STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. IV[1,2]. NOVEL OXYGENATED CATHARANTHINE DERIVATIVES.

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Electrophilic attack of various reagents on the 3,4-double bond of catharanthine derivatives (e.g. II, R = O) furnished novel intermediates, potentially useful in syntheses of naturally occurring bisindole alkaloids.

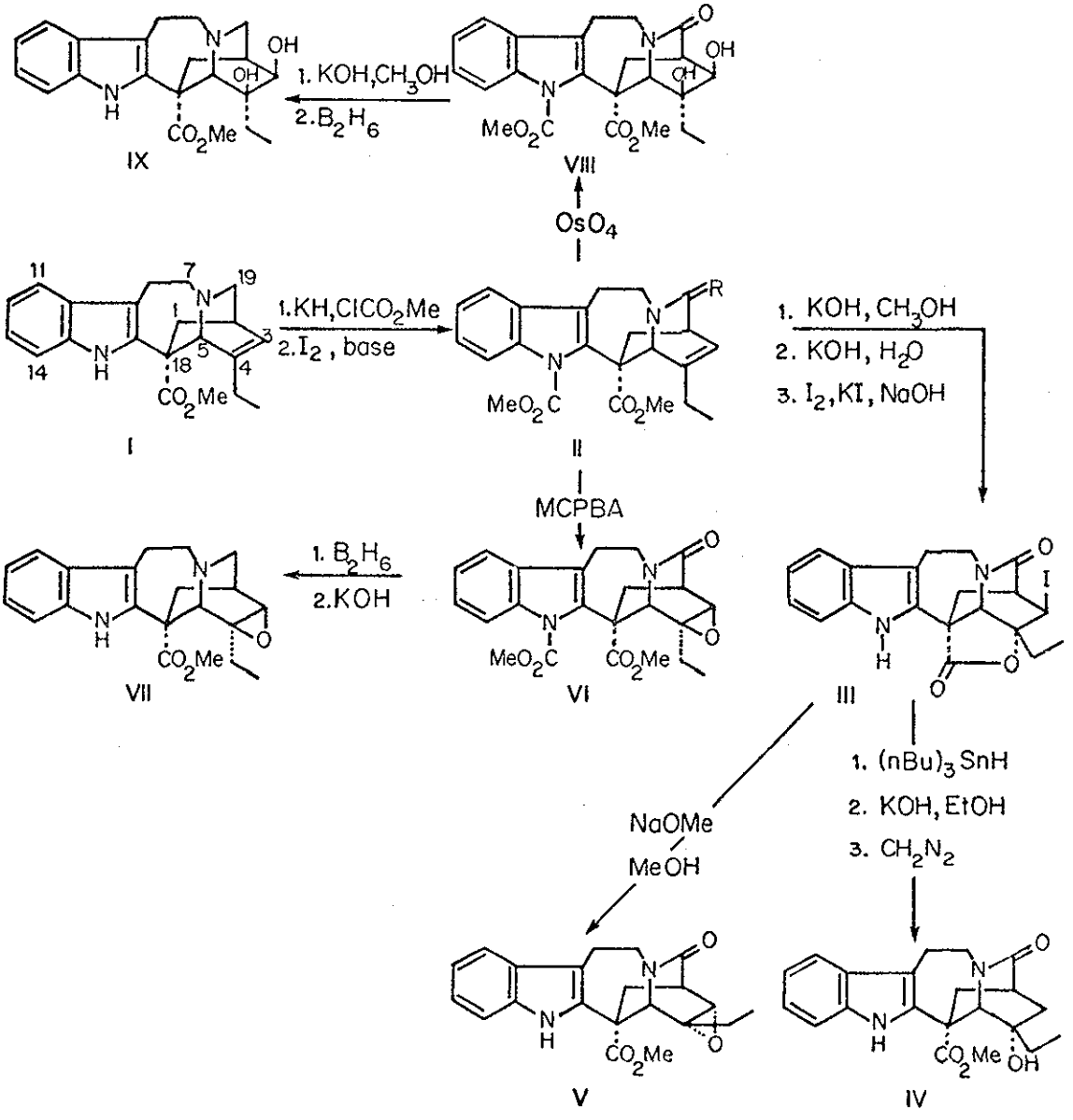
Previous investigations involving the "chloroindolenine"[3,4] and "biogenetic"[5,6] approaches to the synthesis of bisindole alkaloids demonstrated the coupling of indole units from the cleavamine or catharanthine families with appropriate dihydroindole units of the vindoline family to provide synthetic analogues related to the clinically important anti-tumor agents, vinblastine and vincristine.

