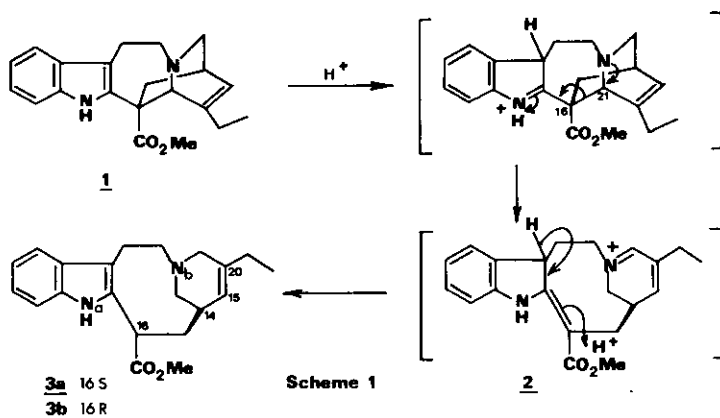


PREPARATION OF 15-OXO-16-METHOXYCARBONYL-15,20-DIHYDRO-CLEAVAMINE AND
COUPLING REACTION WITH VINDOLINE*

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Several derivatives of 16-methoxycarbonyl cleavamines oxygenated in position 15 have been prepared and the coupling reaction of 15-oxo 16S-methoxycarbonyl 15,20-dihydro cleavamine with vindoline has been studied.

The hydrochloride of catharanthine 1, when treated with trifluoroacetic acid at 60°C led, after reduction of the intermediate iminium salt 2 with sodium borohydride, to 16-methoxycarbonyl cleavamines 3a (73%) and 3b (24%) in almost quantitative yield (Scheme 1). This method has to be preferred to the process using acetic acid at higher temperature¹.



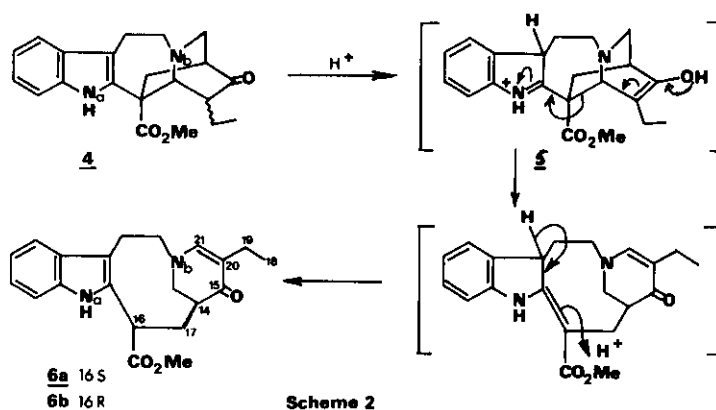
* This article is dedicated to Professor T. Kametani, on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

Likewise, 15-oxo-15,20-dihydro catharanthine 4², in solution in trifluoroacetic acid gave rise, after two hours at 60°C and without reduction, to two compounds whose spectral data are compatible with structure 6 corresponding to 5-oxo Δ^{20} 16-methoxycarbonyl-15,20-dihydro cleavamine :

6a (40%) : ir 3300, 2950, 1735, 1630, 1590 cm^{-1} ; uv(MeOH) λ_{max} nm (ϵ) : 224, 286(7800), 294(7400), 346(9600) ; CD(MeOH) λ_{nm} ($\Delta\epsilon$) : 224(+ 14.9), 274(+ 3.3), 345(+ 9.5) ; ms : 352(M^{+}), 337, 293, 267, 229, 228, 214, 182, 180, 176, 170, 169, 168, 167, 156, 154, 152, 151(100%), 138, 137, 123 ; pmr 240 MHz, $\delta/\text{TMS}(\text{CDCl}_3)$: 8.73 (1H, s, $\text{N}_a\text{-H}$), 7.49 and 7.36 (2 H arom.), 7.17 (2 H arom.), 7.08 (1 H, s, $\text{C}_{21}\text{-H}$), 4.11 (1H, d, $J_{16,17} = 11$ Hz, $\text{C}_{16}\text{-H}$), 3.60 (3 H, s, CO_2CH_3), 2.28 ($\text{C}_{17}\text{-H}$ and $\text{C}_{19}\text{-H}$), 1.08 (3 H, t, $J_{18,19} = 7$ Hz, $\text{C}_{18}\text{-H}$).

