

METHYLENE-INDOLINES, INDOLENINES AND INDOLENINIUMS XVII¹
 REARRANGEMENT OF DE-ETHYLTABERSONINE IN ACETIC ACID

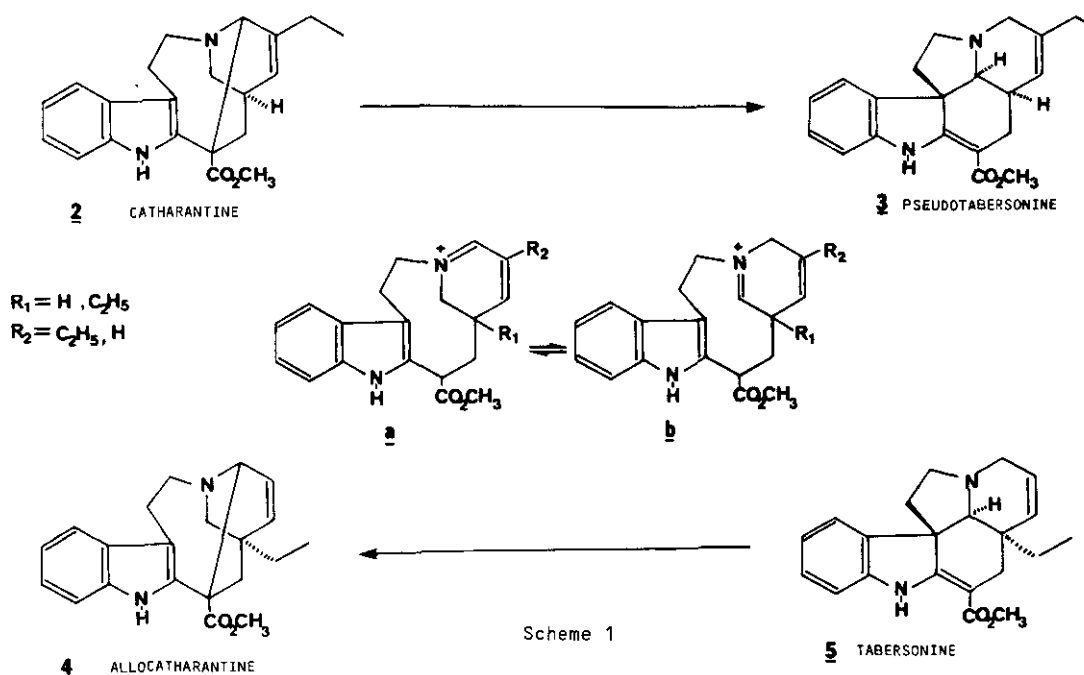
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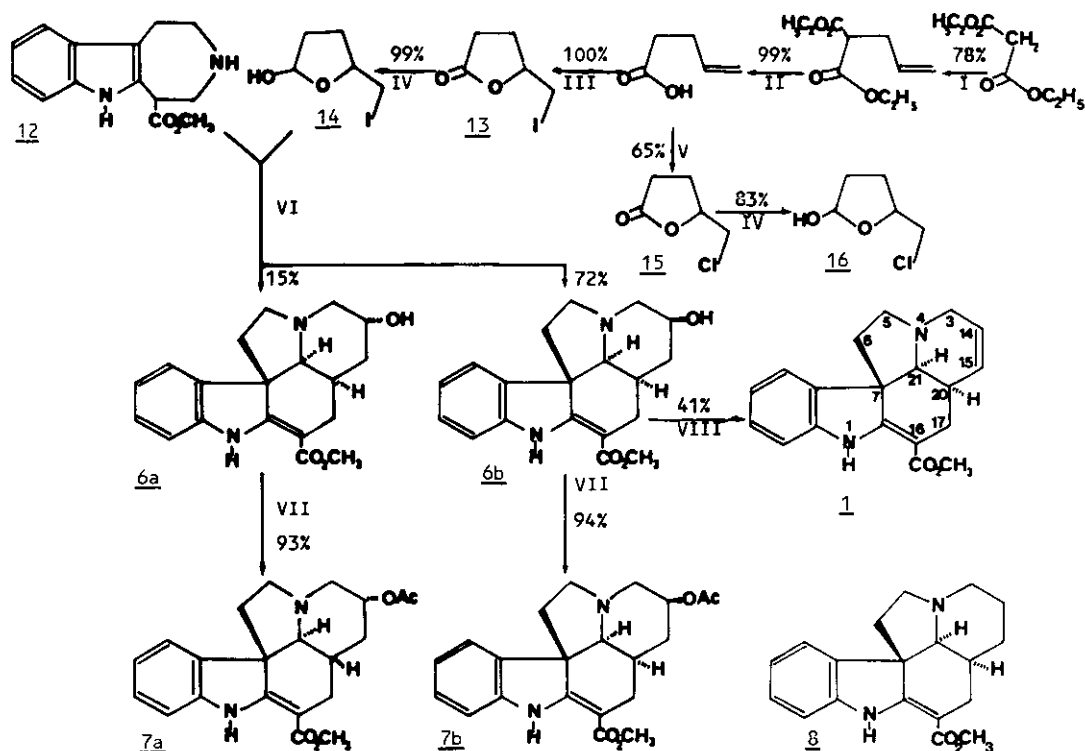
Abstract - De-ethyltabersonine **1** rearranged in boiling acetic acid to de-ethylcoronaridine **2** with a low yield.

