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STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. VII[1]. STEREOCHEMISTRY AND ALTERNATIVE TOTAL SYNTHESIS OF LEUROSINE.

James P. Kutney* and Brian R. Worth,
Department of Chemistry, University of British Columbia,
2075 Wesbrook Place, Vancouver, B.C.
Canada, V6T 1W5

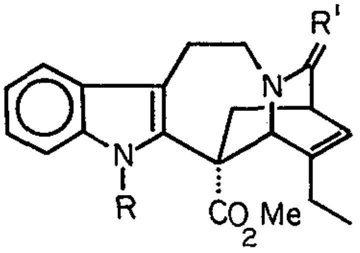
Polonovski-type coupling between 3β,4β-epoxy-3,4-dihydrocatharanthine-N_b-oxide and vindoline provides an alternative route to the anti-tumor agent leurosine. The previously questioned stereochemistry of the oxirane function of this bisindole alkaloid is determined unambiguously.

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 derivatives[1-8]. 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% yield[4]. Stereochemical evaluation at C_3' and C_4' 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-orientation[10] on the basis of the coupling constant observed between signals in the pmr spectrum for protons attached to C_2' and C_3'. On the other hand Wenkert and co-workers[11] 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 IV[12] 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$_z$, $CH_2C\underline{H}_3$), 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. δ8.31 (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: δ8.3 (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-$C\underline{H}_3$); IR: 3450, 1725 cm^{-1}.]. The present route to VII via the thiolactam proved to be more efficient than the diborane reduction reported earlier [12].

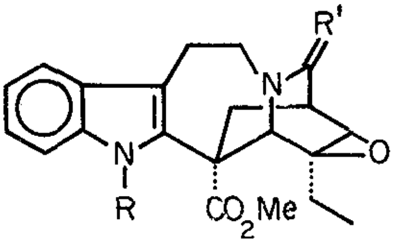
The structure of VII followed from its spectral data. Expected β-attack by m-chloroperbenzoic acid (mCPBA) from the less hindered face of the molecule was confirmed by the non-identity of VII with its 3,4 epimer prepared earlier via an unambiguous route [12].



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

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

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

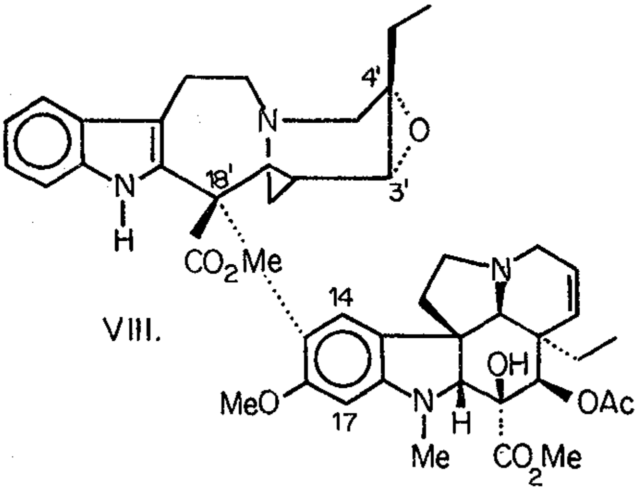


IV $R = CO_2Me$, $R' = O$

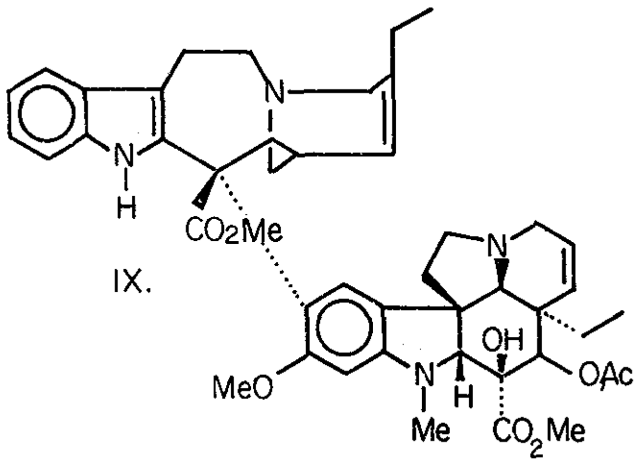
V. $R = H$, $R' = O$

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

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



VIII.



IX.

Coupling of VII with vindoline in the usual manner[2] ((i) mCPBA, CH_2Cl_2, -20°; (ii) vindoline, trifluoroacetic anhydride, -50°; (iii) $NaBH_4$) 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 feasability 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.

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