Synthetic Studies towards anti-Leukaemic Alkaloids, IX

The Synthesis of 15-Acetoxydihydrocatharanthine

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The synthesis of 15-acetoxydihydrocatharanthine, of key intermediate in the synthesis of the anti-cancer alkaloid vinrosidine (8), is described by a novel modification of the Prevost reaction.

We have recently described the synthesis of 20-acetoxydihydrocatharanthine by a novel modification of the Prevost reaction in involving the trapping of the intermediate symmetrical acytoxonium ion (4) with sodium borohydride. This intermediate led us to accomplish the first syntheses of the highly oncolytic binary alkaloids vinblastine (VLB) (1) and vincristine (VCR) (2) by what we consider to be a biomimetic route.

Vinblastine (1): R = CH₃
Isovinblastine (3)
Vincristine (2): R = CHO

We now report the isolation and characterisation of 15-acetoxydihydrocatharanthine, a crucial intermediate for a similar synthesis of the potentially oncolytic dimer (3). When catharanthine was heated in glacial acetic acid in the presence of silver acetate and iodine for 1–3 hours, followed by portion-wise additions of sodium borohydride, t.l.c. showed no unreacted catharanthine but formation of two slower running materials along with faster running by-products. The slowest running material was identified as 20-acetoxydihydrocatharanthine reported previously. The other slow moving substance isolated in 15–20% yields afforded an indolic UV spectrum and showed an ester carbonyl at 1730 cm⁻¹. The NMR spectrum showed the presence of an acetate methyl group as a 3-proton singlet at δ 2.14 and the other ester methyl at δ 3.86. The mass spectrum showed the molecular ion at m/e = 396.2050 in agreement with the formula C₂₃H₂₈N₂O₄ (calculated molecular weight 396.2056). Convincing evidence for the location of the acetate group at C-15 rather than C-20 was provided by the C₁₉-methylene protons of the ethyl group appearing as a 2-proton quintet at δ 1.53 indicating that a proton was lodged at C-20.

Rationalization for the formation of both the C-15 and the C-20 acetoxydihydrocatharanthine can be made on the basis of competitive electronic and steric factors. The intermediate acytoxonium ion (4) when directly attacked by sodium borohydride would tend to afford the 20-acetoxydihydrocatharanthine (7) by attack of hydride at the less hindered C-15 carbon atom. Alternatively, the reaction may proceed through the intermediacy of the carbonium ion intermediate (5) in which case attack of hydride at C-20 would afford 15-acetoxydihydrocatharanthine. The formation of such a planar tertiary carbonium ion in the strained cage-like Iboga structure therefore plays a sufficient part to afford the 15-acetoxy compound. The stereochemical dispositions of the —O Ac group remains to be determined.

An alternative possibility of trapping the carbonium ion in 4 directly to afford the acetal 8 is also under investigation. This would give the diol 9 which could lead to the synthesis of a binary alkaloid with an exciting combination of the anti-tumour activities of vinblastine and vincristine. The synthesis 15-acetoxydihydrocatharanthine thus forms the basis of an approach to Isovinblastine (3) by the application of the modified polonovski reaction developed by Potter and co-workers and applied by us to affect the first syntheses of vinblastine and vincristine. Work in this direction is currently under progress.

* The yields were variable, depending on the rate of heating as well as the reaction temperatures.

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