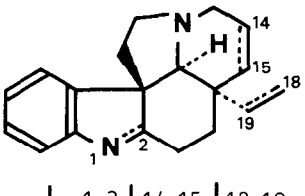


2 vindolinine, Δ^{-14}

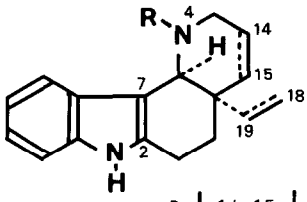
3 14,15-H_2



	14,15	18,19
4	Δ	Δ
5	H	Δ
6	Δ	H



	1,2	14,15	18,19
7	Δ	Δ	Δ
8	H	Δ	Δ
9	Δ	H	Δ
10	H	H	Δ
11	Δ	Δ	H
12	H	Δ	H



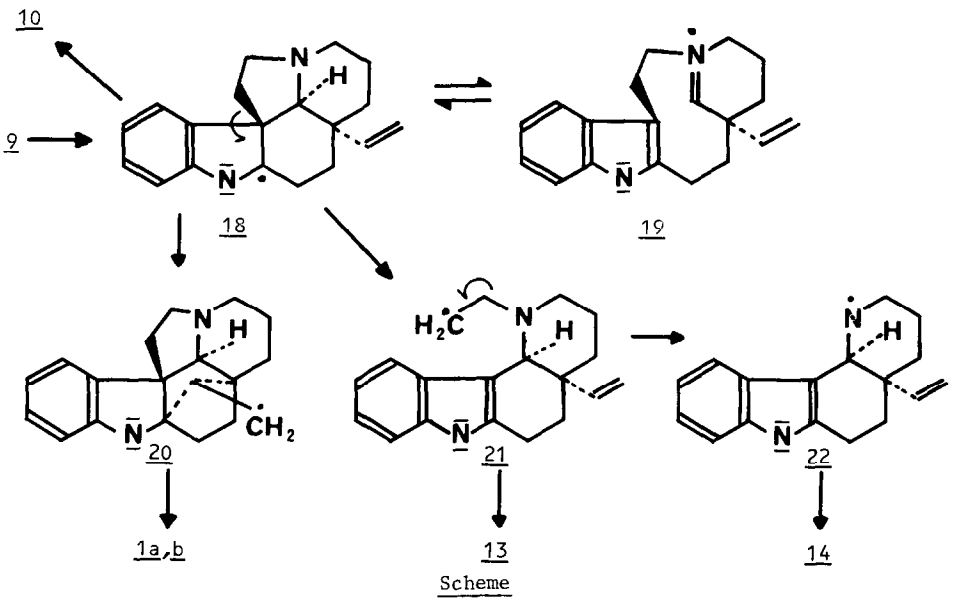
	R	14,15	18,19
13	Et	H	Δ
14	H	H	Δ
15	Et	Δ	H
16	H	Δ	H
17	Ac	Δ	H

Table

Epituboxenine 1b was compared with an authentic sample prepared by epimerization (11) of the main compound.

Apart from the successful synthesis of tuboxenine, obtention of the seco compounds 13 and 14 was of interest. In order to confirm their structure, the reaction was extended to the more readily accessible indolenine 11 which bears an ethyl side chain. Sodium in refluxing THF yielded indoline 12 (15%), the seco-6,7 indolic compound 15 (13) (27%), and its de-ethyl derivative 16 (14) (12%). The ^{1}H NMR spectrum of this last compound was in good agreement with that published by Magnus (15) for the synthetic 16. In order to confirm the relations between 15 and 16, 16 was N-acetylated to 17 and further reduced with $LiAlH_4$ in THF to give 15.

The simultaneous obtention of compounds 10, 13, 14, and tuboxenine 1a from 9 is best accounted for (Scheme) by generation of ion-radical 18 which may immediately pick up an hydrogen from the solvent (→10), or cyclize onto C(19) (→20→1) or suffer the depicted fragmentations to 21, and then to 22, the precursors of 13 and 14 respectively. This last fragmentation process offers a new procedure for generating those indole alkaloids lacking the tryptamine side chain. Absence of cleavage of the 7-21 bond in the reaction may be due to participation of the basic N(4) and to the reversible formation of species 19.



Scheme

The total synthesis of tuboxenine along these lines will be published in a further paper.

References and Notes

1) Preceding paper in this series : G.Hugel and J.Lévy, J.Org.Chem. 1986, 51, 1594.

2) a. C.Kump, J.Seibl and H.Schmid, Helv.Chim.Acta 1964, 47, 358

b. W.G.Kump, M.B.Patel, J.M.Rowson and H.Schmid, Helv.Chim.Acta 1964, 47, 1497.

3) a. C.Djerassi, S.E.Flores, H.Budzikiewicz, J.H.Wilson, L.J.Durham, J.Le Men, M.M.Janot, M.Plat, M.Gorman and N.Neuss, Proc.Nat.Acad.Sci.Wash. 1962, 48, 113.

b. A.Ahond, M.M.Janot, N.Langlois, G.Lukacs, P.Potier, P.Rasoanaivo, M.Sangaré, N.Neuss, M.Plat, J.Le Men,E.W.Hagaman and E.Wenkert, J.Am.Chem.Soc. 1974, 96, 633.

4) L.Diatta, R.Z.Andriamialisoa, N.Langlois and P.Potier, Tetrahedron 1976, 32, 2839.

5) P.S.Mariano, Tetrahedron 1983, 39, 3845.

6) D.Belotti, J.Cossy, J.P.Pète and C.Portella, Tetrahedron Lett. 1985, 26, 4591.

We thank Prof. J.P.Pète for valuable discussions.

7) 10 : $(\alpha)_D$:-28°(c=0,9,$CHCl_3$) ; UV(MeOH):208,240,292nm ; MS:m/e280($M^{+\cdot}$),252,122 ; ^{13}C NMR,$CDCl_3$(numbering of C atoms):21.75(14),23.31(16),25.32(15),28.34(17), 36.53(20),37.89(7),39.09(6),52.65(3)*,53.56(5)*,65.08(21),70.55(2),110.33(12), 111.49(18),118.90(9+10),123.13(11),127.20(8),145.36(19),149.75(13)

(*,may be inverted).