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

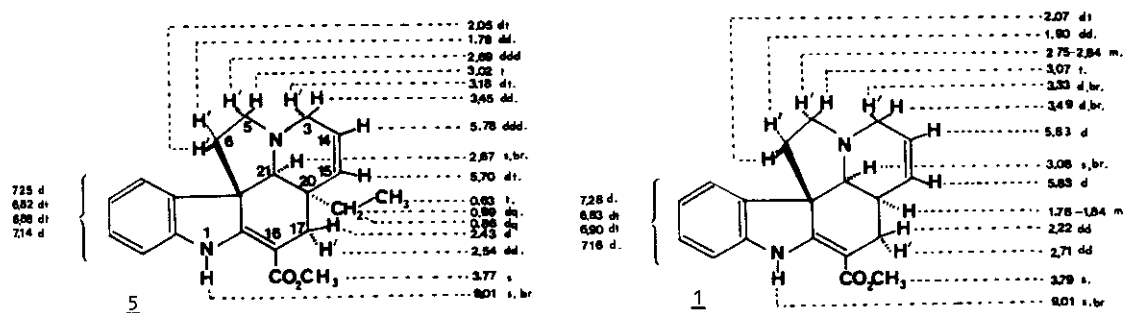
In order to study the reactivity of a compound lacking the crucial ethyl side chain, Kuehne's general synthesis of tabersonine **4** was adapted to de-ethyltabersonine **1** (scheme 2)⁵: condensation of indoloazepine **12**⁴ and iodo-lactol **14** (or chloro-lactol **16**) yielded the 14-hydroxy-de-ethylvincadifformines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



I : allyl bromide, EtONa ; reflux 3 hrs. II : 1) NaOH, EtOH, Δ; 2) 120° 2 hrs. III : I₂, KI NaHCO₃, r.t. 36 hrs. IV : DiBAH, toluene, -72°. V : Cl₂, CH₂Cl₂ 0°. VI : 1) TsOH, MeOH, reflux 24 hrs ; 2) Et₃N, reflux 15 hrs. VII : Ac₂O, Py r.t. 24 hrs. VIII : 1) Ph₃P, CCl₄ 2) Et₃N-CH₃CN 90°.

Scheme 2

Dehydration of **6b** yielded de-ethyltabersonine **1** : the occurrence of Bohlmann's band (IR) and the coupling constant ($J_{20,21}^{\text{H}}$) 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 :

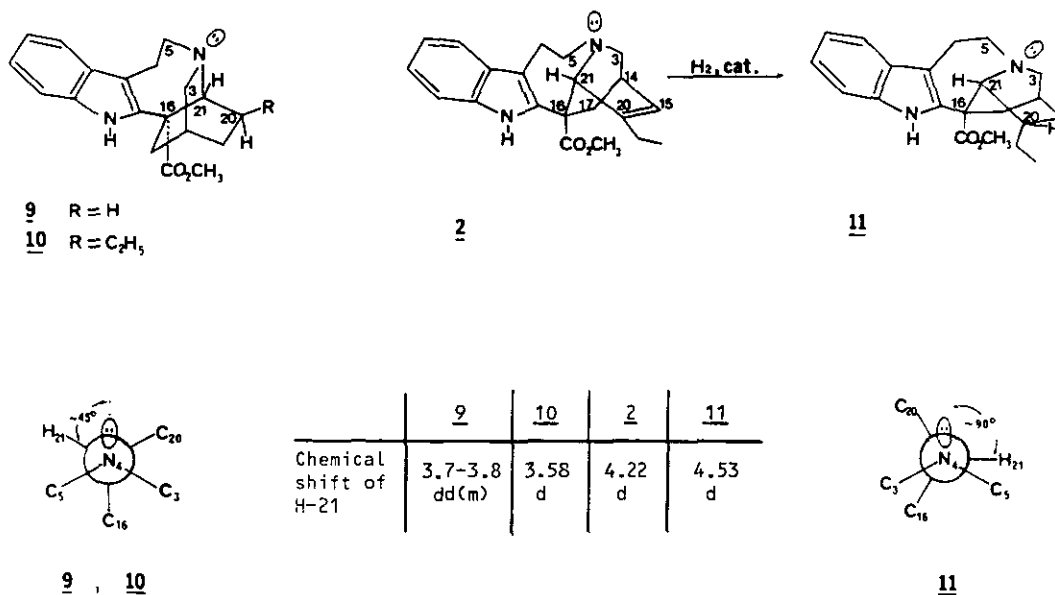
- The starting material 1 (36.3%).

