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STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. XII[1]. DERIVATIVES OF VINCRISTINE.

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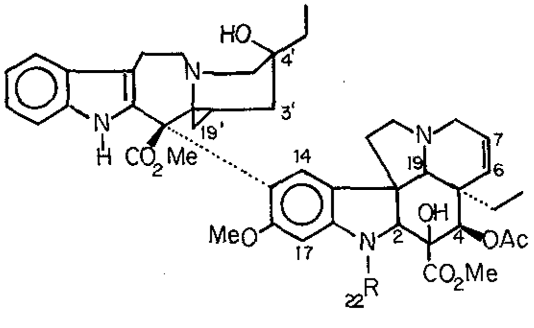
Specific Jones' oxidation of 3',4'-dehydrovinblastine, leurosine, 19'-oxoleurosine, 6,7-dihydro-4'-deoxyleurosidine and 3',4'-dehydro-3-descarbomethoxy-3-N-methylcarboxamidovinblastine provided the corresponding 22-oxo-derivatives of the vincristine series. Further oxidation of 22-oxoleurosine, with iodine/sodium bicarbonate, gave the 19'-oxo-bisindole.

Clinical treatments in the area of the bisindole alkaloids have progressed beyond the sole use of the natural products vinblastine (I) and vincristine (II). Extensive programs on the evaluation of structure-activity relationships for bisindole derivatives have provided valuable information concerning activity and toxicity of various potential agents. For example, 22-oxoleurosine (III) ("N-formylleurosine") is presently used in clinical studies in Hungary[2], while 3',4'-dehydro-4-desacetylvincristine was reported by the Lilly group[3] to exhibit decreased toxicity and increased potency against a tumor system in which vincristine has little effect. Notably, each of these agents possesses the N-formyl functionality of the vincristine series, and it was of interest to synthesize a variety of vincristine analogues from the vinblastine derivatives prepared earlier[4-10]. This communication describes some of our results in this area.

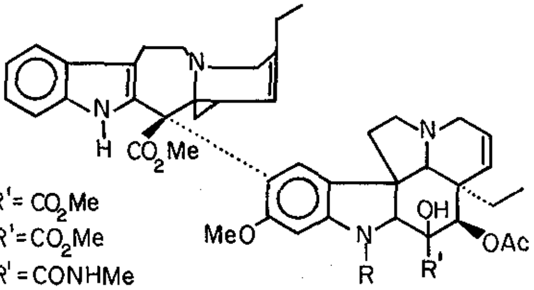


I, R = CH_3
II, R = CHO

Indeed a procedure for the chromate oxidation of the parent amine, vinblastine, has appeared[11]. In our hands, however, "chromic acid" (CrO_3), used as described for the oxidation of vinblastine to vincristine, was ineffectual in oxidising 3',4'-dehydrovinblastine (IV). Modification of the procedure did enable specific oxidation of various bisindole derivatives. Generally, reaction with Jones reagent (large excess) at -78° in a mixture of acetone and acetic anhydride gave, reproducibly, high yields of the required N-formyl compounds.

Using this method, IV gave an 80% yield of 3',4'-dehydrovincristine (V) [ν_{max} 3460, 1740, 1680 cm^{-1}; λ_{max} 218 (4.69), 255 (4.20), 296 nm (4.20); δ 8.80 (1H, bs, -NCHO), 8.10 (1H, bs, -NH), 6.90 (1H, s, C_{14}-H), 5.93 (1H, m, C_7-H), 5.25 (1H, s, C_4-H), 5.36 - 5.58 (2H, m, $C_{3'}$-H and C_6-H), 3.91 (3H, s, $-OCH_3$), 3.76 (3H, s, $-OCH_3$), 3.68 (3H, s, $-OCH_3$), 2.06 (3H, s, $-OCOCH_3$), 1.00 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$), 0.82 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$)]. Similarly the amide VI gave VII [53%; ν_{max} 3440, 1730, 1675 cm^{-1}; δ 8.80 (1H, s, -NCHO), 8.19 and 8.11 (2H, 2 x s, 2 x -NH), 6.89 (1H, s, C_{14}-H), 5.96 (1H, m, C_7-H), 5.2 - 5.7 (3H, envelope, $C_{3'}$, C_4, C_6-H), 3.92 (3H, s, $-OCH_3$), 3.71 (3H, s, $-OCH_3$), 2.04 (3H, s, $-OCOCH_3$), 1.04 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$), 0.76 (3H, t, J = 7 Hz, $-CH_2\underline{CH_3}$); m/e 805.4023. Calcd. for $C_{46}H_{55}N_5O_8$: 805.4049].