6b (25%) : ir 3240, 2950, 1735, 1620, 1575 cm^{-1} ; uv(MeOH): 224, 286, 294, 344 ; CD (MeOH) : 240(- 3.0), 284(- 2.1), 315(+ 4.8), 342(+ 7.2) ; ms : 352(M^{+} , 100%), 337, 293, 267, 256, 229, 228, 214, 202, 182, 180, 176, 170, 169, 168, 167, 156, 154, 152, 151, 138, 137, 123 ; pmr 60 MHz, $\delta/\text{TMS}(\text{CDCl}_3)$: 8.70 (1 H, $\text{N}_a\text{-H}$), 6.62 (1 H, s, $\text{C}_{21}\text{-H}$), 3.62 (3 H, s, CO_2CH_3), 0.89 (3 H, t, $J_{18,19} = 7$ Hz ($\text{C}_{18}\text{-H}$)).

In this case, the enolic form 5 could well be an intermediate which participates in the $\text{C}_{16}\text{C}_{21}$ fragmentation reaction (Scheme 2).



The configurations at C₁₆ for 16-methoxycarbonyl cleavamines 3a and 3b are easily deduced from examination of the CD curves³ or from the pmr spectra where the chemical shift of C₁₆-H is typical of the configuration at this centre⁴ : in the 16S epimeric compound 3a, the close proximity of C₁₆-H and the lone pair of electrons of the nitrogen atom (N_b) accounts for the low field resonance of this proton. However, the attribution of the configuration at C₁₆ by pmr for the compounds 6 is only possible after reduction of the enaminone function.

(a) Treatment of compound 6a with an excess of sodium borohydride for 25 min. at room temperature afforded not only compound 7 (40%) but also compounds 8 (20%) and 9 (20%) in which the methoxycarbonyl group is also reduced.

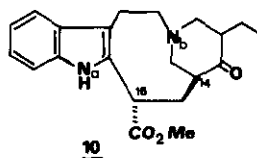
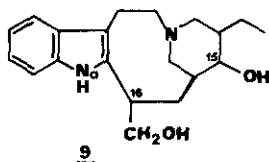
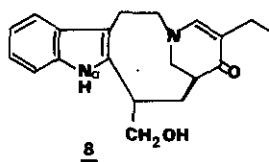
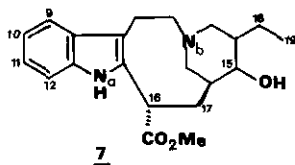
7 ir : 3400, 3300(sh), 1725 cm⁻¹ ; uv : 227, 286, 293 nm ; CD : 207(-), 229(+), 275(+) ; ms : 357, 356(M⁺), 297, 226, 216, 215, 155, 154(100%), 142, 140, 124 ; pmr 400 MHz, δ /TMS(CDCl₃) : 8.77 (1 H, s, N_a-H), 7.46 and 7.32 (2 H, 2 d, J ~ 8 Hz, C₉-H and C₁₂-H), 7.13 and 7.07 (2 H, 2 dd, J ~ 8 Hz, C₁₀-H and C₁₁-H); 5.10 (1 H, d, J_{16,17} = 12 Hz, C₁₆-H), 3.80 (3 H, s, CO₂CH₃), 1.48 (2 H, 2 m, C₁₉-H), 0.90 (3 H, t, J_{18,19} = 7 Hz, C₁₈-H).

8 ir : 3300(br), 2920, 1625, 1560 cm⁻¹ ; uv : 225, 285, 293, 346 nm ; CD : 207(-), 228(+), 346(+) ; ms : 324(M⁺), 151(100%), 138, 123 ; pmr 400 MHz : 9.0 (1 H, s, N_a-H), 7.48 and 7.34 (2 H, 2 d, J ~ 8 Hz, C₉-H and C₁₂-H), 7.16 and 7.10 (2H, 2 dd, J ~ 8 Hz, C₁₀-H and C₁₁-H), 4.55 (1 H, m, attributed to C₁₆-H), 1.08 (t, J ~ 7 Hz, C₁₈-H).

9 ir : 3420, 3320 cm⁻¹ ; uv : 228, 286, 294 ; sm : 328(M⁺), 154(100%).

