STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. XV[1,2]. A SYNTHESIS OF VINAMIDINE (CATHARININE).

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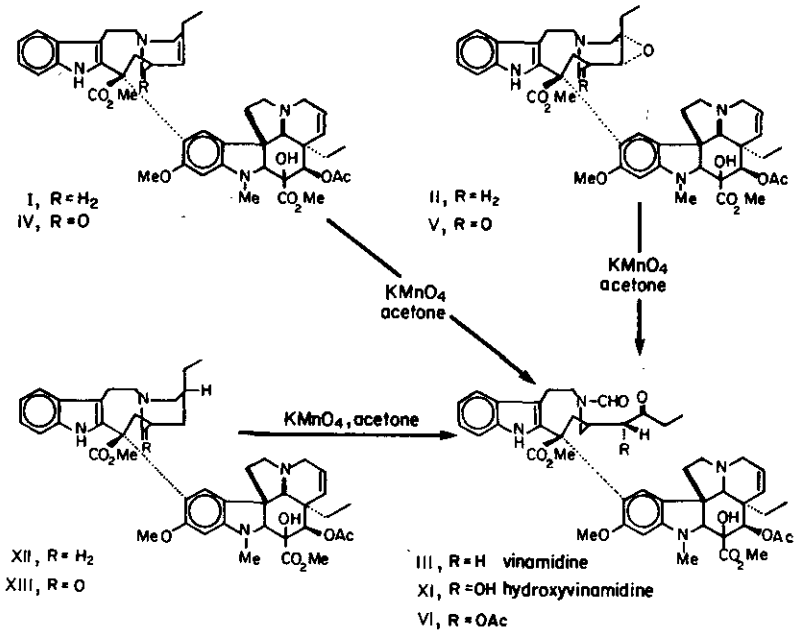
Oxidation of 4'-deoxyleurosidine with potassium permanganate provided the first synthesis of the alkaloid vinamidine (catharinine). Similar oxidation of leurosine or 3',4'-dehydrovinblastine gave 3'-hydroxyvinamidine.

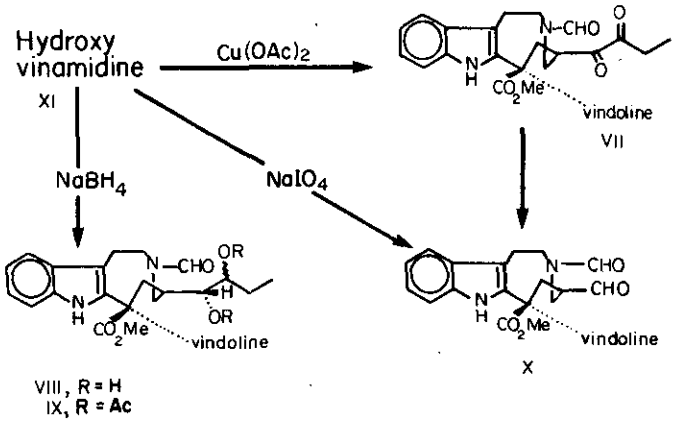
The synthetic intermediate 3',4'-dehydrovinblastine (I) has been utilised in the syntheses of the alkaloids leurosine (II)[3,4] and catharine[4,5] as well as for the preparation of numerous analogues of the "bisindole" alkaloids. This report describes an extension of this approach providing access to the alkaloid vinamidine (III)[6] and several derivatives with the seco-4',5'-skeleton.

A recent report by a French group[6] described the isolation of the alkaloid catharinine (III) and showed its identity with vinamidine previously isolated by Lilly workers[7]. X-ray crystal analysis[6] of a derivative enabled the assignment III in preference to that reported earlier[7]. Derivation of III from "bisindole"-type alkaloids within the vinblastine family implicated C_4'-C_5' bond cleavage, a process which had been demonstrated in these laboratories during the course of potassium permanganate oxidation studies in this area.

Thus oxidation of either I or II with potassium permanganate in acetone solution gave, together with the lactams IV (10%) and V (19%)[4,8], a ketol (42%) (M^+ 840.3966, $C_{46}H_{56}N_4O_{11}$; mp (methanol) 198 - 202°; IR 1660 cm^{-1}; 'Hmr δ: 3.97 (1H, bs, C_3'-H), 7.32 (1H, s, $-N_b'$,CHO)) containing a formamide group. The product readily formed an acetate VI (M^+ 882.4046, $C_{48}H_{58}N_4O_{12}$; 'Hmr δ: 2.10 (3H, s, -OAc), 2.14 (3H, s, -OAc), 4.80 (1H, bs, C_3'-H)) and cupric acetate oxidation gave the corresponding α-diketone VII (M^+ 838.3770, $C_{46}H_{54}N_4O_{11}$; IR 1713 cm^{-1}). Reduction of the ketol with sodium borohydride gave a diol VIII (M^+ 842.4060, $C_{46}H_{58}N_4O_{11}$) which was acetylated to IX (M^+ 926.4331, $C_{50}H_{62}N_4O_{13}$; 'Hmr δ: 1.97 (3H, s, -OAc), 2.08 (3H, s, -OAc), 2.12 (3H, s, -OAc), 4.41 (1H, t, J = 6 Hz, C_3'-H), 4.89 (1H, m, C_4'-H)). Oxidation of the ketol with sodium periodate gave an aldehyde X (M^+ 782.3484, $C_{43}H_{50}N_4O_{10}$; 'Hmr δ: 9.20 (1H, s, -CHO)). The loss of a three carbon unit immediately confirmed the position of initial cleavage (C_4'-C_5') and aldehyde formation indicated the 3'-hydroxy-4'-oxo-pattern XI. The 3'(R)-assignment XI was based on the assumption that the configuration at C_3' remained unchanged from that in leurosine (II).



The structural similarities between XI and vinamidine (III) suggested a possible transformation to the natural product. In this regard however, all attempts to deoxygenate the ketol were unsuccessful. At this point it was reasoned that a substrate of lower oxidation state than II might be oxidised by potassium permanganate, directly to III. Indeed oxidation, as above, of the readily available 4'-deoxyleurosidine (XII)[9] gave the expected 19'-oxo-derivative XIII (11%) (M^+ 808.4046, $C_{46}H_{56}N_4O_9$; IR 1640 cm^{-1}; ^{1}Hmr δ: 4.84 (1H, m, C_2'-H)) together with a cleavage product (25%) ($[\alpha]_D$ -35°, lit.[6] -33°) identical with an authentic sample[10] of vinamidine (III). Reduction of synthetic III with sodium borohydride in methanol gave the corresponding alcohol; $[\alpha]_D$ -78°, lit.[6] -80°.



Thus potassium permanganate oxidation of 4'-deoxyleurosidine (XII) provided the C_4'-C_5' cleavage product vinamidine (catharinine) III, in complement to the C_2'-C_{19}' cleavage observed with tert-butyl hydroperoxide[5].

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