ION-RADICAL PROMOTED CYCLIZATION OF A δ,ε-VINYLIMINE : THE TOTAL SYNTHESIS OF (±)-TUBOXENINE

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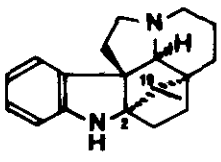
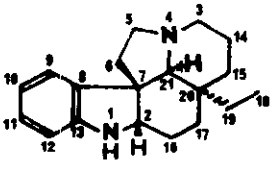
Abstract - 3-Oxo-1,2,18,19-tetradehydroaspidospermidine 8b was synthesized by a modification of a previous synthesis of vincadifformine 10. It was cyclized (Na/THF) to 3-oxotuboxenine 22, which was reduced with $LiAlH_4$ to (±)-tuboxenine 1.

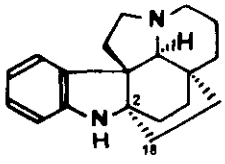
Both hexacyclic indole alkaloids tuboxenine 1 and aspidofractinine 3 derive from the pentacyclic aspidospermidine 2 framework through carbon-carbon bond formation. While several biomimetic[2] or non biomimetic[3] total syntheses of 3 and its congeners have been published, this paper reports on the first total synthesis of (±)-tuboxenine 1.



1 tuboxenine



2 aspidospermidine

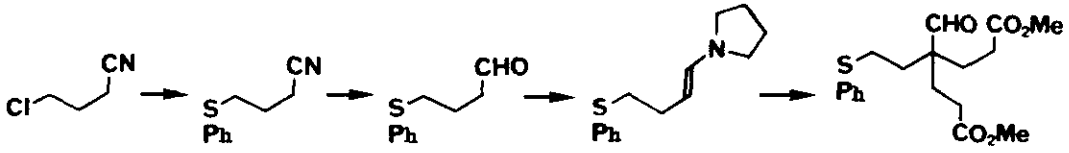


3 aspidofractinine

We found recently that the crucial 2-19 bond could be formed upon an ion-radical promoted cyclization[1] : heating 1,2,18,19-tetradehydroaspidospermidine 4 with sodium in THF yielded tuboxenine 1 (30%) along with compounds 5b, 6 and 7 as by-products. In order to avoid the formation of the seco-compounds 6 and 7, the 16-oxo indolenine 8b was chosen as an intermediate synthetic target. A further interest in the synthesis of such aspidosperma precursors bearing a vinyl side chain is related with the in vitro transformation of 18,19-dehydrotabersonine 9 into andranginine[4] on one hand, and with our recent synthesis of the tetrahydroquinolone Melodinus alkaloids[5] on the other. For this purpose, we engaged in a modification of our previous syntheses of vincadifformine 10[6] and tabersonine 11[7] (scheme 1). During completion of this work, Saxton published[8] an independant synthesis of 12 and its derivatives, which was based on a totally similar approach, i.e. the constructing 3-oxo-18,19-dehydrovincadifformine 21b using dimethyl-4-formyl-4-(phenylthio)-ethylpimelate 13

and 2-hydroxytryptamine as building blocks. Our synthesis differs from that of Saxton only in details concerning the obtention of 13, and in the order of the steps. While Saxton first elaborated the phenyl sulfide 13 to a vinyl derivative, which was further condensed with 2-hydroxytryptamine, we first reacted 13 with 2-hydroxytryptamine and were able to produce the vinyl side chain at a later stage.

In our hands, the aliphatic synthon 13 was prepared[9] from 4-chloro butyronitrile 14 through phenylthionitrile 15 (1)NaI/MeOH,1h ; 2)PhSH,MeONa,refl.,12h 76%), phenylthiobutyraldehyde 16 (DIBAH/PhH,20°C,1h ; 98%), and enamine 17 (pyrrolidine,PhH,K_2CO_3,0°C), which gave 13 (40% from 16) upon reaction with methyl acrylate in MeOH (refl., 3 days).



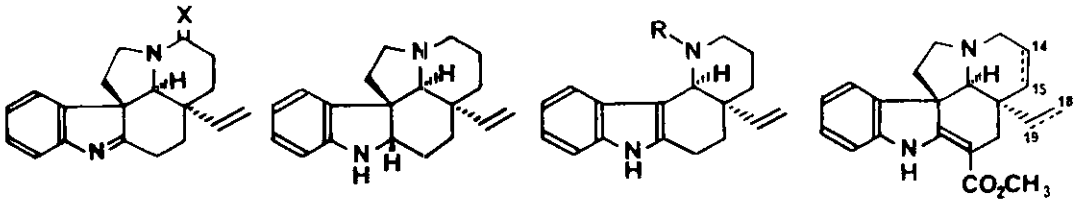
14 15 16 17 13

From there on, our scheme was largely comparable with that of the British team, i.e. : (scheme 2)

- Reaction with 2-hydroxytryptamine (PhH,refl. with water abstraction, 2h ; then AcOH, refl. 3h) to the four diastereoisomeric oxindoles 18a-d (70%), which were separated by tlc. The ratio of the four isomers in order of growing polarity were a:b:c:d=2:2:2.5:3.5.

