STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. III[1],[2]

THE SYNTHESIS OF LEUROSINE AND 3'-HYDROXYVINBLASTINE.

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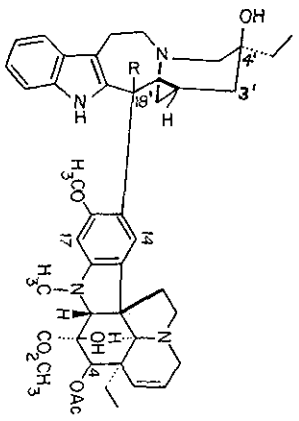
An interesting reaction which allows direct functionalization of the 3,4-double bond in the cleavamine series has been developed. Application of this reaction to the previously synthesized 3',4'-dehydrovinblastine (VIII, R = CO_2CH_3) allows a direct synthesis of the dimeric Vinca alkaloid leurosine (IX, R = CO_2CH_3).

In another series of investigations directed at functionalizing the 3',4'-double bond of VIII (R = CO_2CH_3) osmylation of the N-oxide intermediate of the latter has allowed the synthesis of 3'-hydroxyvinblastine (XI, R = CO_2CH_3), a close relative of the alkaloid vincadioline.

In continuing our studies on the synthesis of vinblastine (I) and related bisindole alkaloids, it was desirable to develop an approach which

would allow direct introduction of oxygen functionality at the 3',4'-positions in the synthetic dimers available from the previous studies[1,3]. It has been already established from numerous structural elucidation studies that a number of the bisindole alkaloids contain oxygen functionality at these positions. Thus vinblastine (I) possesses a tertiary hydroxyl group at C_4', leurosidine has been recently[4] assigned as the C_4' hydroxy epimer, leurosine is shown[5,6,4] to possess a $C_{3'},_{4'}$-epoxy group while vincadioline[7] contains a vicinal diol system at these positions.

An obvious approach to the introduction of oxygen functions at $C_{3'}$ and/or C_4' in the synthetic dimers[1,3] involves electrophilic addition to the



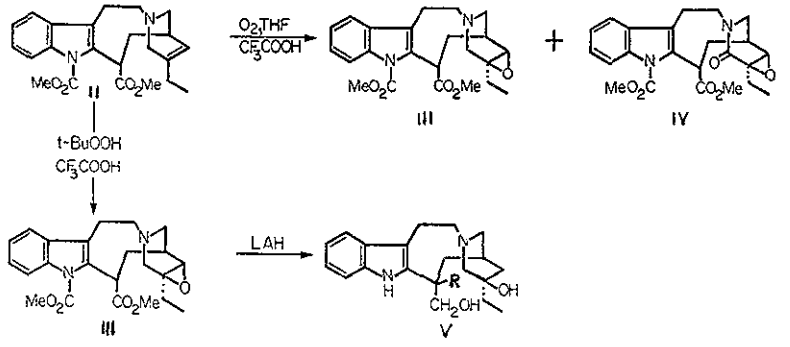
I, R = $COOCH_3$

double bond. However restrictions to the utilization of this approach with such reagents as peracids and positive halogen became rather severe since

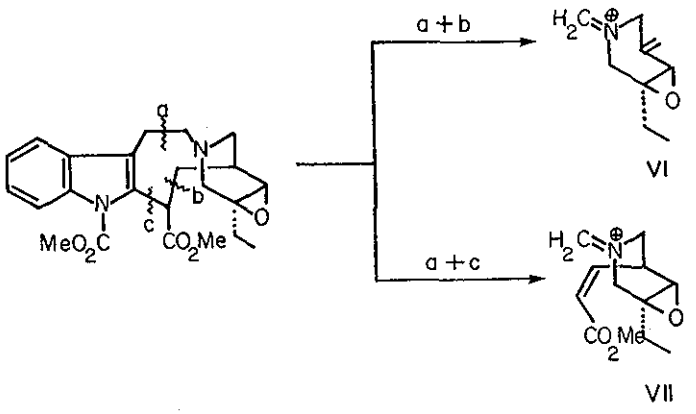
reactions at the indole system and/or the basic nitrogen atom occur in preference to the double bond. We therefore turned our attention to the air and/or hydroperoxide oxidation of the alkene system, a reaction which is not frequently employed by synthetic chemists[8-11].