More recently the latter approach has been extended to provide the first synthesis of the bisindole alkaloid leurosine and of 3'-hydroxyvinblastine.[1] In order to provide a general route to these alkaloids it was necessary to synthesize derivatives of catharanthine oxygenated at C_3 and/or C_4.

Observations in our laboratories revealed that electrophilic additions to the olefinic linkage of catharanthine (or cleavamine) were complicated by competitive attack of the reagents at either the indole ring or the basic nitrogen atom. Appropriate protection of the indole unit and/or the basic nitrogen atom was mandatory before satisfactory yields of desired derivatives could be realized. N_a-Carbomethoxy-19-oxocatharanthine (II, R = O) proved to be a suitable intermediate for the syntheses of such derivatives.

Reaction of catharanthine (I) with potassium hydride and methyl chloroformate provided N_a-carbomethoxycatharanthine (II, R = H_2), which on oxidation with iodine/base[7] gave the required lactam (II, R = O) in 70% yield [MS: m/e 408 (M^+, $C_{23}H_{24}N_2O_5$); 285 (base peak); NMR: 6.24 (m, olefinic), 3.95 and 3.62 (2s, 2 x $CO_2\underline{CH}_3$): IR: 2940, 2890, 1735, 1670, and 1650 cm^{-1}][8].

A very efficient conversion of this lactam to the iodolactone III was accomplished as follows. Deprotection and hydrolysis of II (R = O) with base to the C_{18} carboxylic acid and subsequent iodolactonization (I_2, KI, NaOH) afforded 4α-hydroxy-3β-iodo-19-oxo-dihydrocatharanthinic acid lactone (III) [MS: m/e 462 (M^+, $C_{20}H_{19}N_2O_3I$), 397, 336, 291, 117, 112 (base peak); NMR: 9.45 (bs, 1H, N$\underline{H}$), 4.6 (dd, 1H, J = 3.5, 1.5 Hz,


1. KOH, CH3OH
2. B2H6
OsO4
1. KH, ClCO2Me
2. I2, base
1. KOH, CH3OH
2. KOH, H2O
3. I2, KI, NaOH
MCPBA
1. B2H6
2. KOH
1. (nBu)3SnH
2. KOH, EtOH
3. CH2N2
NaOMe
MeOH
IX
VIII
I
II
III
VII
VI
V
IV

CHI), 2.2 (m, 2H, $C\underline{H}_2CH_3$), 1.06 (t, 3H, J ≈ 7 Hz, $CH_2C\underline{H}_3$); IR: 3435, 1770 and 1690 cm^{-1}].

Deiodination of III with tri-n-butyltin hydride in tetrahydrofuran furnished 4α-hydroxy-19-oxodihydrocatharanthinic acid lactone (III, iodine replaced by H) in 80% yield [MS: m/e 366 (M^+, $C_{20}H_{20}N_2O_3$, base peak), 195, 182, 181, 180, 169, 168, 167, 117; NMR: 9.56 (bs, 1H, NH), 1.06 (t, 3H, J ≈ 7 Hz, $CH_2C\underline{H}_3$); IR: 3440, 1765 and 1680 cm^{-1}]. Hydrolysis (KOH/C_2H_5OH) of this lactone and subsequent esterification (CH_2N_2) provided 4α-hydroxy-19-oxodihydrocatharanthine (IV) [MS: m/e 336 $(M-CH_3OH)^+$, base peak), 195, 182, 181, 180, 169, 168, 167, 117; NMR (pyridine - d_5): 3.6 (s, 3H, $CO_2C\underline{H}_3$), 1.85 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 1.15 (t, 3H, J ≈ 7.5 Hz, $CH_2C\underline{H}_3$); IR: 3400, 1725 and 1635 cm^{-1}]. The overall sequence, II → IV, represents an effective method for the stereospecific introduction of an hydroxyl function at C_4, thereby providing an intermediate of potential importance in syntheses of vinblastine and vincristine.