- Elaboration of the vinyl side chain via elimination of the sulfoxides : oxindoles 19a-d (1)MCPBA,1 eq,0°C,20 min ; 2)$CaCO_3$,tol.,refl.,12h,89%). (This reaction, although it had been checked by Saxton et al., apparently resulted in a much lower yield in their hands).

- Preparation of iminoethers 20a-d (CH_2Cl_2, trimethyloxonium fluoroborate,6eq.,20°C, 3 days, 97%). The cyclization was performed using NaH in DMF as base (refl.,3h), which avoids[6] formation of the by-products resulting from the attack of the methyl ester by dimethyl sulfoxide. Thus, treatment of the block of four iminoethers 20a-d yielded the two anilinoacrylic esters 21a (less polar) and 21b (more polar) with a total 29% yield (a:b=3:7). The esters were saponified and decarboxylated (4N HCl, reflux 2.5h) to indolenines 8a (less polar,27%) and 8b (more polar, 48%). In order to assess their relative configuration, both indolenines were separately reduced with $LiAlH_4$ to the corresponding deoxoindolines (90%). The more polar indolenine 8b was thus shown to possess the natural relative configuration, as it yielded an indoline identified with 18,19-dehydroaspidospermidine 5b through comparison with an authentic sample of the optically active compound[1]. Reduction of the less polar indolenine lactam 8a gave indoline 5a, which was definitively different from 5b. The ^1H and ^{13}C nmr spectra of 8a,b and 5a,b confirmed the depicted configurations[10].



