METHYLENE-INDOLINES, INDOLENINES AND INDOLENINIUMS XVII [1]
REARRANGEMENT OF DE-ETHYLTABERSONINE IN ACETIC ACID

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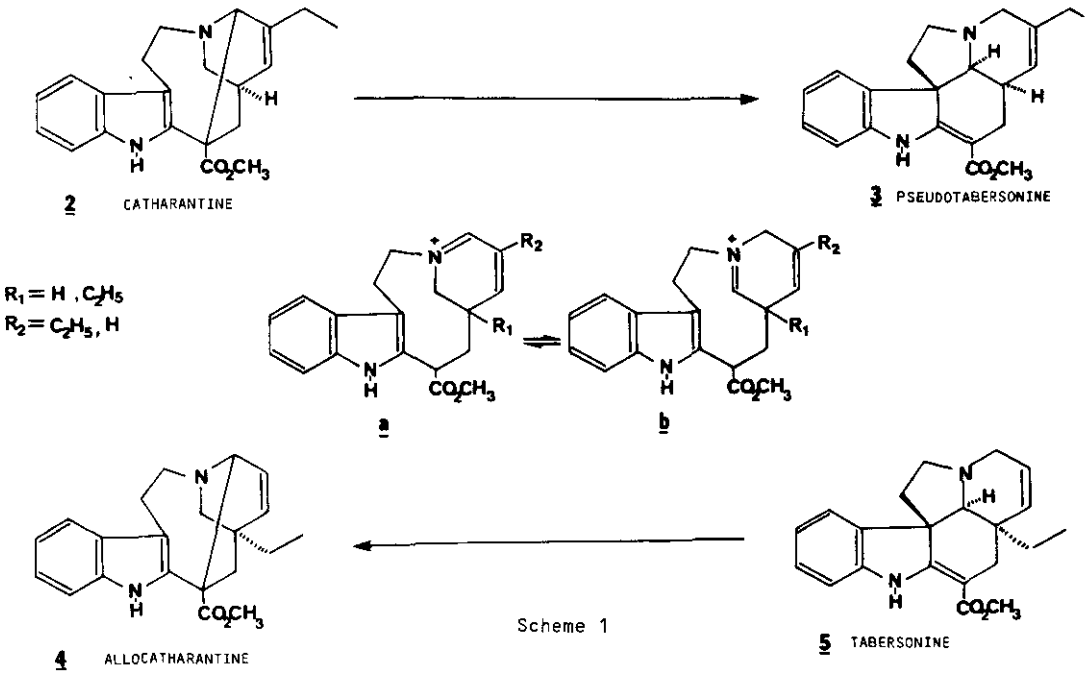
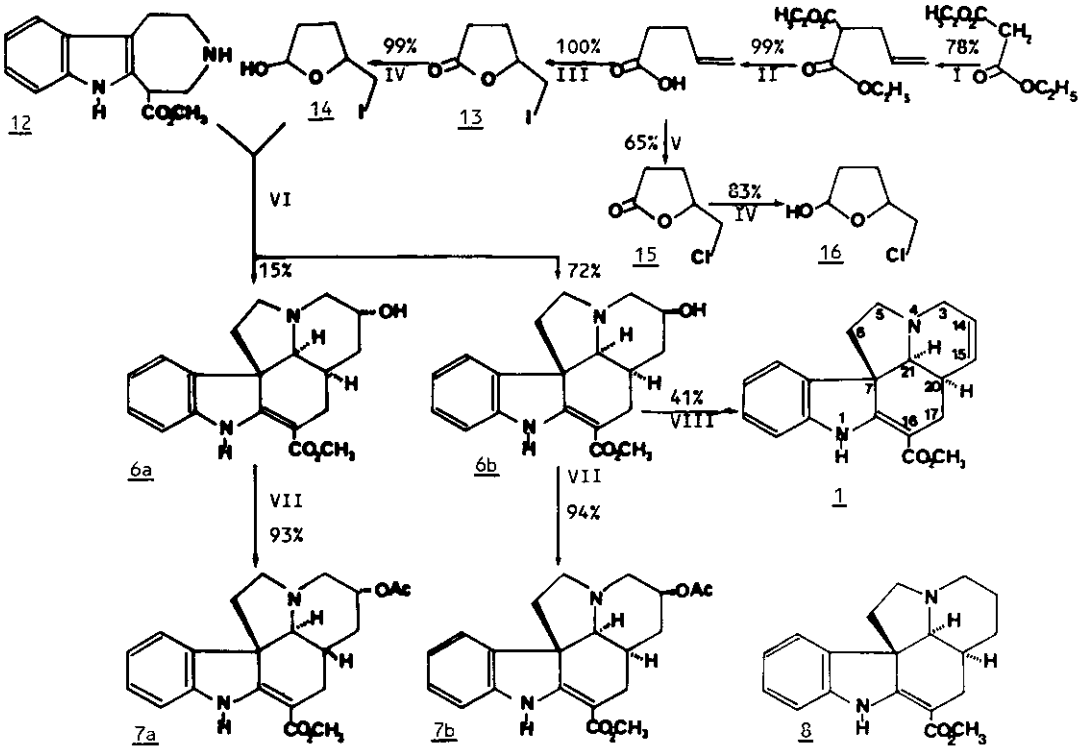
Abstract - De-ethyltabersonine 1 rearranged in boiling acetic acid to de-ethyl-coronaridine 9 with a low yield.