The N_a-carbomethoxy derivative of 18β-carbomethoxycleavamine (II), obtained from reaction of the known 18β-carbomethoxycleavamine[12] with strong base (usually potassium hydride) and methyl chloroformate, is reacted with tert-butyl hydroperoxide in aqueous trifluoroacetic acid to provide the epoxide III, m.p. 131-132°, in 67% yield. This substance exhibited the following spectroscopic data. IR ($CHCl_3$): 1725 cm^{-1}; UV (CH_3OH): 227, 262, 268 (sh), 283 (sh), 294 nm; NMR (100 MHz in τ values): 1.9-2.7 (4H, aromatic), 4.17 (1H, d, J = 6 Hz, $C_{18}H$), 6.09, 6.43 (2 x 3H, s, CO_2CH_3), 9.01 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$); MS: Found: 412.202, $C_{23}H_{28}N_2O_5$ requires 412.200.

The mass spectral fragmentation pattern of III was particularly informative and served to provide strong evidence for the presence of an epoxide



in III. The most important fragmentation occurs in the manner indicated, with cleavage at "a" and "b" providing the ion VI (m/e 224, base peak, $C_{12}H_{18}NO_3$ requires 224.129; found: 224.128) and at "a" and "c" to provide ion VII (m/e 152, 17%, $C_9H_{14}NO$ requires 152.107; found: 152.106).



The presence of the epoxide ring in III was further substantiated by the carbon-13 magnetic resonance spectrum of III wherein signals at δ 60.6 and 62.7 ppm for the C_3 and C_4 carbon atoms respectively were observed. We have done a very extensive CMR study in this series and the results of these investigations will be published elsewhere.

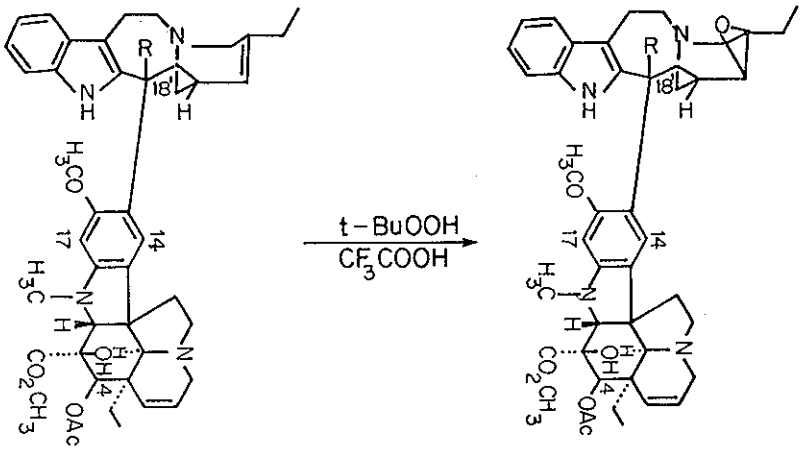
Chemical evidence which completed the structural and stereochemical assignments as depicted in III came from reduction studies. Lithium aluminum hydride reduction of III (N-methylmorpholine, reflux)

provided the diol V (R = H) in good yield. The structure of the latter derives from the fact that the previously known triol[13] (V, R = OH) is similarly reduced to the identical product V (R = H). Since the subsequent interrelationship of V (R = OH) with isovelbanamine has already been accomplished[13] the absolute configuration of the tertiary hydroxyl group at C_4 is established and in turn, the β stereochemistry of the epoxide ring in III is now also known with certainty.

The formation of III can also be observed when II is treated with oxygen in the presence of trifluoroacetic acid and tetrahydrofuran as solvent. In this instance, however, the yield of III is low (around 10-15%) and other products become predominant. One of the major components isolated (51% yield) from this reaction is tentatively assigned the lactam epoxide structure IV although its structure proof is deferred to a later publication.