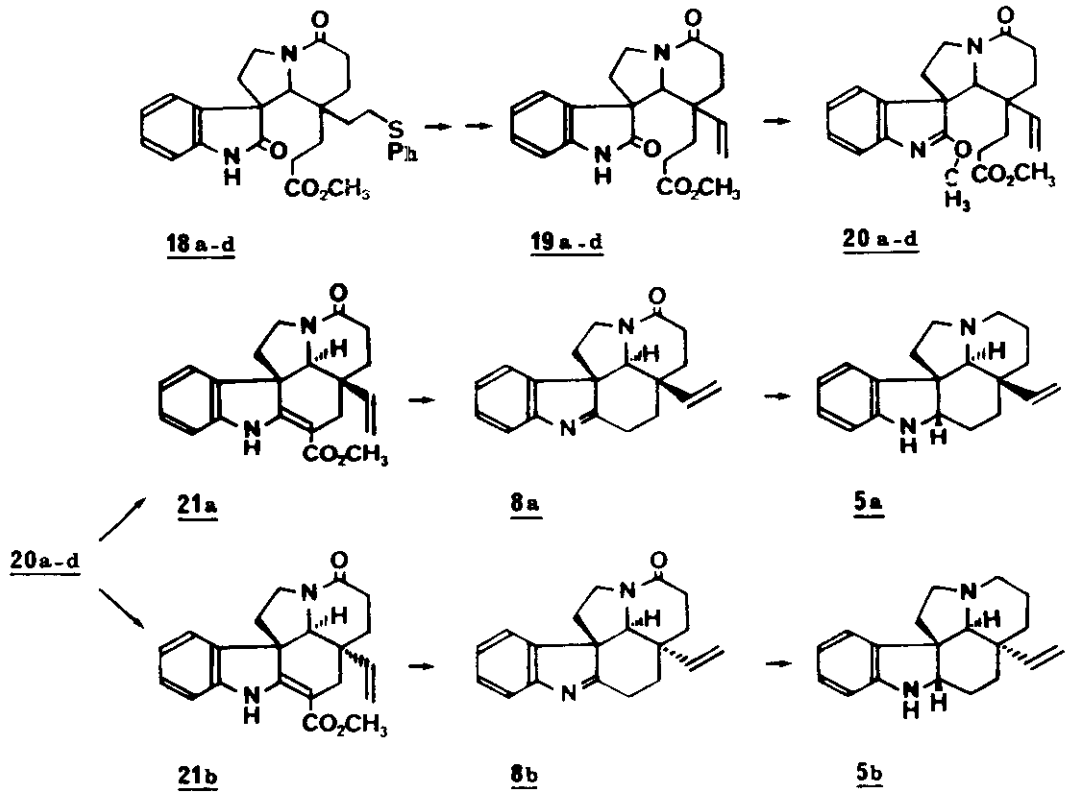
4 X = H_2
8b X = O

5b

6 R = Et
7 R = H

	14 – 15	18 – 19
9	H_2	Δ
10	H_2	H_2
11	Δ	H_2
12	Δ	Δ

Scheme 1



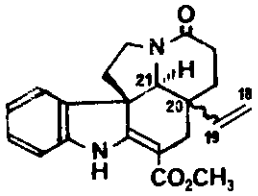
18a-d → **19a-d** → **20a-d**

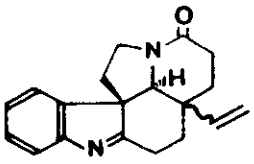
20a-d → **21a** → **8a** → **5a**

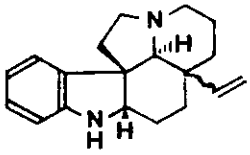
20a-d → **21b** → **8b** → **5b**

Scheme 2

The signals of H_{18},H_{19} and H_{21} in compounds 21a,b, 8a,b and 5a,b (where -a refers to the less polar compound in each couple) is of high diagnostic value : the vinylic protons are strongly influenced by the magnetic anisotropy of the benzene ring in the "natural" series (which corresponds to the -b isomers in each case), while the chemical shift of H_{21} depends on the ring junction (Table).







	21a	21b	8a	8b	5a	5b
H_{18}	5.10 ; 5.15	4.46;4.86	5.34 ; 5.40	4.60;4.85	5.13 ; 5.20	4.76 ; 4.85
H_{19}	5.87	5.52	6.05	5.44	6.45	5.82
H_{21}	3.95	4.02	3.22	4.00	2.30	2.38

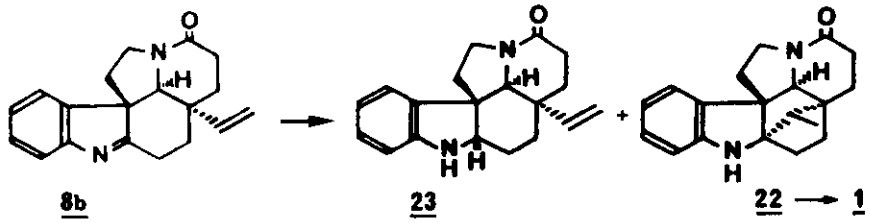
a : ß-20,19 bond

b : α-20,19 bond

Table - Selected ^{1}H nmr data in $CDCl_3$ solution ; δppm

The range of values ascribed by Saxton et al. to these vinylic protons in compounds 21a (4.95-5.30 and 5.76-6.10) and 21b (4.5-5.8) fits completely with our results. On the other hand however, they assume that an indolenine (numbered 23 in their paper) with δ values of 5.10-5.50 and 5.80-6.20, belongs to the "natural" b-series, whereas this range of values obviously corresponds to the "unnatural" a-series, and fits with our compound 8a. Most probably Saxton's compound "23" did not originate from 21b as claimed, but rather from 21a. This slight confusion does not alter the remarkable nmr study of the stereochemistry of the epimeric oxindoles in Saxton's paper.

Indolenine-lactam 8b was thus shown to be suitable for further elaboration to tuboxenine. It was then refluxed for 2.5h in THF admixed with sodium. In sharp contrast with our results in the non oxygenated series, no fragmentation of the tryptamine chain occured and 3-oxo-tuboxenine 22 was isolated with a 55% yield (mp 255-260°C ; ^{1}H nmr : 4.35(1H,ddd ; J_1=11,J_2=9,J_3=2.2 ; H_5) ; 3.79(1H,s ; H_{21}) ; 3.62(1H,dt,J_1=7.5,J_2=11 ; H_5) ; 0.95(3H,d;J=7 ; H_{18})).



This important improvement due to the influence of the lactam group in 8b suggests that the basic N_4 is involved in the fragmentation process affecting indolenine 4. In this case, an intermediate transient aziridine radical would simply account for the formation of 6 (hydrogen abstraction from the solvent) and of 7 (ethylene elimination and hydrogen abstraction).

A small amount (5%) of indoline 23 was formed and only traces of the 19-epi derivative were to be seen on the ^{1}H nmr of the crude product, giving rise to a small methyl doublet centered at 0.53 ppm.

Finally, reduction of 22 with $LiAlH_4$ afforded (±)-tuboxenine (84% ; mp(picrate) 164-165°C), which was identified by its uv, nmr and mass spectra[11] and through tlc comparison with an hemisynthetic sample[1]. The yield of (±)-tuboxenine from 2-hydroxytryptamine was c.a. 3.8%.

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