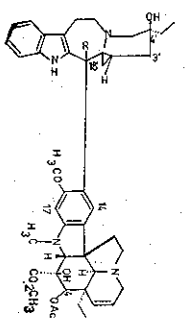
PL 6

STUDIES ON THE SYNTHESIS OF CLINICALLY IMPORTANT ANTI-TUMOUR ALKALOIDS OF THE VINBLASTINE--VINCRISTINE FAMILY

James P. Kutney

Chemistry Depatment, University of British Columbia, Vancouver, Canada

The clinical importance of the bisindole alkaloids vinblastine (1) and vincristine (1, N-CH_3 replaced by N-CHO) as active agents for the treatment of various types of cancer is well known. The most recent investigations have been directed at developing



1, R = $COOCH_3$

drugs within this family which would exhibit more potent or broader activity against a spectrum of tumours and hopefully lower levels of toxicity. Such considerations in our laboratory have led to the development of a synthetic program which has allowed the preparation of various bisindole alkaloids and closely related analogues. Three approaches which have been utilized for this purpose will be discussed and their relative merits presented.

Figure 1 illustrates the application of the chloroindolenine approach to this family of alkaloids.

Figure 2 ilustrates the results obtained when hydrazine method is involved.

Figure 3 summarizes our results when the „biogenetic approach" employing N-oxide intermediates is utilized.

The main emphasis in the lecture will be placed on the recent results obtained from the N-oxide fragmentation reaction.

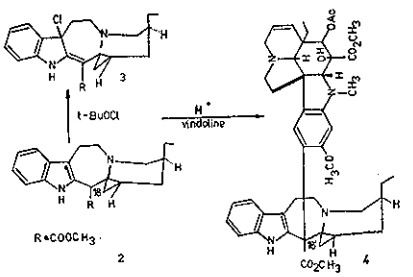


Figure 1. The coupling of 18β-carbomethoxy-4β-dihydrocleavamine (2) via its chloroindolenine intermediate 3, with vindoline.

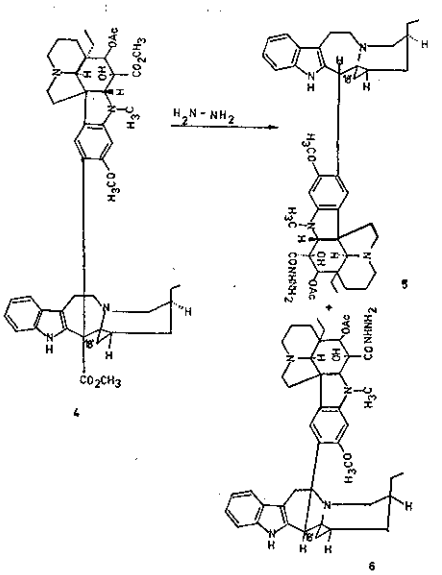


Figure 2. Reaction of 18'-epi-4'-deoxo-4'-epidihydrovinblastine (4) with hydrazine. The isomerization of $C_{18'}$-unnatural stereochemistry to $C_{18'}$-natural stereochemistry.

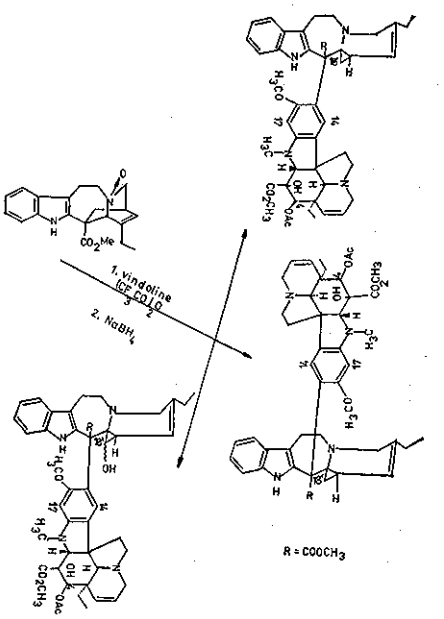


Figure 3. Summary of results obtained when catharanthine N-oxide (7) is coupled with vindoline.