Rearrangements of catharanthine 2 to pseudotabersonine 3 [2] and of tabersonine 5 to allocatharanthine 4 [3] in boiling acetic acid curiously follow opposit courses, depending on the position of the ethyl side chain. These rearrangements probably both imply an equilibrium between the highly strained dihydropyridinium species a and b (scheme 1).



Scheme 1

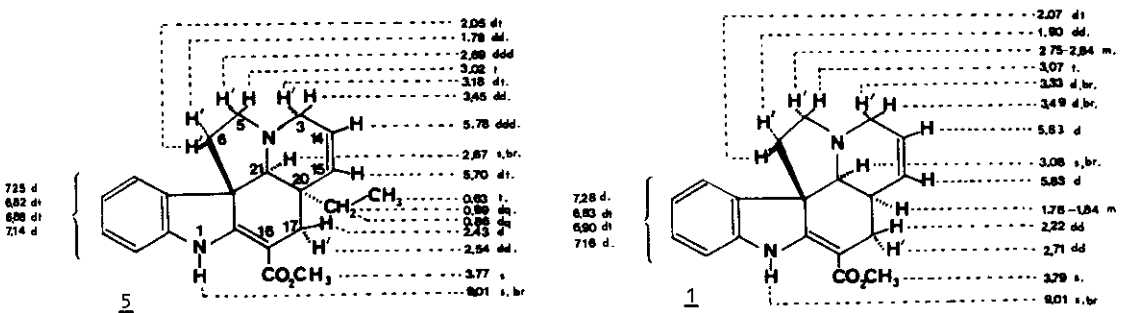
In order to study the reactivity of a compound lacking the crucial ethyl side chain, Kuehne's general synthesis of tabersonine [4] was adapted to de-ethyltabersonine 1 (scheme 2) [5] : condensation of indoloazepine 12 [4] and iodo-lactol 14 (or chloro-lactol 16) yielded the 14-hydroxy-de-ethylvincadifformines 6a,b, the relative configuration of which was based on the ^{1}H NMR spectra of their acetyl derivatives 7a,b, compared with that of 14α and 14β-acetoxy-vincadifformine [6].



I : allyl bromide, EtONa ; reflux 3 hrs. II : 1)NaOH, EtOH,Δ ;2) 120° 2 hrs. III : I_2,KI $NaHCO_3$, r.t. 36 hrs. IV : DiBAH, toluene, -72°. V : Cl_2, CH_2Cl_2 0°. VI : 1)TsOH, MeOH, reflux 24 hrs ; 2)Et_3N, reflux 15 hrs. VII : Ac_2O, Py r.t. 24 hrs. VIII : 1)Ph_3P, CCl_4 2)Et_3N-CH_3CN 90°.

Scheme 2

Dehydration of 6b yielded de-ethyltabersonine 1 : the occurrence of Bohlmann's band (IR) and the coupling constant ($J_{20,21}$ ~0) on its 400MHz ^1H NMR spectrum (see scheme 3) are fully consistent with the depicted configuration[7].