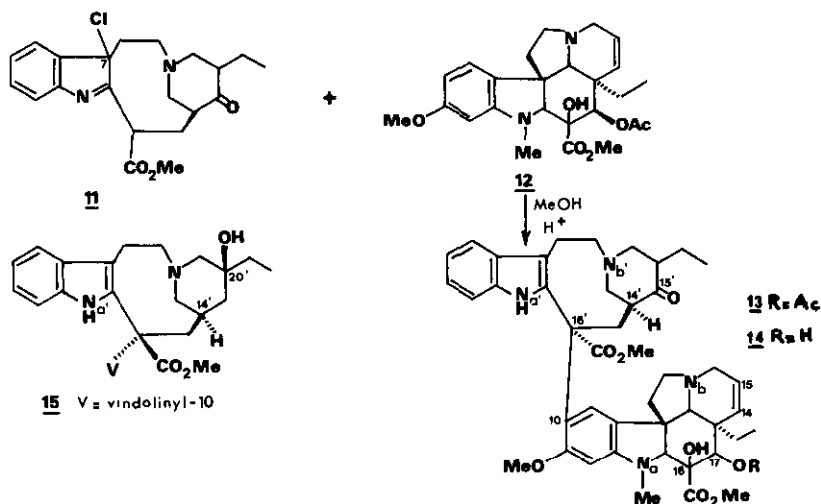
(b) Catalytic hydrogenation of 6a (H₂, Pd/C 10%, pH 3-4) afforded after 24 h the alcohol 7 (50%) and the saturated ketone 10 (20%) : ir : 3380, 2920, 1725, 1710 cm⁻¹ ; uv : 228, 288, 295 nm ; CD : 208(-), 230(+), 275(+) ; ms : 354 (M⁺ 100%) 325, 323, 295, 257, 224, 215, 214, 209, 202, 182, 177, 169, 156, 153, 152, 151, 140, 139, 138 ; pmr 60 MHz, CDCl₃ : 8.50 (1 H, N_a-H ; 7.1 - 7.6 (arom.), 4.76 (1 H, d, J_{16,17} = 10 Hz, C₁₆-H), 3.85 (3 H, s, CO₂CH₃), 1.10 (3 H, t, J_{18,19} = 7 Hz, C₁₈-H).

(c) The enamine function of compound 6a was selectively reduced by sodium cyanoborohydride at pH 3-4 and 15-oxo 16S methoxycarbonyl 15,20-dihydro cleavamine 10 was obtained quantitatively.



The chemical shifts of C_{16} -H in compounds 7 and 10 are in accordance with $16S$ configuration ; the hypothesis of an epimerisation at this center during the process (b) or (c) can be eliminated and $16S$ configuration can be attributed to the 6a precursor. Examination of CD curves shows that the presence of a ketone has no influence on the most characteristic part of the curves and that the $14S$ configuration is retained in 7 and 10.

The 7-chloroindolenine 11 of the ketone 10 was prepared in quantitative yield (N-chlorobenzotriazol, CH_2Cl_2 , $0^\circ C$). The unstable compound 11 (uv(EtOH) : 228, 264, 329 nm ; EtOH + H^+ : 283, 292 ep., 329) was directly coupled with vindoline 12 in acidic medium (MeOH/ HCl)⁵ (Scheme 3), affording in good yield the dimeric compound 13 (55%) and the deacetylated derivative 14 (11%, ms : $766(M^{+})$, 240).
13 : ir : 3440, 1740, 1715(sh), 1615 cm^{-1} ; uv EtOH, $\lambda_{max}^{nm}(\epsilon)$: 224(30000), 262(12000), 306(9000) ; CD, EtOH, $\lambda_{max}^{nm}(\Delta\epsilon)$: 212(+ 17.5), 225(-30.0), 260(-3.5), 275(+ 3.5), 308(+ 4.5) ; ms : 822($M+CH_2$), 808(M^{+}), 749, 732, 689, 649, 596, 541, 527, 481, 379, 366, 352, 323, 293, 282, 222, 152, 135(100%), 122, 121, 107.
 pmr 60 MHz, $\delta/TMS(CDCl_3)$: 9.24 (1 H, N_a -H (or C_{16} -OH), 7.3 - 6.9 (arom.), 6.70 and 5.96 (2 H, 2 s, C_9 -H and C_{12} -H), 5.78 (1 H, C_{14} -H), 5.38 (C_{15} -H), 5.35 (s, C_{17} -H), 3.90, 3.81 and 3.76 (9 H, 3 s, C_{11} -OCH₃, C_{16} -CO₂CH₃ and C_{16} -CO₂CH₃), 2.66 (N_a -CH₃), 2.11 (3 H, s, OCOCH₃), 0.98 and 0.59 (6 H, 2 t, J ~ 7 Hz, C_{18} -H and C_{18} -H).



Scheme 3

The CD curve of the dimer 13 indicates configurations $16'R$ and $14'S$; the relative configuration of these two centres is therefore the reverse of that found in the antitumour alkaloids of the vinblastine type (15).

It is known that configurations at $16'$ and $14'$ are essential for the biological activity and that the configuration at $20'$ is much less important⁶.

In the case of dimeric compounds accessible by a coupling reaction between vindoline and a racemic 7-chloro indolenine, the presence of a carbonyl function in C_{15}' could allow an inversion of the configuration at C_{14}' .

This epimerisation, applied to the diastereoisomer $16'S$, could lead to antitumour compounds⁷, having the same configurations at C_{16}' and C_{14}' , as in vinblastine 15.

Indeed, the coupling reactions between 7-chloro indolenines and nucleophiles like vindoline 12 are stereospecific^{8,9} and are controlled by the chirality at C_{14} of the indolic precursor^{9,10}.

This approach is under current investigation in our laboratory.

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