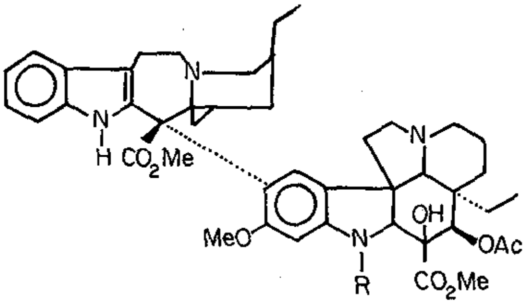
Further exploitation of the method enabled specific oxidation of 6,7-dihydro-4'-deoxyleurosidine (VIII) to the vincristine derivative IX (63%; ν_{max} 3480, 1730, 1680 cm^{-1}; λ_{max} 218 (4.51), 248 (3.96), 292 nm (4.00); δ 8.01 (1H, bs, -NH), 6.82 (1H, s, C_{14}-H), 5.38 (1H, s, C_4-H),



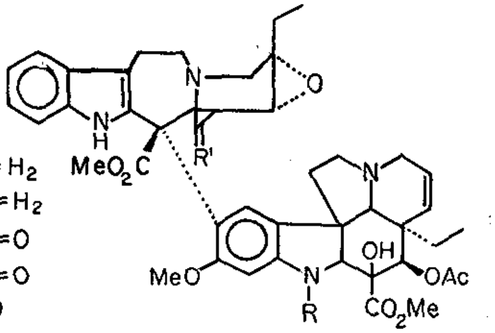
IV, R = CH_3, R' = CO_2Me
V, R = CHO, R' = CO_2Me
VI, R = CH_3, R' = CONHMe
VII, R = CHO, R' = CONHMe

4.61 (1H, s, C_2-H), 3.90 (3H, s, $-OCH_3$), 3.79 (3H, s, $-OCH_3$), 3.62 (3H, s, $-OCH_3$), 2.02 (3H, s, $-OCOCH_3$), 0.92 (6H, t, J = 7 Hz, $-CH_2C\underline{H}_3$)). Under analogous conditions 22-oxo-leurosine (III) was obtained from leurosine (X). Further oxidation with iodine in the presence of sodium bicarbonate gave the 19'-oxo-compound XI [66%, ν_{max} 3478, 1740, 1678, 1645, 1600 cm^{-1}; λ_{max} 217 (4.78), 258 (4.24), 280 (4.17), 288 (4.23), 296 nm (4.27); δ 8.82 (1H, bs, -NCHO), 8.06 (1H, bs, -NH), 7.16 (1H, s, C_{17}-H), 6.93 (1H, s, C_{14}-H), 5.97 (1H, dd, J = 10, 4 Hz, C_7-H), 5.47 (1H, d, J = 10 Hz, C_6-H), 5.28 (1H, s, C_4-H), 4.74 (2H, m, $C_{2'}$-H and C_2-H), 3.95 (3H, s, $-OCH_3$), 3.78 (3H, s, $-OCH_3$), 3.68 (3H, s, $-OCH_3$), 2.10 (3H, s, $-OCOCH_3$), 1.02 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$), 0.87 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$)]. Alternatively, Jones' oxidation of the lactam XII gave XI together with the secondary amine XIII (ν_{max} 3476, 1735, 1645, 1620 cm^{-1}; λ_{max} 212 (4.70), 224 sh (4.58), 252 (4.10), 279 (4.09), 286 (4.11), 294 (4.07), 314 sh (3.75); δ 8.02 (1H, bs, -NH), 6.66 (1H, s, C_{14}-H), 6.30 (1H, s, C_{17}-H), 5.89 (1H, dd, J = 10, 3.5 Hz, C_7-H), 5.57 (1H, s, C_4-H), 5.34 (1H, d, J = 10 Hz, C_6-H), 4.78 (2H, m,

C_2'-H and -NH), 4.19 (1H, bs, C_2-H), 3.81 (6H, s, 2 x $-OCH_3$), 3.62 (3H, s, $-OCH_3$), 2.14 (3H, s, $-OCOCH_3$), 1.02 (3H, t, J = 7.5 Hz, $-CH_2C\underline{H}_3$), 0.84 (3H, t, J = 7 Hz, $-CH_2C\underline{H}_3$); m/e 808.3618. Calcd. for $C_{45}H_{52}N_4O_{10}$: 808.3593.].



VIII, $R = CH_3$
IX, $R = CHO$



X, $R = CH_3$, $R' = H_2$
III, $R = CHO$, $R' = H_2$
XI, $R = CHO$, $R' = O$
XII, $R = CH_3$, $R' = O$
XIII, $R = H$, $R' = O$

Thus selection of different oxidants allowed specific oxidations of variously substituted bisindole derivatives. Comparison of biological data for the N-formyl compounds with that of their parent amines is expected to contribute significantly to the understanding of the action of these molecules.

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