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

- De-ethylvincadifformine 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 Sundberg⁹. However careful examination of the reaction mixture did not allow detection of the sought after de-ethylcatharanthine.

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



The aromatic part of the spectra are very similar. A striking difference lies in the chemical shift of H(21), which is considerably 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, R₁=R₂=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 reaction¹⁰

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5. Spectral data for new compounds and intermediates :

1 : mp 97-98°C ; IR(CHCl₃, film) : 3380, 2780-2730-2700 (Bohlmann's bands), 1670, 1610 cm⁻¹; UV(MeOH λ_{max}) : 227, 308, 338 nm ; MS m/e : 308 (M⁺), 229, 214, 168, 154, 149, 107, 94 ; ¹H NMR(CHCl₃, 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(CHCl₃, film) : 3600-3100, 2780-2720-2700 (Bohlmann's bands), 1680, 1609 cm⁻¹ ; UV(MeOH, λ_{max}) : 228, 300, 329 nm ; MS m/e : 327(M⁺), 326(M⁺), 308, 295, 280, 248, 214, 180, 167, 154, 149, 113, 112 ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 3600-3200, 2780-2720 (Bohlmann's bands), 1670, 1605 ; UV(MeOH, λ_{max}) : 228, 300, 328 nm ; MS m/e : 327(M⁺), 326(M⁺), 308, 295, 280, 248, 214, 180, 167, 154, 113, 112 ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 3380, 2799-2750-2690 (Bohlmann's bands), 1730, 1680, 1615 cm⁻¹ ; UV(MeOH, λ_{max}) : 227, 300, 329 nm ; MS m/e : 368(M⁺), 308, 280, 154 ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 3380, 2799-2740-2680 (Bohlmann's bands), 1730, 1675, 1610 cm⁻¹; UV(MeOH, λ_{max}) : 227, 300, 329 nm ; MS m/e : 368(M⁺), 308, 280, 154 ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 3280, 2780-2730 (Bohlmann's bands), 1722, 1670, 1608 cm⁻¹ ; UV(MeOH, λ_{max}) : 220, 292, 324 ; MS m/e : 310(M⁺), 214, 96 ; ¹H NMR(CDCl₃, 200MHz, TMS δ=0) : 8.94(br, s, 1H), 7.38-6.78(m, 4H), 3.78(s, 3H).
- 9 : IR(CHCl₃, film) : 3290, 1730 cm⁻¹ ; UV(MeOH, λ_{max}) : 224, 285, 293(indole type) ; MS (high resolution) m/e : 310(M⁺, C₁₉H₂₂N₂O₂), 255(C₁₅H₁₅N₂O₂), 214(C₁₃H₁₂N₂O₂) ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 1785 cm⁻¹ ; MS m/e : 226(M⁺), 169, 141, 128, 99, 85 ; ¹H NMR(CDCl₃, 60MHz, TMS δ=0) : 5.10-4.50(m, 1H), 3.66(d, 2H), 3.06-1.92(m, 4H).
- 14 : IR(CHCl₃, film) : 3200 cm⁻¹ ; MS m/e : 238(M⁺), 211, 207, 171, 141, 128, 101, 87 ; ¹H NMR(CDCl₃, 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(CHCl₃, film) : 1785 cm⁻¹ ; MS m/e : 134(M⁺), 99, 85 ; ¹H NMR(CDCl₃, 60MHz, TMS δ=0) : 5.10-4.50(m, 1H), 3.80(dd, 2H), 2.82-2.00(m, 4H).
- 16 : IR(CHCl₃, film) : 3200 cm⁻¹ ; ¹H NMR(CDCl₃, 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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