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SYNTHETIC STUDIES OF ANTI-LEUKAEMIC ALKALOIDS.VII
THE PARTIAL SYNTHESIS OF VINBLASTINE

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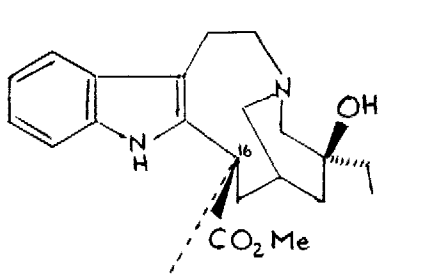
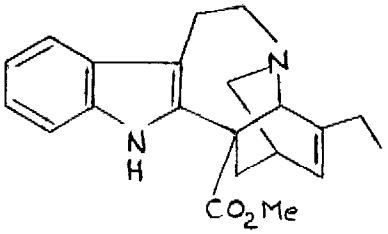
Of the vast array of indole alkaloids found in nature, none are biologically more important or present a more exciting challenge to the synthetic chemist than the binary anti-cancer alkaloids vinblastine (VLB)(1)[1] and vincristine (VCR)(2)[2,3]. Our earlier studies in this area have resulted in the closest synthetic [4-7] and semi-synthetic[8] analogues of vinblastine, i.e., demothoxycarbonyldeoxy-vinblastine and "anhydrovinblastine"[8] respectively, the latter having a non-natural configuration at C_{16}.[11,16]

We have previously proposed that these binary alkaloids may arise by direct attack of vindoline on pentacyclic catharanthine derivatives[8,9], and, to predict by study of models that such an attack would afford significant quantities of the binary compound bearing the natural configuration at C_{16}.[8,9] Recently Potier[11] and Scott[17] have





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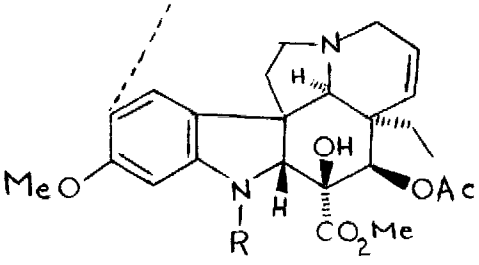
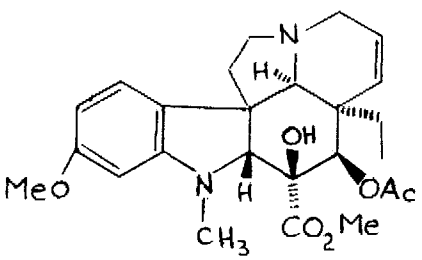


(1) : R = CH_3

(2) : R = CHO

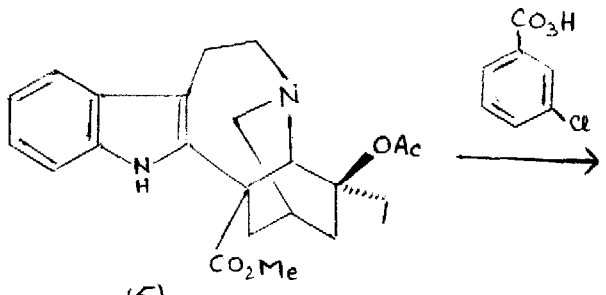


(3)

independently reported a procedure based on circular dichroism studies for ascertaining the configuration at $C_{16'}$ of such binary molecules. It is only recently that Potier and co-workers have been able to achieve a coupling reaction leading to compounds having the natural configuration at $C_{16'}$[11]. The French group have also demonstrated, using circular dichroism studies, that "anhydrovinblastine" described by us and prepared by the chloroindolenine method[10] possessed an "unnatural" configuration at $C_{16'}$.

We report here the first partial synthesis of vinblastine (1) starting from catharanthine (4) and vindoline (3). We have recently described[12] the preparation of 20-acetoxydihydrocatharanthine (5) by a novel modification of the Prevost reaction involving the trapping of the acytoxonium ion intermediate of catharanthine with hydride. The $N_{(b)}$-oxide (6) with trichloroacetic anhydride and vindoline afforded the quaternary immonium compound (7) which was reducible with sodium borohydride to 20-acetylvinblastine (8). Mild alkaline hydrolysis afforded desacetylvinblastine (9) which was acetylated with acetic anhydride-fused sodium acetate to afford vinblastine (1) (35% overall yield starting from 20-acetoxydihydrocatharanthine and vindoline), chromatographically and spectroscopically identical with a sample of natural authentic vinblastine. Small amounts of the binary substance isomeric at $C_{16'}$ and separable by t.l.c., were also obtained. Since vinblastine was oxidatively convertible to vincristine[13], this also constitutes a formal partial synthesis of vincristine.

We have previously described the synthesis of dihydrocatharanthine[5,9] which is convertible to catharanthine[14]. The synthesis of vindoline has also been recently reported[15]. This study thus constitutes the first syntheses of these highly oncolytic binary alkaloids[16].



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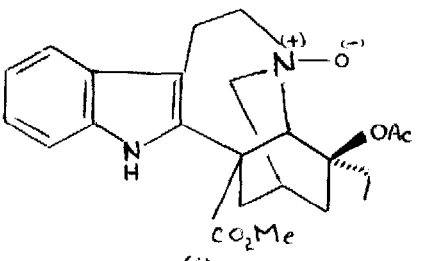

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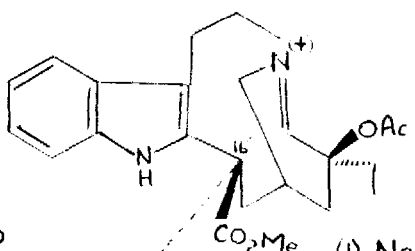
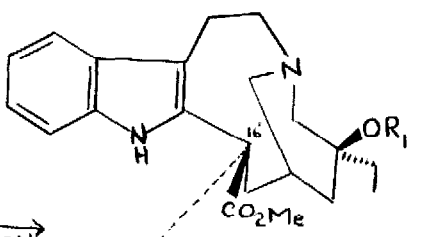
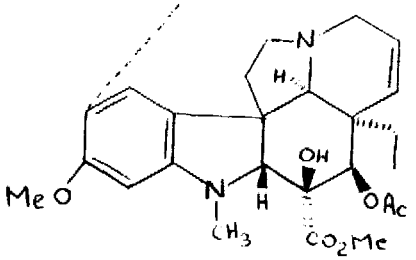


$(CCl_3CO)_2O$
VINDOLINE

(1) $NaBH_4$/Hydrol.
(2) $(CH_3CO)_2O$, CH_3COONa





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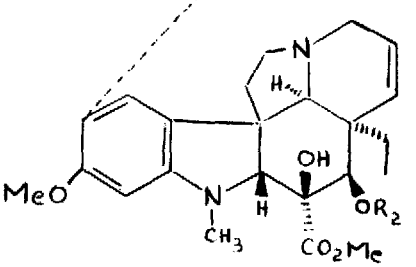

(8) : $R_1 = COCH_3$, $R_2 = COCH_3$
(9) : $R_1 = H$, $R_2 = H$
(1) : $R_1 = H$ $R_2 = COCH_3$

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