Pure & Appl. Chem., Vol. 62, No. 7, pp. 1299–1302, 1990.
Printed in Great Britain.

Indole alkaloids in human medicine

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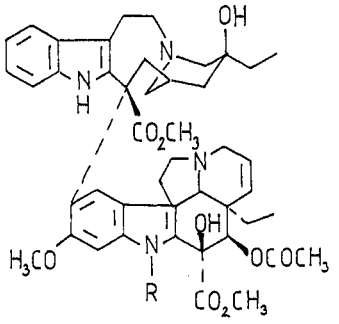
Abstract - Total synthesis of several pharmacologically active indole alkaloids isolated from Vinca minor and Catharanthus roseus present a real challenge. Several aspects of synthesis of these alkaloids are discussed and a new skeletal rearrangement of the 1,2-dehydro-Ψ-aspidospermane into a Ψ-eburnane--type skeleton is presented.

It is common knowledge that plants are useful sources of many valuable medicines. Among them several indole alkaloids can be found, e.g. reserpine and deserpidine from *Rauwolfia serpentina*, ajmalicine and yohimbine from *Corinanthe yohimbe*.

(+)-Vincamine, an alkaloid first isolated from *Vinca minor* has gained in recent years wide application as a specific cerebral vasodilator. Another alkaloid from the same species, (-)-eburnamonine is marketed with a similar indication. A semisynthetic derivative of vincamine, the (+)-apovincaminic acid ethyl ester is produced in Hungary under the trade name CAVINTON^R. Under the trade name CALAN^R in Japan the same compound has a substantial share of the market.



1 R = CH_3 vinblastine

2 R = CHO vincristine

The dimeric Catharanthus alkaloids vinblastine and vincristine are clinically widely used anticancer agents and are applied routinely for the treatment of a number of human cancers[2].

The industrial total synthesis of all these compounds is a real challange.

A retrosynthetic analysis shows that coupling of the two main parts of the alkaloids, namely the catharanthine and vindoline units may provide the end product.

A less toxic derivative synthesized by Potier and others starting from anhydrovinblastine[3] was put on the market by Pierre Fabre in 1989 under the trade name NAVELBIN^R.

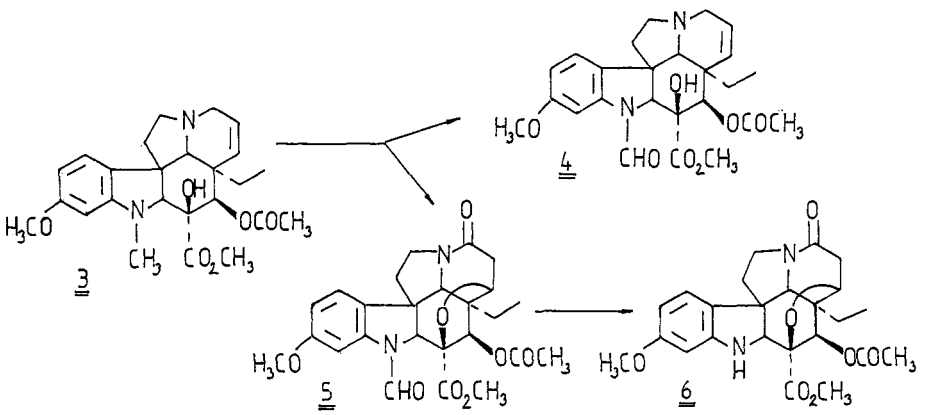
Very recently the synthesis of a new photoreactive derivative of vinblastine (Napavin) was reported[4].

The crucial point of the synthesis is to find a coupling method which would give the desired compound with the correct C (16'S) configuration. The 16'R compound is ineffective. Such method was published by Potier[5] et al. and Kutney[6] et al.

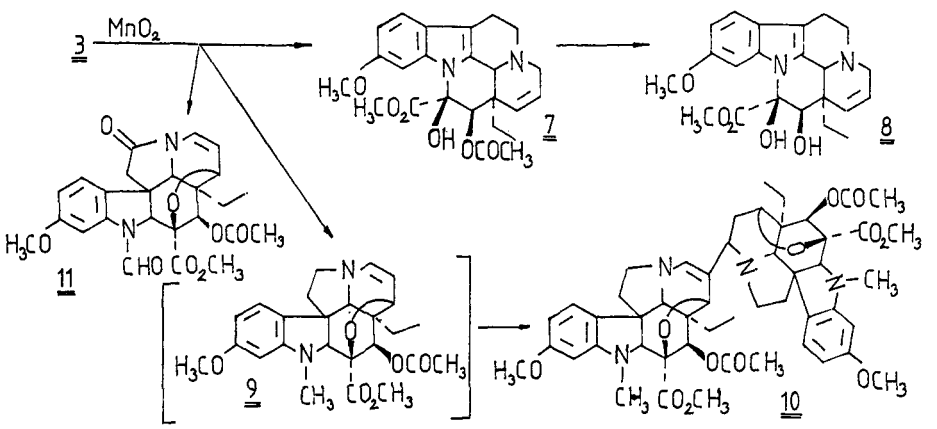
Although (-)-vindoline is a major alkaloid in Catharanthus roseus and is readily isolated, the (+)-catharanthine is only a minor component. An advantageous solution to this problem would involve the coupling of synthetic catharanthine with readily available natural (-)-vindoline.

