

STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. VII¹.
STEREOCHEMISTRY AND ALTERNATIVE TOTAL
SYNTHESIS OF LEUROSINE.

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Polonovski-type coupling between 3 β ,4 β -epoxy-3,4-dihydro-catharanthine-N_b-oxide and vindoline provides an alternative route to the anti-tumor agent leurosine. The previously questioned stereochemistry of the oxirane function of this bisindole alkaloid is determined unambiguously.

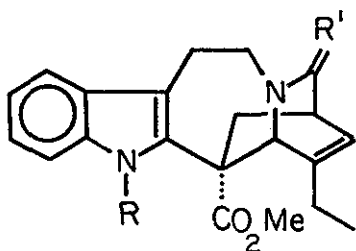
The realisation that "biogenetic-type" coupling between catharanthine and vindoline units could yield the skeleton of the Vinca bisindole alkaloids, enabled facile entry into the field of these topical anti-tumor agents^{2, 3}. Subsequent investigations in these and other laboratories led to syntheses of several natural products and derivatives¹⁻⁸. Two earlier routes to leurosine VIII have been accomplished^{4, 9}. For example, reaction of 3', 4'-dehydrovinblastine IX with t-butyl hydroperoxide and trifluoroacetic acid in tetrahydrofuran gave VIII in 51% yield⁴. Stereochemical evaluation at C₃' and C₄' was however not possible from the available data. At least two independent discussions regarding the stereochemistry of leurosine have appeared. The oxirane function had been tentatively assigned the β -orientation¹⁰ on the basis of the coupling constant observed between signals in the pmr spectrum for protons attached to C₂' and C₃'. On the other hand Wenkert and co-workers¹¹ suggested an α -orientation to explain the facile acid catalysed rearrangement of leurosine. The present work describes a total synthesis of VIII which allows unambiguous assignment of α -stereochemistry as shown.

Part IV¹² of this series described the preparation of several, novel, oxygenated catharanthine derivatives intended for use in the syntheses of the corresponding "dimers". The epoxide IV (obtained from catharanthine, I, in 49% yield), under

mild hydrolytic conditions, gave the indole V quantitatively [MS: m/e 366 (M^+ , $C_{21}H_{22}N_2O_4$, base peak), 228, 214, 195, 154; PMR: δ 8.28 (bs, 1H, N-H), 4.77 (d, 1H, $J=1H_z$, C_5-H), 4.28 (m, 1H, C_2-H) 3.64 (s, 3H, CO_2CH_3), 0.97 (t, 3H, $J=7H_z$, CH_2CH_3), IR: 3425, 1725 and 1665 cm^{-1} ; m.p. 275-278° (decomp.)].

Reaction of V with phosphorous pentasulphide in dry benzene provided the thiolactam VI in 73% yield. [MS: m/e 382 (M^+ , $C_{21}H_{22}N_2O_3S$, base peak), 227, 195; PMR. δ 8.31 (bs, 1H, N-H), 5.05 (m, 1H, C_2-H), 4.92 (d, 1H, $J=1H_z$, C_5-H), 3.78 (s, 3H, CO_2CH_3), 1.00 (t, 3H, $J=7H_z$, CH_2CH_3), IR: 3450, 1730, 1480, 1455 cm^{-1} ; m.p. 259-260°]. Subsequent desulphurisation with Raney nickel gave a 53% yield of the required progenitor VII. [MS: m/e 352 (M^+ , $C_{21}H_{24}N_2O_3$), 323, 138 (base peak); PMR: δ 8.3 (bs, 1H, N-H), 4.18 (s, 1H, C_5-H), 3.78 (s, 3H, CO_2CH_3), 0.98 (t, 3H, $J=7H_z$, CH_2-CH_3); IR: 3450, 1725 cm^{-1}]. The present route to VII via the thiolactam proved to be more efficient than the diborane reduction reported earlier¹².

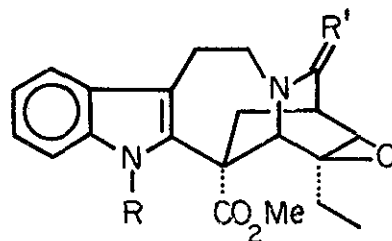
The structure of VII followed from its spectral data. Expected β -attack by *m*-chloroperbenzoic acid (mCPBA) from the less hindered face of the molecule was confirmed by the non-identity of VII with its 3,4 epimer prepared earlier via an unambiguous route¹².



I. $R = H, R' = H_2$

II. $R = CO_2Me, R' = H_2$

III. $R = CO_2Me, R' = O$

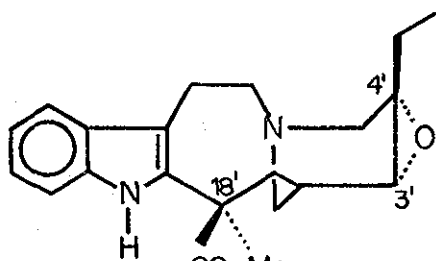


IV. $R = CO_2Me, R' = O$

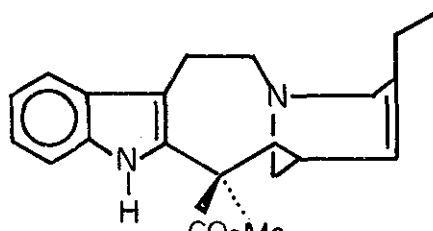
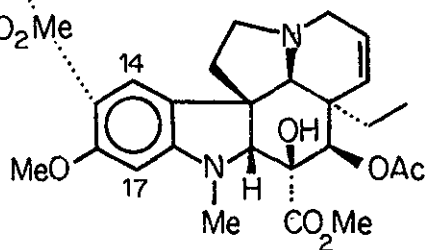
V. $R = H, R' = O$

VI. $R = H, R' = S$

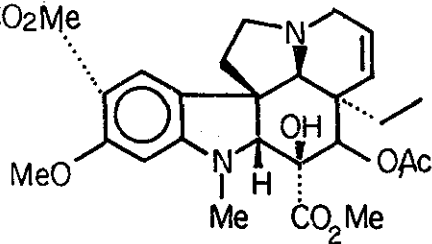
VII. $R = H, R' = H_2$



VIII.



IX.



Coupling of VII with vindoline in the usual manner²

((i) mCPBA, CH₂Cl₂, -20°; (ii) vindoline, trifluoroacetic anhydride, -50°; (iii) NaBH₄) proceeded efficiently to give VIII (m.p. 198-201°, m/e M⁺ 808) identical with an authentic sample of leurosine (m.p., mixed m.p., p.m.r., m.s., uv, tlc behaviour).

In conclusion the above synthesis settles the question of stereochemistry of the oxirane function in leurosine as shown, and demonstrates the feasibility of coupling catharanthine units oxygenated at C_{3/4}. Further examples of this mode of producing oxygenated "dimers" will be the subject of later publications.

Acknowledgement:

Financial aid from the National Research Council of Canada and from Contract N01-CM-23223, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, is gratefully acknowledged.

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Received, 29th September, 1976