The reaction of catharanthine under modified prevost reaction conditions has afforded 20-acetoxydihydrocatharanthine, an important intermediate for the synthesis of anti-leukaemic alkaloids, vinblastine and vincristine.

The two remaining problems in the synthesis of vinblastine are a) the functionalization of catharanthine (or carbomethoxycleavamine) at C-20 to afford the Markownikov hydration product and b) obtaining the natural stereochemistry at C-16 during the combination of the indole moiety with vindoline.

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We report here the satisfactory resolution of the first of these two problems as applied to catharanthine. The double bond of 16-carbomethoxyceleavamine was found to be remarkably inert to the usual olefin reactions e.g. oxomercuration (both with mercuric acetate and mercuric trifluoroacetate), epoxidation, bromination, acid hydration and isomerization. It was therefore decided to attempt the functionalization of the corresponding double bond in catharanthine where the ring strain in this cage-like Iboga alkaloidal structure may impart a greater reactivity to the olefinic system.

After conventional reactions had failed to afford any addition product, a novel approach involving the trapping of the Prevost intermediate (9) was attempted. The Prevost reaction involves the treatment of the olefin with silver acetate (or benzoate) and iodine in hot glacial acetic acid (or benzene) resulting in the generation of a symmetrical acytoxonium ion (9). In the absence of moisture, this intermediate is attacked by another molecule of acetic acid to afford the trans-diacetate (11). Woodward and others later showed that if the reaction was carried out in moist acetic acid, the intermediate acytoxonium ion (9) could be attacked by water resulting in the preferential formation of the cis-hydroxyacetate (13).

It appeared interesting to us attempt to trap the symmetrical acytoxonium ion (9) with hydride. This should result in the overall addition of acetic acid to the olefin. Moreover, hydride should attack from the least hindered side affording preferentially the Markownikov product (14).

Catharanthine (3) was heated in glacial acetic acid in the presence of silver acetate and iodine for four hours under nitrogen. Excess of sodium borohydride was added in small portions to the brownish solution with stirring. The solution was allowed to stand overnight, basified with ice cold ammoniacal solution and exhaustively extracted first with ethylacetate and then chloroform. Evaporation of the combined organic extracts afforded a pale brown gum in 95% yield. T.L.C. on the gum in 70% ethyl acetate with 30% methanol showed that there was no unreacted catharanthine and three new substances had been formed of which the slowest moving was the major one. The substances were separated by preparative t.l.c. The two faster moving materials possessed indolic UV spectra and afforded molecular ions at m/e = 338 (other major peaks at 279, 223, 213, 171, 170, 168, 149, 141, 123, 122, 77, 57, and 55) and m/e = 340 (other major peaks at 279, 278, 223, 202, 170, 149, 141, 136, 125, 123, 122, 110, 96, 77, 59, 57 and 55). Since these materials were formed in only trace quantities, they were not investigated further. The major slower component tended to stick to the plates and the isolated yields were initially poor. However, on washing the adsorbed band several times with methanol and finally acetic acid, most of the material could be eluted off to afford yields of 45-55%.

The product possessed an indolic ultra-violet spectrum. The IR spectrum showed ester absorption at 1730 cm\(^{-1}\). The molecular ion in the mass spectrum of the substance appeared at m/e = 396, 60 mass units higher than that of catharanthine, indicating that a molecule of acetic acid had been added. A prominent loss of 60 m.u. to afford m/e = 336 supported such a conclusion. High resolution mass spectrometry showed the measured molecular weight to be 396.2048, in agreement with the molecular formula C\(_{23}\)H\(_{28}\)N\(_{2}\)O\(_{4}\) (calculated molecular weight 396.2056). The fragmentation pattern of the substance was also in accordance with the proposed structure (15) for the product. Confirmation of the presence of an acetate moiety in the molecule was obtained from the NMR spectrum which showed a sharp 3-proton singlet at
\[ \text{CO}_2\text{Me} \text{CO}_2\text{Me} \]

\( \gamma 2.04 \) assigned to the \(-\text{OCOCH}_3\) group. Another three proton singlet occurred at \( \gamma 3.85 \) due to the \(-\text{COOCH}_3\) protons. That the acetoxy group was located at C-20 rather than C-15 was shown by the ethyl group resonating in a triplet-quartet pattern.

The reactions of catharanthine in hot acetic acid have previously been examined at length by Scott\(^\text{13}\) and Smith\(^\text{14}\) but the formation of dihydroacetocatharanthine does not take place under those conditions. The functionalization of catharanthine by this new reaction constitutes a major step forward to the semisynthetic approach to these binary anti-leukaemic alkaloids. The generality of this reaction to other olefins, and in particular to 16-carbomethoxycleavamine, are being studied.