An industrially feasible total synthesis of (+)-catharanthine has been performed in our laboratories[7,8].

Vindoline was also subjected to different chemical transformations in the hope of obtaining biologically active derivatives.



It has been reported that oxidation of vindoline (3) with manganese dioxide in dichloromethane at room temperature gave N-demethyl-N-formyl--vindoline (4)[9]. Under slightly modified conditions (longer reaction time, MnO_2 prepared by Attenburrow's method[10]), the main product proved to be another N-formyl derivative, the lactam 5 containing oxygen atom at position C(8) and possessing an ether linkage. The latter compound was synthesized earlier by Kutney et al[11], through oxidation of the corresponding N-methyl lactam ether. The acidic treatment of 5 gave the N-deformyl derivative 6. In addition the rearranged product 7 was isolated in 7 % yield. The structure of crystalline 7 was corroborated by X-ray analysis. Treatment of 7 with acid or hydrazine in water/acetic acid, gave the deacetyl derivative 8 in 81 % yield.



The aspidospermane → eburnane skeletal rearrangement is well known when starting from vincadifformine or tabersonine[12], but not in the case of vindoline.

A small amount (3 %) of vindoline dimer 10 was also separated from the above reaction of 3 with MnO_2. Rosazza et al.[13] have isolated the same compound from the microbial transformation of 3.

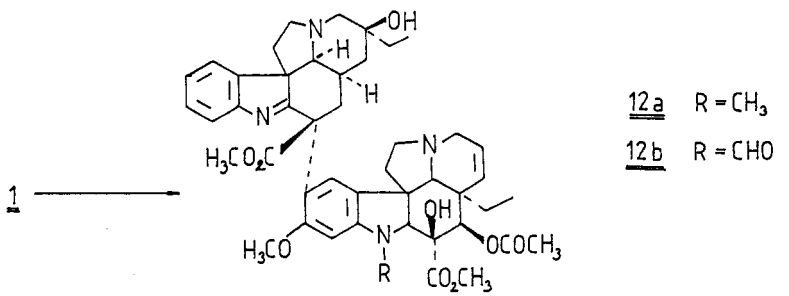
They supposed an enamine intermediate (9) in the multistep reaction sequence. A similar enamine 11, but in oxidized form, possessing lactam and N-formyl group was also isolated (10 %) a result of oxidation of 3 with MnO_2. The structure of the new compound was elucidated by spectroscopic methods.

Interestingly enough we could observe aspidospermane → eburnane skeletal rearrangements even with the dimeric bis-indoles. If 1 is oxidised as a free base with chromium (VI), a hitherto unknown compound is obtained as the main product, in which the velbanamine moiety of the dimer has undergone a transannular cyclization to a ψ-aspidospermane-type skeleton[14].

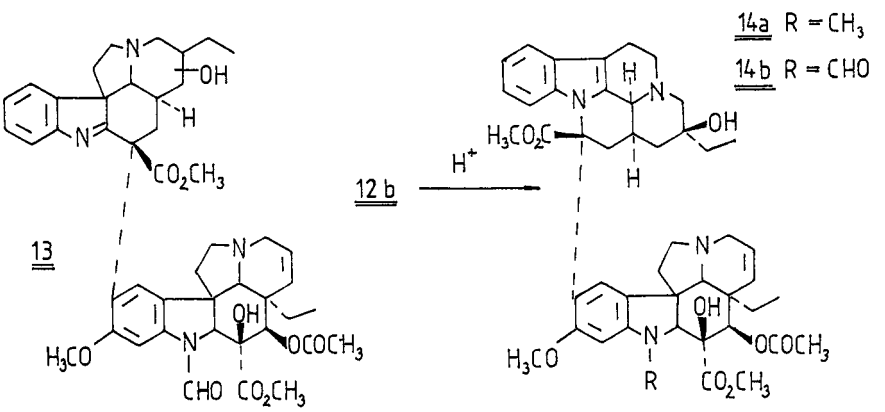
The cyclovinblastine (12a) could be transformed upon oxidation with chromyl acetate into cyclovincrystine (12b).

These cyclo derivatives contain a ψ-aspidosperma-aspidosperma type skeleton, a new kind of dimeric connection. There is only one known representative of this skeleton, the vincovalicine (13)[15] not identical with our compounds.

Upon deformylating 12b with diluted acid, again a dimer was obtained, which, upon reformylation gave 14b instead of the starting 12b.



The above results show that acid not only catalyses deformylation, but also a skeletal rearrangement of the 1,2-dehydro-ψ-aspidospermane into a ψ-eburnane-type skeleton.



There were earlier speculations about the role played by aspidosperma-eburnane skeletal rearrangements in the biosynthesis of alkaloids and its mechanism[16]. In our case the mechanism has to be different from that discussed earlier.

The compounds containing the ψ-eburnane-aspidospermane skeleton (14) are the first known representatives of this new type of bis-indole system.

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* The above paper is regarded as the 50-eth communication in the series: "Synthesis of Vinca Alkaloids and Related Compounds".