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 catharanthine[5-8] 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 communication[9] describes the use of such compounds in the synthesis of bisindole alkaloid derivatives.

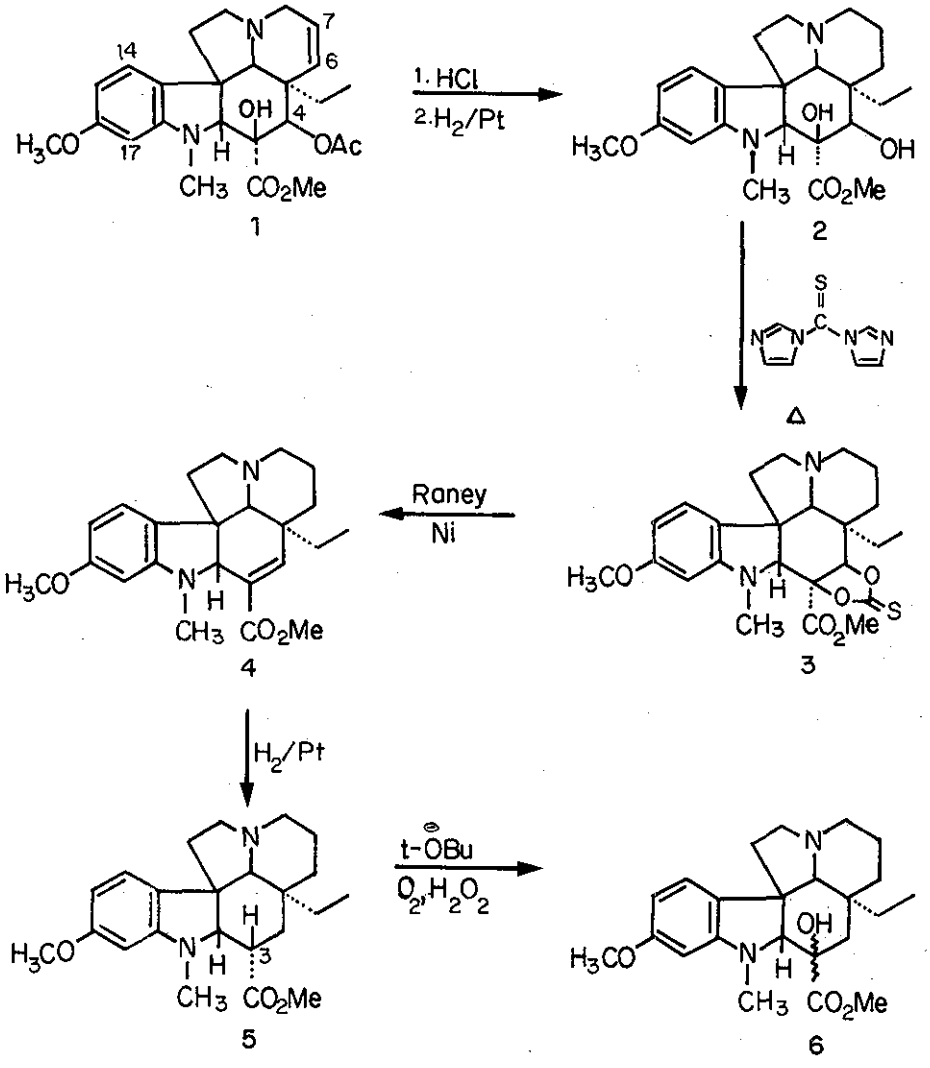
Vindoline (1) a readily available alkaloid from Catharanthus roseus G. Don (Vinca rosea L.), was selected as the starting material for our extensive studies in this area. It has been anticipated for some time that possible alterations in biological properties of the clinically important anti-tumor agents, 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 procedure[10], was reacted with N,N'-thiocarbonyldiimidazole[11] 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, C_{14}-H), 3.63 (q, J = 2.3 and 8 Hz, C_{15}H), 3.90 (d, J = 2.3 Hz, C_{17}-H), 4.69 (s, C_4-H), 6.07 (s, CO_2CH_3), 6.2 (s, C_2-H), 6.24 (s, OCH_3), 7.34 (s, NCH_3), 9.54 (t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 458 (M^+, $C_{24}H_{30}N_2O_5S$), 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, C_4-H), 5.73 (s, C_2-H), 6.22 (s, CO_2CH_3), 6.25 (s, OCH_3), 7.25 (s, NCH_3), 9.41 (t, J = 7 Hz, $CH_2\underline{CH_3}$); 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-H), 6.32 and 6.34 (2s, 6H, CO_2CH_3 and OCH_3), 6.4 (d, J = 2 Hz, C_2-H), 7.45 (s, NCH_3), 9.5