Scheme 3

De-ethyltabersonine 1 was boiled for 15 hrs in acetic acid under argon. Repeated t.l.c. allowed isolation of four major compounds :

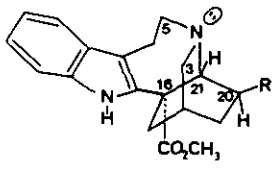
- The starting material 1 (36.3%).

- A fraction (6-10%) constituted of compounds with an anilino-acrylic chromophor from which 14α-acetoxy de-ethylvincadifformine 7a was isolated (1%), and identified (t.l.c., M.S.) with an authentic specimen obtained from 14α-hydroxy-de-ethylvincadifformine 6a.

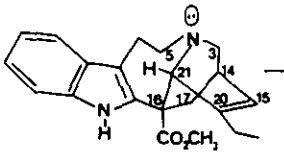
- De-ethylvincadifformine 8[8] (7.4%), which was identified by comparison with an authentic specimen, uneconomically prepared by catalytic hydrogenation of de-ethyltabersonine 1.

- De-ethylcoronaridine 9 (3.4%), identified by comparison with an authentic sample kindly provided by Dr Sundberg[9]. However careful examination of the reaction mixture did not allow detection of the sought after de-ethylcatharanthine.

Of interest is the ^{1}H NMR spectrum of de-ethylcoronaridine 9 as compared with those of coronaridine 10, 15β,20β-dihydrocatharanthine 11, and of catharanthine 2.



9 R = H
10 R = C_2H_5



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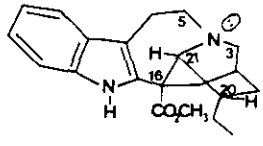

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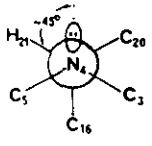
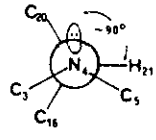


9 , 10

	9	10	2	11
Chemical shift of H-21	3.7-3.8 dd(m)	3.58 d	4.22 d	4.53 d



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The aromatic part of the spectra are very similar. A striking difference lies in the chemical shift of H(21), which is considerally deshielded in 11, due to the steric interactions between the endo ethyl side chain and the methoxycarbonyl group. This results in ring deformation and the dihedral angle between the lone pair of electrons of N(4) and H(21) then opens from ~45° (9,10) to ~90°(11). The isolated derivatives 7 and 8 reflect an easy disproportionation of the intermediate dihydropyridiniums a and b (scheme 1, R_1=R_2=H). Such unrearranged and rearranged dihydroderivatives had been previously obtained through acetic acid treatment of tabersonine 5, although the rearranged

allocatharanthine was in that case the main product of the reaction[10].

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5 . Spectral date for new compounds and intermediates :

1 : mp 97-98°C ; IR($CHCl_3$, film) : 3380, 2780-2730-2700 (Bohlmann's bands)1670,1610 cm^{-1};UV(MeOH λmax) : 227,308,338 nm ; MS m/e : 308 ($M^{+\cdot}$),229,214,168,154,149,107,94 ; ^1H NMR($CHCl_3$,400MHz) : (see scheme 3) 5.83(d,$J_{14(15),3}$ ∿2Hz), 3.49(br.d,$J_{3,3'}$=16Hz,$J_{14(15),3}$ ∿2Hz), 3.33(br.d,$J_{3,3'}$=16Hz $J_{3',20}$∿2Hz), 3.08(br.s,$J_{21,17'}$∿1Hz), 3.07(t,$J_{5,5'}$=7Hz,$J_{5,6'}$=5Hz,$J_{5,6}$ =7Hz), 2.84-2.75 (m, $J_{5',5}$ = 7Hz), 2.71(dd,$J_{17',17}$=15Hz,$J_{17',20}$=3Hz,$J_{17',21}$∿1Hz), 2.22(dd,$J_{17,17'}$=15Hz, $J_{17,20}$=11Hz), 2.07(dt,$J_{6,6'}$=10Hz,$J_{6,5}$ =7Hz), 1.90(dd,$J_{6,6'}$=10Hz,$J_{6',5}$=5Hz), 1.84-1.78(m, $J_{20,17'}$=3Hz).

