

STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. IX^{1,2}.

THE SYNTHESIS OF NOVEL VINDOLINE DERIVATIVES.

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A detailed study involving the degradation of vindoline (1) provides a series of novel vindoline derivatives which are important intermediates in the synthesis of bisindole alkaloids.

In our continuing program concerned with the synthesis of bisindole alkaloids within the vincristine-vinblastine family, it became essential to develop efficient synthetic pathways to a series of novel vindoline derivatives. Such intermediates could be employed in subsequent coupling reactions with indole units of the cleavamine^{3,4} or catharanthine⁵⁻⁸ series to provide syntheses of bisindole alkaloids or closely related derivatives. This communication describes our investigations directed at the syntheses of

various novel vindoline derivatives while the accompanying communication⁹ describes the use of such compounds in the synthesis of bisindole alkaloid derivatives.

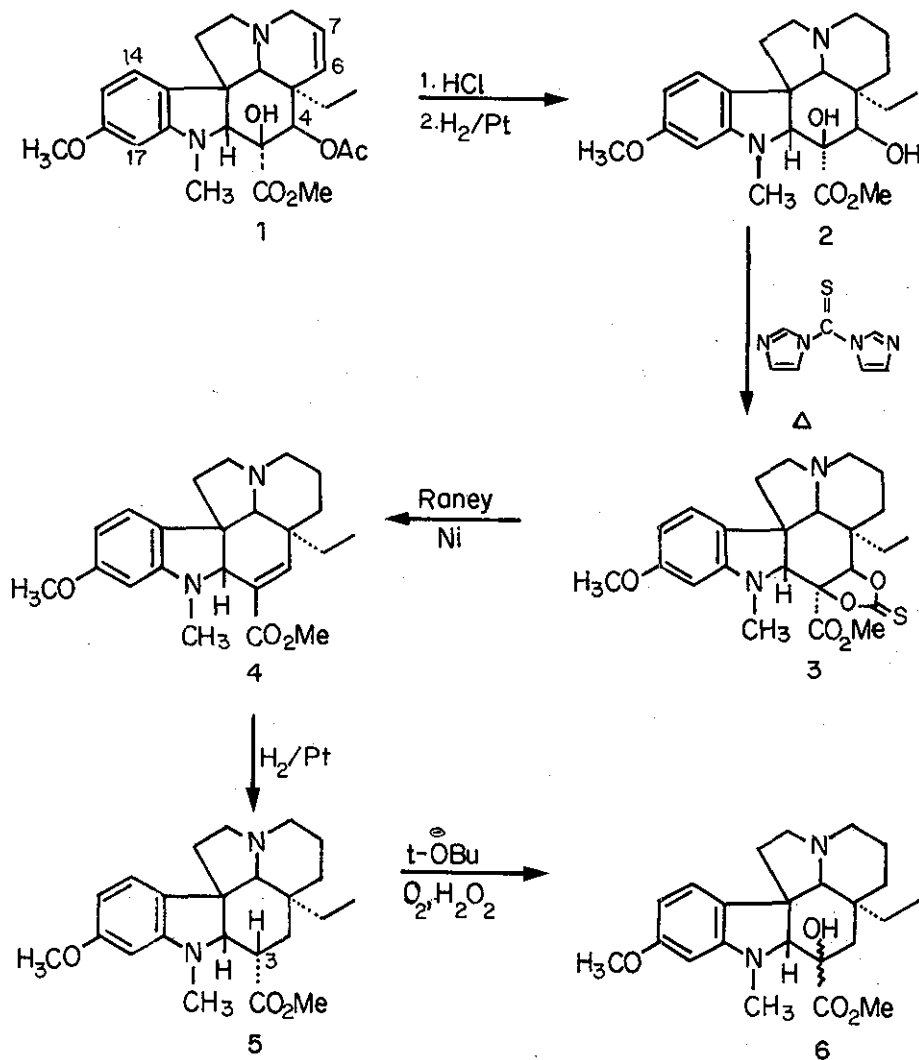
Vindoline (1) a readily available alkaloid from Catharanthus roseus G. Don (Vinca rosea L.), was selected as the starting material for our extensive studies in this area. It has been anticipated for some time that possible alterations in biological properties of the clinically important anti-tumor agents, vinblastine and vincristine, could be achieved by changes in the dihydroindole unit of the bisindole system. For this reason our initial investigations in this area have focussed on the selective removal of the oxygen functionality in ring C of the vindoline system. Clearly the bisindole derivatives which would result from the coupling of such novel vindoline derivatives with the appropriate indole units would shed some light on this important area of structure-activity relationships.