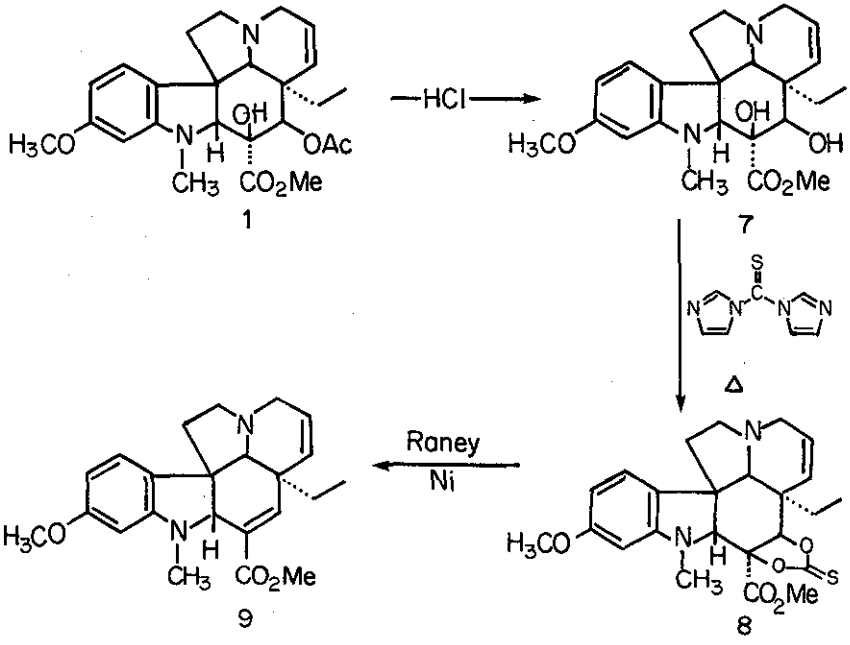
(t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 384 (M^+, $C_{23}H_{32}O_3N_2$), 298, 210, 124].

Epimerization of 5 (potassium t-butoxide, room temperature) provided the crystalline 3-epi-3,4-desoxydihydrovindoline (5, β-$COOCH_3$ at C_3), m.p. 162-164° [IR: 1725 cm^{-1}; 6.15 (s, J = 10 Hz, C_2-H), 6.24 and 6.31 (2s, 6H, CO_2CH_3 and OCH_3), 7.29 (s, NCH_3), 9.33 (t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 384 (M^+, $C_{23}H_{32}O_3N_2$), 298, 188 and 124]. The stereochemical assignment of the C_3 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 C_3 α-ester group the coupling constant for the vicinal C_2- and C_3 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-CO_2CH_3 at C_3), the N-CH_3 group (τ-7.45) lies in the shielding cone of the carbonyl of the ester function while in 5 (β-CO_2CH_3 at C_3), this is not the case and a lower field signal (τ 7.29) is observed, as expected.

Introduction of a tertiary hydroxyl group at C_3 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 C_3 cannot be made from the obtained data [PMR: τ 6.13 (s, C_2-H), 6.16 and 6.22 (2s, 6H, CO_2CH_3 and OCH_3), 7.22 (s, NCH_3), 9.32 (t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 400 (M^+, $C_{23}H_{32}O_4N_2$), 298, 188, 174, 124]. This type of intermediate is important in the synthesis of desacetoxyvinblastine, an alkaloid recently isolated by the Lilly group[13].

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, C_4-H), 2.97 (d, J = 8 Hz, C_{14}-H), 3.72 (q, J = 2 and 8 Hz, C_{15}-H), 3.99 (d, J = 2 Hz, C_{17}-H) 4.0-4.35 (m, 2H, C_6 and C_7-H), 5.74 (s, C_2-H), 6.20 (2s, 6H, CO_2CH_3 and OCH_3), 7.26 (s, NCH_3), 9.37 (t, $CH_2\underline{CH_3}$); MS: m/e 380 (M^+, $C_{23}H_{28}N_2O_3$), 350, 321, 297, 282, 244, 220, 208, 205, 188, 174, 149].



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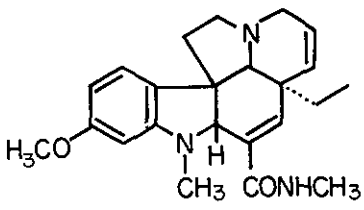
In an earlier study[6] we had established the successful coupling of vindoline amide derivatives with the catharanthine system to provide bisindole alkaloid derivatives closely related to the clinically interesting vinblastine amide system[14]. On this basis it was important to prepare a series of vindoline

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: 1650, 1620 cm^{-1}; PMR: τ 3.52 (s, 1H, C_4-H), 4.0-4.4 (m, 2H, C_6 and C_7-H), 5.76 (s, C_2-H), 6.23 (s, OCH_3), 7.13 (d, J = 5 Hz, $NH\underline{CH_3}$), 7.24 (s, NCH_3), 9.40 (t, J = 7.5 Hz, $CH_2\underline{CH_3}$); MS: m/e 379 (M^+, $C_{23}H_{29}N_3O_2$, base peak), 321, 188, 174, 149] was obtained.



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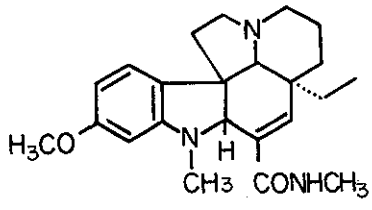

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In similar fashion, the unsaturated ester 4 is converted to the amide 11 [IR: 1660, 1605 cm^{-1}; PMR: τ 3.66 (s, C_4-H), 5.76 (s, C_2-H), 6.28 (s, OCH_3), 7.12 (d, J = 4 Hz, $NH\underline{CH_3}$), 7.26 (s, NCH_3), 9.40 (t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: m/e 381 (M^+, $C_{23}H_{31}N_3O_2$), 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 communication[9].

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