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

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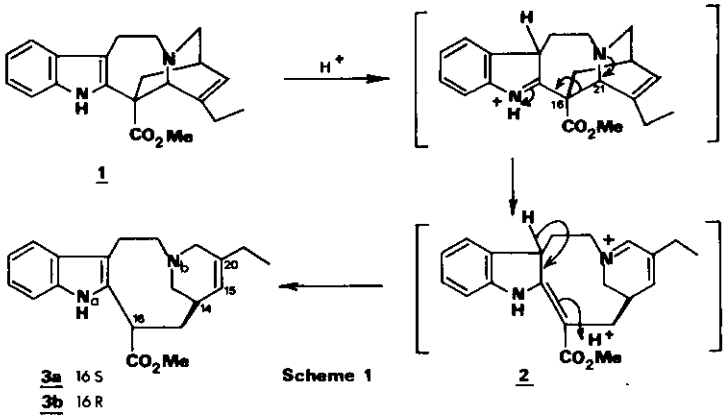
Several derivatives of 16-methoxycarbonyl cleavamines oxygenated in position 15 have been prepared and the coupling reaction of 15-oxo 16S-methoxycarbonyl 15,20-dihydro cleavamine with vindoline has been studied.

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 temperature[1].



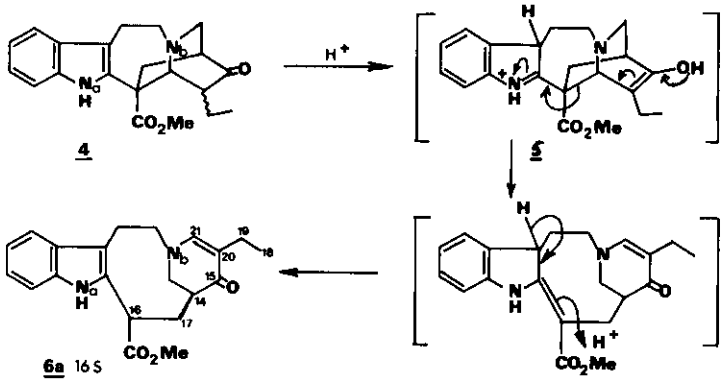
* This article is dedicated to Professor T. Kametani, on the occasion of his retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

Likewise, 15-oxo-15,20-dihydro catharanthine 4[2], 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($\Delta\varepsilon$) : 224(+ 14.9), 274(+ 3.3), 345(+ 9.5) ; ms : 352($M^{+\cdot}$), 337, 293, 267, 229. 228, 214, 182, 180, 176, 170, 169, 168, 167, 156, 154, 152, 151(100%), 138, 137, 123 ; pmr 240 MHz, δ/TMS($CDCl_3$) : 8.73 (1H, s, N_a-H), 7.49 and 7.36 (2 H arom.), 7.17 (2 H arom.), 7.08 (1 H, s, C_{21}-H), 4.11 (1 H, d, $J_{16,17}$ = 11 Hz, C_{16}-H), 3.60 (3 H, s, CO_2CH_3), 2.28 (C_{17}-H and C_{19}-H), 1.08 (3 H, t, $J_{18,19}$ = 7 Hz, C_{18}-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($M^{+\cdot}$ 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, δ/TMS($CDCl_3$) : 8.70 (1 H, N_a-H), 6.62 (1 H, s, C_{21}-H), 3.62 (3 H, s, CO_2CH_3), 0.89 (3 H, t, $J_{18,19}$ = 7 Hz (C_{18}-H).

In this case, the enolic form 5 could well be an intermediate which participates in the C_{16}-C_{21} fragmentation reaction (Scheme 2).



Scheme 2

The configurations at C_{16} for 16-methoxycarbonyl cleavamines 3a and 3b are easily deduced from examination of the CD curves[3] or from the pmr spectra where the chemical shift of C_{16}-H is typical of the configuration at this centre[4] : in the 16S epimeric compound 3a, the close proximity of C_{16}-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 C_{16} 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.

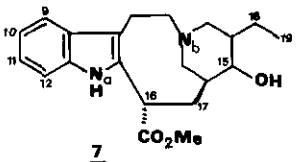
7 ir : 3400, 3300(sh), 1725 cm^{-1} ; uv : 227, 286, 293 nm ; CD : 207(-), 229(+), 275(+) ; ms : 357, 356($M^{+\cdot}$), 297, 226, 216, 215, 155, 154(100%), 142, 140, 124 ; pmr 400 MHz, δ/TMS($CDCl_3$) : 8.77 (1 H, s, N_a-H), 7.46 and 7.32 (2 H, 2 d, J ~ 8 Hz, C_9-H and C_{12}-H), 7.13 and 7.07 (2 H, 2 dd, J ~ 8 Hz, C_{10}-H and C_{11}-H); 5.10 (1 H, d, $J_{16,17}$ = 12 Hz, C_{16}-H), 3.80 (3 H, s, CO_2CH_3), 1.48 (2 H, 2 m, C_{19}-H), 0.90 (3 H, t, $J_{18,19}$ = 7 Hz, C_{18}-H).