Desacetyldihydrovindoline (2) prepared by a known procedure¹⁰, was reacted with N,N'-thiocarbonyldiimidazole¹¹ in refluxing anhydrous butanone to provide, in 88% yield, the crystalline desired thiocarbonate derivative (3)¹², m.p. 222-223° [IR: 1739 cm⁻¹; PMR: τ 3.02 (d, J = 8 Hz, C₁₄-H), 3.63 (q, J = 2.3 and 8 Hz, C₁₅H), 3.90 (d, J = 2.3 Hz, C₁₇-H), 4.69 (s, C₄-H), 6.07 (s, CO₂CH₃), 6.2 (s, C₂-H), 6.24 (s, OCH₃), 7.34 (s, NCH₃), 9.54 (t, J = 7 Hz, CH₂CH₃); MS: m/e 458 (M⁺, C₂₄H₃₀N₂O₅S), 381, 298, 149, 124].

An efficient conversion (81% yield) of the thiocarbonate derivative 3 to the α,β -unsaturated ester 4 was achieved by reaction of 3 with Raney Ni (THF, reflux) [IR: 1703 cm⁻¹; PMR: τ 2.77 (bs, C₄-H), 5.73 (s, C₂-H), 6.22 (s, CO₂CH₃), 6.25 (s, OCH₃), 7.25 (s, NCH₃), 9.41 (t, J = 7 Hz, CH₂CH₃); MS:

m/e 382 (M^+ , $C_{23}H_{30}O_3N_2$), 263, 208, 174, 149, 124].

Saturation of the double bond in 4 was accomplished by catalytic methods to provide one component (80% yield) for which the structure and stereochemistry at C_3 is as shown in 5. [IR: 1735 cm^{-1} ; PMR; τ 5.9 (m, $C_3\text{-H}$), 6.32 and 6.34 (2s, 6H, CO_2CH_3 and OCH_3), 6.4 (d, $J = 2\text{ Hz}$, $C_2\text{-H}$), 7.45 (s, NCH_3), 9.5



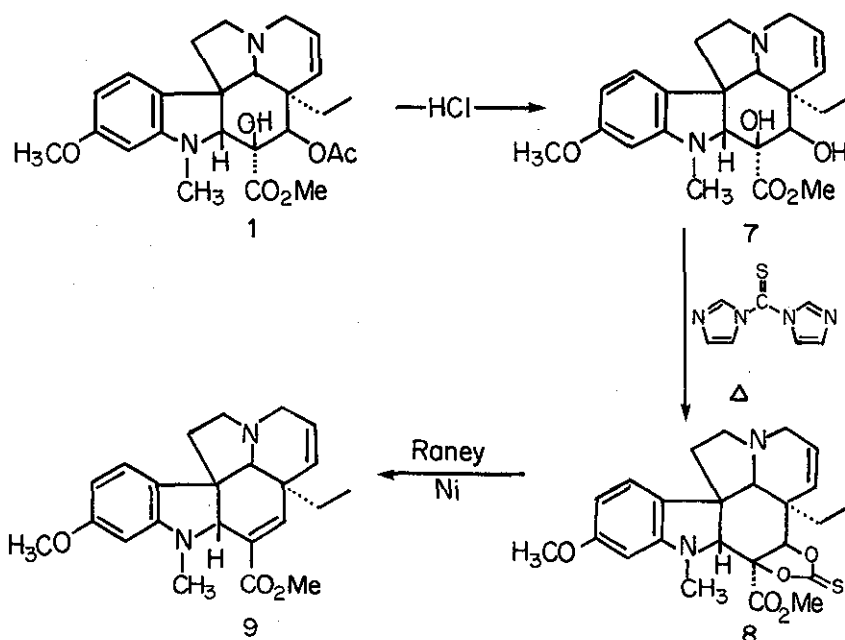
(t, J = 7 Hz, CH₂CH₃); MS: m/e 384 (M⁺, C₂₃H₃₂O₃N₂), 298, 210, 124].

Epimerization of 5 (potassium t-butoxide, room temperature) provided the crystalline 3-epi-3,4-desoxydihydrovindoline (5, β-COOCH₃ at C₃), m.p. 162-164° [IR: 1725 cm⁻¹; 6.15 (s, J = 10 Hz, C₂-H), 6.24 and 6.31 (2s, 6H, CO₂CH₃ and OCH₃), 7.29 (s, NCH₃), 9.33 (t, J = 7 Hz, CH₂CH₃); MS: m/e 384 (M⁺, C₂₃H₃₂O₃N₂), 298, 188 and 124]. The stereochemical assignment of the C₃ ester group in the latter and, in turn, in the former isomer 5 can be readily made from the PMR data. It is to be noted that in the compound with the C₃ α-ester group the coupling constant for the vicinal C₂- and C₃ protons is 2 Hz while in the β ester, J_{2,3} = 10 Hz in accord with expectation in terms of the dihedral angles involved. Further in 5 (α-CO₂CH₃ at C₃), the N-CH₃ group (τ-7.45) lies in the shielding cone of the carbonyl of the ester function while in 5 (β-CO₂CH₃ at C₃), this is not the case and a lower field signal (τ 7.29) is observed, as expected.