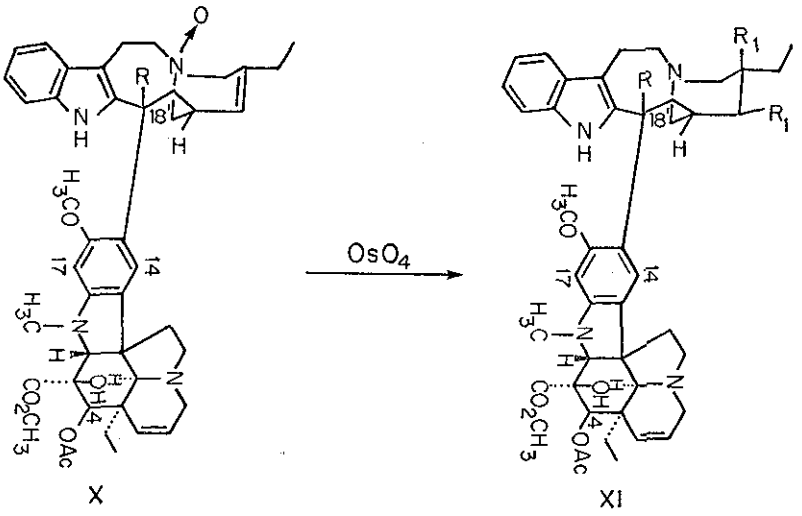
Application of the above reaction to the bisindole series was now considered and the previously known 3',4'-dehydrovinblastine (VIII, R = CO_2CH_3)[1] was treated with t-butyl hydroperoxide and trifluoroacetic acid in tetrahydrofuran as solvent. Isolation and purification of the resultant product mixture afforded the bisindole alkaloid leurosine (IX, R = CO_2CH_3) in 51% yield. The identity of this compound was established by spectral comparison (IR, NMR, MS) and mixed melting point determination with an authentic sample[14].

It should be noted at this point that although as already mentioned above, numerous investigations have been directed at the structure proof of leurosine[5,6,4], direct evidence as to the stereochemistry of the epoxide ring is still lacking. The synthetic conversion VIII → IX cannot obviously



VIII IX

provide any further direct evidence in this direction. However, we have found that approach of reagents onto the 3'-4'-double bond of VIII is preferred from the β face of the indole unit, i.e. the side opposite that being occupied by the large vindoline molecule. If a similar circumstance were to prevail in this conversion as well, the β-epoxide as shown in IX would be formed. However this assignment is to be considered as tentative at this time. We hope to provide further results in this area in a study to be published later.



X XI

In a related study directed at introducing hydroxyl functionality at the C_3' and/or C_4'-positions in the synthetic dimers, it was found that osmylation of the double bond in VIII (R = CO_2CH_3) could not be accomplished in a satisfactory manner. However the N-oxide intermediate of VIII (X, R = CO_2CH_3), formed from VIII (R = CO_2CH_3) and m-chloroperbenzoic acid, is a desirable substrate. Reaction of the latter with osmium tetroxide in pyridine and tetrahydrofuran as solvent, followed by reductive (H_2S) workup, does provide 3'-hydroxyvinblastine (XI, R_1 = OH; R = CO_2CH_3) as one of the products.

This substance exhibited the following spectral data. IR ($CHCl_3$): 1735 and 1610 cm^{-1}; UV (*EtOH*): 212, 258, 285 and 294 nm; NMR (100 MHz in τ values): 2.5 (m, 1H, $C_{14}'H$); 2.85 (m, 3H, C_{11}'-$C_{13}'H$); 3.40 (s, 1H, $C_{14}H$); 3.87 (s, 1H, $C_{17}H$); 4.14 (m, 1H, C_7H); 4.52 (s, 1H, C_4H); 4.70 (d, 1H, J = 10 Hz, C_6H); 6.18, 6.20, 6.37 (s, 3 x OCH_3); 7.28 (s, 3H, N-CH_3); 7.90 (s, 3H, $COCH_3$); 9.04 (t, 3H, J = 7 Hz, $CH_2\underline{CH_3}$); 9.10 (t, 3H, J = 8 Hz, $CH_2\underline{CH_3}$); MS: 106, 107, 121, 122, 135, 136, 285 (base peak), 809, 826. Found: 826.417; $C_{46}H_{58}N_4O_{10}$ requires: 826.415.

The stereochemistry portrayed in XI with respect to the hydroxyl groups at C_3' and C_4', is based on the assumption that approach of the reagent occurs from the β face of the molecule in accord with previous comments. Further results bearing on these points will be published later. It is clear that the synthetic product (XI, R = CO_2CH_3; R_1 = OH) is a close relative of the Vinca alkaloid vincadioline[7] although a comparison sample was unavailable.

In conclusion the above studies have provided the first laboratory synthesis of leurosine and, in addition, a synthetic entry into a family of dimers possessing oxygen functionality at C_3' and/or C_4'. Further studies in this direction will form the subject of future communications.

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