8 ir : 3300(br), 2920, 1625, 1560 cm^{-1} ; uv : 225, 285, 293, 346 nm ; CD : 207(-), 228(+), 346(+) ; ms : 324($M^{+\cdot}$), 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, C_9-H and C_{12}-H), 7.16 and 7.10 (2H, 2 dd, J ~ 8 Hz, C_{10}-H and C_{11}-H), 4.55 (1 H, m, attributed to C_{16}-H), 1.08 (t, J ~ 7 Hz, C_{18}-H).

9 ir : 3420, 3320 cm^{-1} ; uv : 228, 286, 294 ; sm : 328($M^{+\cdot}$), 154(100%).

(b) Catalytic hydrogenation of 6a (H_2, 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 ($M^{+\cdot}$ 100%) 325, 323, 295, 257, 224, 215, 214, 209, 202, 182, 177, 169, 156, 153, 152, 151, 140, 139, 138 ; pmr 60 MHz, $CDCl_3$: 8.50 (1 H, N_a-H ; 7.1 - 7.6 (arom.), 4.76 (1 H, d, $J_{16,17}$ = 10 Hz, C_{16}-H), 3.85 (3 H, s, CO_2CH_3), 1.10 (3 H, t, $J_{18,19}$ = 7 Hz, C_{18}-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.



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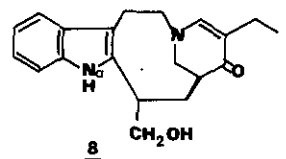

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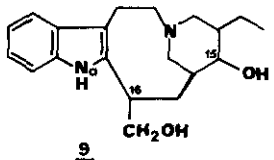

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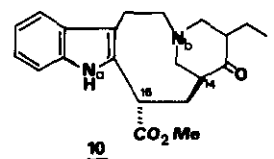

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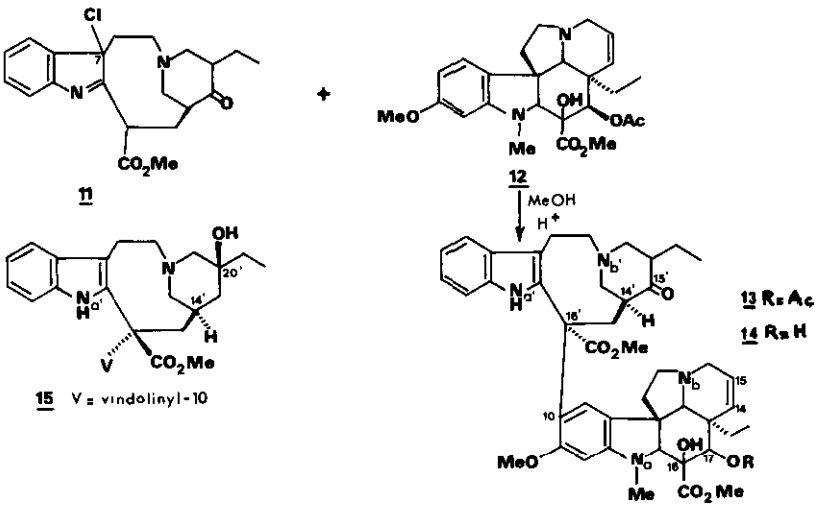
The chemical shifts of C_{16}-H in compounds 7 and 10 are in accordance with 16S configuration ; the hypothesis of an epimerisation at this center during the process (b) or (c) can be eliminated and 16S configuration can be attributed to the 6a precursor. Examination of CD curves shows that the presence 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°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($M^{+\cdot}$), 240). 13 : ir : 3440, 1740, 1715(sh), 1615 cm^{-1} ; uv EtOH, λ_{max}^{nm} (ε) : 224(30000), 262 (12000), 306(9000) ; CD, EtOH, λ_{max}^{nm} ($\Delta\varepsilon$) : 212(+ 17.5), 225(-30.0), 260(-3.5), 275(+ 3.5), 308(+ 4.5) ; ms : 822($M+CH_2$), 808($M^{+\cdot}$), 749, 732, 689, 649, 596, 541, 527, 481, 379, 366, 352, 323, 293, 282, 222, 152, 135(100%), 122, 121, 107. pmr 60 MHz, δ/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}-OCH_3, C_{16}-CO_2CH_3 and $C_{16'}$-CO_2CH_3), 2.66 (N_a-CH_3), 2.11 (3 H, s, $OCOCH_3$), 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 important[6].

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 compounds[7], 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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