Introduction of a tertiary hydroxyl group at C₃ of the saturated ester 5 was achieved when the latter was reacted with hydrogen peroxide-oxygen in the presence of lithium diisopropylamide (THF, room temperature). The resulting product 6 is the desired intermediate although a firm assignment to the stereochemistry at C₃ cannot be made from the obtained data [PMR: τ 6.13 (s, C₂-H), 6.16 and 6.22 (2s, 6H, CO₂CH₃ and OCH₃), 7.22 (s, NCH₃), 9.32 (t, J = 7 Hz, CH₂CH₃); MS: m/e 400 (M⁺, C₂₃H₃₂O₄N₂), 298, 188, 174, 124]. This type of intermediate is important in the synthesis of desacetoxyvinblastine, an alkaloid recently isolated by the Lilly group¹³.

The generality of the thiocarbonate method for efficient removal and alteration of ring C functionality in the vindoline system was exemplified by

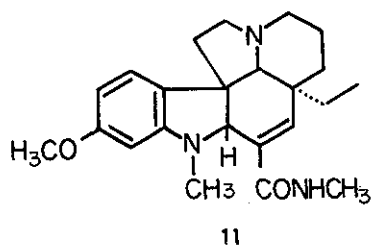
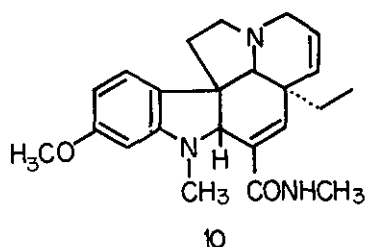
further studies. Desacetylvindoline (7)¹⁰ was converted in the above-described manner to the thiocarbonate 8, m.p. 184-186°, in 76% yield and the latter on Raney Ni treatment provided an 84% yield of the unsaturated ester 9 [IR: 1705, 1615 cm^{-1} ; PMR: τ 2.74 (s, C₄-H), 2.97 (d, J = 8 Hz, C₁₄-H), 3.72 (q, J = 2 and 8 Hz, C₁₅-H), 3.99 (d, J = 2 Hz, C₁₇-H) 4.0-4.35 (m, 2H, C₆ and C₇-H), 5.74 (s, C₂-H), 6.20 (2s, 6H, CO₂CH₃ and OCH₃), 7.26 (s, NCH₃), 9.37 (t, CH₂CH₃); MS: m/e 380 (M⁺, C₂₃H₂₈N₂O₃), 350, 321, 297, 282, 244, 220, 208, 205, 188, 174, 149].



In an earlier study⁶ we had established the successful coupling of vindoline amide derivatives with the catharanthine system to provide bisindole alkaloid derivatives closely related to the clinically interesting vinblastine amide system¹⁴. On this basis it was important to prepare a series of vindoline

amide derivatives lacking oxygen functionality in ring C and experiments involving two such preparations are described.

The unsaturated ester 9 was reacted with methylamine at 60°, and after purification of the product mixture, a quantitative yield of the desired amide 10, m.p. 196-198° [IR: 1630, 1620 cm⁻¹; PMR: τ 3.52 (s, 1H, C₄-H), 4.0-4.4 (m, 2H, C₆ and C₇-H), 5.76 (s, C₂-H), 6.23 (s, OCH₃), 7.13 (d, J = 5 Hz, NHCH₃), 7.24 (s, NCH₃), 9.40 (t, J = 7.5 Hz, CH₂CH₃); MS: m/e 379 (M⁺, C₂₃H₂₉N₃O₂, base peak), 321, 188, 174, 149] was obtained.



In similar fashion, the unsaturated ester 4 is converted to the amide 11 [IR: 1660, 1605 cm⁻¹; PMR: τ 3.66 (s, C₄-H), 5.76 (s, C₂-H), 6.28 (s, OCH₃), 7.12 (d, J = 4 Hz, NHCH₃), 7.26 (s, NCH₃), 9.40 (t, J = 7 Hz, CH₂CH₃); MS: m/e 381 (M⁺, C₂₃H₃₁N₃O₂), 367, 366, 352, 351, 350, 349, 336, 323, 321, 207, 188, 174, 124 (base peak)].

The utilization of these vindoline derivatives in the synthesis of novel bisindole systems closely related to vinblastine is the subject of the accompanying communication⁹.

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