Synthetic Studies towards anti-Leukaemic Alkaloids, IX
The Synthesis of 15-Acetoxydihydrocatharanthine

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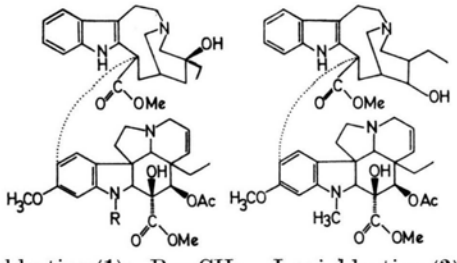
Vinblastine, Isovinblastine, anti-Cancer Alkaloids, Prevost Reaction, Sodium Borohydride

The synthesis of 15-acetoxydihydrocatharanthine, of key intermediate in the synthesis of the anti-cancer alkaloid vinrosidine (**3**), is described by a novel modification of the PREVOST reaction.

We have recently described[1] the synthesis of 20-acetoxydihydrocatharanthine by a novel modification of the Prevost reaction[2] 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**)[3] by what we consider to be a biomimetic route.

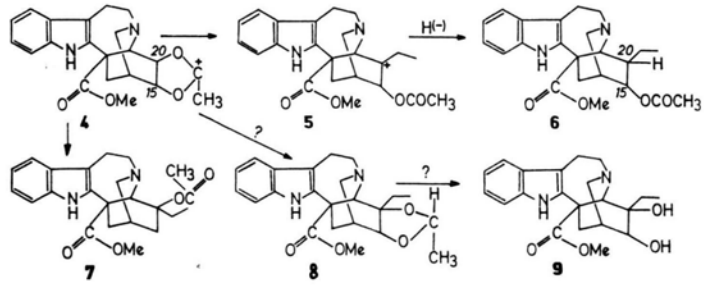


Vinblastine (**1**): R = CH_3 Isovinblastine (**3**)
Vincristine (**2**): R = CHO

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 γ 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 $C_{23}H_{28}N_2O_4$ (calculated molecular weight 396.2056). Convincing evidence for the location of the acetate grouping at C-15 rather than C-20 was provided by the C_{19}-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 hindred 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 —OAc 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 antitumour 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 POTIER and co-workers[4] and applied by us to affect the first syntheses of vinblastine and vincristine[3]. Work in this direction is currently under progress.



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

Requests for reprints should be sent to Prof. Dr. ATTA-UR-RAHMAN, H. E. J. Postgraduate Institute of Chemistry, University of Karachi, *Karachi-32*, Pakistan.

[1] ATTA-UR-RAHMAN, NIGHAT WAHEED, and MARYAN GHAZALA, Z. Naturforsch. **31b**, 264 [1976].
[2] C. PREVOST, C. R. Acad. Sci., Paris **196**, 1129 [1933]; **197**, 1661 [1933].
[3] ATTA-UR-RAHMAN, ANWER BASHA, and MARYAM GHAZALA, Tetrahedron Letters, in press.
[4] P. POTIER, N. LANGLOIS, Y. LANGLOIS, and F. GUERITTE, Chem. Commun. **1975**, 670.