6a : IR($CHCl_3$, film) : 3600-3100, 2780-2720-2700 (Bohlmann's bands), 1680, 1609 cm^{-1} ; UV(MeOH,λmax) : 228,300,329 nm ; MS m/e : 327($M^{+\cdot}$1),326($M^{+\cdot}$),308,295,280,248,214,180,167,154, 149,113,112 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 8.88(br,s,1H), 7.40-6.60(m,4H), 4.30-3.80(m,1H), 3.75(s,3H).

6b : mp 189-190°C ; IR($CHCl_3$,film) : 3600-3200, 2780-2720 (Bohlmann's bands), 1670, 1605 ; UV(MeOH,λmax) : 228,300,328 nm ; MS m/e : 327($M^{+\cdot}$),326($M^{+\cdot}$),308,295,280,248,214,180,167,154, 113,112 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 8.92(br,s,1H), 7.40-6.70(m,1H), 4.10-3.80(m,1H), 3.75(s,1H).

7a : IR($CHCl_3$,film) : 3380, 2799-2750-2690 (Bohlmann's bands), 1730, 1680, 1615 cm^{-1} ; UV(MeOH,λmax) : 227,300,329 nm ; MS m/e : 368($M^{+\cdot}$),308,280,154 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 8.90(br,s,1H), 7.35-6.65(m,4H), 5.34-4.75(m,1H,J=7Hz), 3.75(s,3H).

7b : mp 172.5-174°C ; IR($CHCl_3$,film) : 3380, 2799-2740-2680 (Bohlmann's bands), 1730, 1675, 1610 cm^{-1};UV(MeOH,λmax) : 227,300,329 nm ; MS m/e : 368($M^{+\cdot}$),308,280,154 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 8.90(br,s,1H), 7.35-6.70(m,4H), 5.05-4.80(m,1H,J=3Hz), 3.75(s,3H).

8 : IR($CHCl_3$,film) : 3280, 2780-2730 (Bohlmann's bands), 1722, 1670, 1608 cm^{-1} ; UV(MeOH,λmax) : 220,292,324 ; MS m/e : 310($M^{+\cdot}$),214,96 ; ^1H NMR($CDCl_3$,200MHz,TMS δ=0) : 8.94(br,s,1H), 7.38-6.78 (m,4H), 3.78(s,3H).

9 : IR($CHCl_3$,film) : 3290, 1730 cm^{-1} ; UV(MeOH,λmax) : 224,285,293(indole type) ; MS (high resolution) m/e : 310($M^{+\cdot}$,$C_{19}H_{22}N_2O_2$), 255($C_{15}H_{15}N_2O_2$), 214($C_{13}H_{12}NO_2$) ; ^1H NMR($CDCl_3$,200MHz,TMS δ=0): 7.72(s,1H), 7.48(dd,1H), 7.30-7.05(m,3H), 3.75(s+m,4H).

13 : IR($CHCl_3$,film) : 1785 cm^{-1} ; MS m/e : 226($M^{+\cdot}$),169,141,128,99,85 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 5.10-4.50(m,1H), 3.66(d,2H), 3.06-1.92(m,4H).

14 : IR($CHCl_3$,film) : 3200 cm^{-1} ; MS m/e : 238($M^{+\cdot}$),211,207,171,141,128,101,87 ; ^1H NMR($CDCl_3$, 60MHz,TMS δ=0) : 5.85-5.45(m,1H), 4.50(s,1H), 4.70-4.00(m,1H), 3.40(dd,2H), 2.65-1.55(m,4H).

15 : IR($CHCl_3$,film) : 1785 cm^{-1} ; MS m/e : 134($M^{+\cdot}$),99,85 ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 5.10-4.50(m,1H), 3.80(dd,2H), 2.82-2.00(m,4H).

16 : IR($CHCl_3$,film) : 3200 cm^{-1} ; ^1H NMR($CDCl_3$,60MHz,TMS δ=0) : 5.80-5.40(m,1H), 4.82(s,1H), 4.70-4.00(m,1H), 3.6(dd,2H), 2.65-1.55(m,4H).

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