The iodolactone III was also utilized in the stereospecific preparation of the corresponding epoxide thus providing an entry into bisindole alkaloids such as leurosine.[9-11] Reaction of III with sodium methoxide in methanol gave, in 79% yield, 3α,4α-epoxy-19-oxodihydrocatharanthine (V) [MS: m/e 366 (M^+, $C_{21}H_{22}N_2O_4$, base peak), 308, 195 and 164; NMR: 3.8 (s, 3H, $CO_2C\underline{H}_3$), 1.02 (t, 3H, J ≈ 7 Hz, $CH_2C\underline{H}_3$); IR: 3425, 1725 and 1665 cm^{-1}]. The α-orientation of the epoxide shown in V follows from the mandatory stereochemistry of III.

Alternatively, direct epoxidation of the lactam (II, R = O) with m-chloroperbenzoic acid provided an isomeric epoxide, N_a-carbomethoxy-3α,4α-epoxy-19-oxodihydrocatharanthine (VI) in 80% yield [MS: m/e 424 (M^+, $C_{23}H_{24}N_2O_6$), 285 (base peak); NMR: 3.7 (s, 3H, C_{18}-CO_2CH_3), 3.98 (s, 3H, N-CO_2CH_3): IR: 1720 and 1665 cm^{-1}]. The β-orientation of the epoxide, as shown in VI, is based on the comparison of this compound with V.

Reduction of the lactam carbonyl in VI, and indeed in any of the derivatives discussed, was accomplished by careful reaction with diborane. Finally removal of the N_a-carbomethoxy group (KOH/CH_3OH) yielded 3β,4β-epoxydihydrocatharanthine (VII) [MS: m/e 352 (M^+, $C_{21}H_{24}N_2O_3$), 323, 138 (base peak); NMR: 8.3 (bs, 1H, NH), 3.72 (s, 3H, CO_2CH_3), 0.94 (t, 3H, J = 7 Hz, CH_2CH_3); IR: 1725 cm^{-1}].

A potential intermediate in the synthesis of compounds related to vincadioline[12] was available through osmylation of II (R = O). Thus reaction with osmium tetroxide at low temperature produced (72%) N_a-carbomethoxy-3β,4β-dihydroxy-19-oxodihydrocatharanthine (VIII) [MS: m/e 442 (M^+, $C_{23}H_{26}N_2O_7$, base peak), 410, 384 and 285; NMR: 4.87 (bs, 1H, OH), 4.28 (bs, 1H, OH), 3.92 and 3.62 (2s, 6H, 2 x CO_2CH_3), 3.87 (d, 1H, J = 2 Hz, C_3-H), 0.91 (t, 3H, J = 7 Hz, CH_2CH_3); IR: 3700-3150, 1735 and 1660 cm^{-1}]. Since electrophilic attack at the double bond in II (R = O) by iodine (see iodolactone III) and by peracid (see VI and VII) occurred from the β-face of the molecule, a similar assumption is made for the osmylation process. At this stage further direct evidence is lacking but subsequent inter-relation with the natural bisindole alkaloids will settle this question unambiguously.

Selective hydrolysis (KOH, CH_3OH) of VIII and diborane reduction to remove the lactam carbonyl provided 3β,4β-dihydroxydihydrocatharanthine (IX) [MS: m/e 370 (M^+, $C_{21}H_{26}N_2O_4$, base peak), 353, 313, 282, 228, 168, 165 and 156; NMR: 7.79 (bs, 1H, NH), 3.73 (m, 2H, C_3-H and C_5-H), 3.67 (s, 3H, CO_2CH_3), 0.99 (t, 3H, J = 7 Hz, CH_2CH_3); IR: 3560-3400 and 1720 cm^{-1}].

In conclusion the above studies provide a series of novel, oxygenated catharanthine derivatives which we believe to be important in the syntheses of a variety of bisindole alkaloids. Studies in this direction are continuing.

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