Synthetic Studies of *anti*-Leukaemic Alkaloids, IX*

Some Aspects of the Chemistry of Catharanthine

Atta-ur-Rahman, Sadiqa Firdous, and Anwer Basha

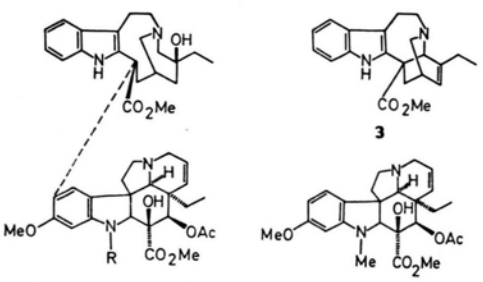
HEJ Postgraduate Institute of Chemistry, University of Karachi, Karachi-32, Pakistan

Z. Naturforsch. **33b**, 469–470 (1978); received December 5, 1977

Vinblastine, Vincristine, Decarbomethoxylation, *anti*-Cancer Drugs, Indole Alkaloids

Vinblastine and Vincristine are binary indole-indoline alkaloids occurring in traces in the leaves of *Vinca rosea*. They are among the most powerful chemotherapeutic agents available to man for the treatment of a variety of cancers. Their high cost and complexity of structure has attracted the attention of many eminent chemists towards their synthesis. The first synthesis of both these *anti*-tumour alkaloids was reported by us last year [7] starting from two major alkaloids, catharanthine and vindoline, which co-occur in the same plant. Some aspects of the chemistry of catharanthine are now presented including a novel one-step decarbomethoxylation reaction with H_2S in glacial acetic acid and a reversible isomerization of catharanthine with sodium borohydride. A study of the life-time of catharanthine in hot glacial acetic acid substantiates the earlier work of the Anglo-French group on the biosynthesis of indole alkaloids.

Our past efforts [1–8] in the field of synthesis of the binary *anti*-leukaemic alkaloids, vinblastine (**1**) and vincristine (**2**) which occur in *Vinca rosea* have recently led to the first synthesis of these highly active drugs starting from catharanthine (**3**) and vindoline (**4**). Since the pentacyclic *Iboga* alkaloid catharanthine played a pivotal role in this synthesis, we decided to investigate some of the chemistry of this substance.



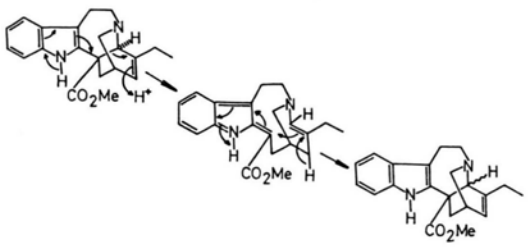
3

1) Vinblastine , R = CH_3
2) Vincristine , R = CHO

4

When catharanthine (**3**) was dissolved in dichloromethane and allowed to react with sodium borohydride at 22 °C, a mild effervescence was observed. On standing for several hours, most of the starting material was found to be converted to a new faster moving spot on thin layer chromatography. This substance was isolated by preparative t.l.c. and afforded a normal indolic ultra-violet spectrum. The IR spectrum showed the presence of an ester carbonyl group (1730 cm^{-1}). The mass spectrum afforded the M^+ at $m/e = 336$ showing that no reduction had occurred. The fragmentation pattern was also found to be broadly similar to catharanthine (**3**). The NMR spectrum in d_6-DMSO showed that the C-20 proton, which appears at δ 3.71 in catharanthine was shifted upfield to δ 3.62 in the new product. The olefinic protons appeared at δ 5.81 as against δ 6.12 of catharanthine.

When a solution of the product was allowed to stand for a few hours, t.l.c. showed that it was converted back to catharanthine indicating that catharanthine and "isocatharanthine" were in equilibrium, isocatharanthine being the less stable of the two substances and the equilibrium being therefore displaced gradually towards catharanthine. When an NMR spectrum of the equilibrium mixture was recorded, the two peaks at δ 3.71 and δ 3.62 appeared distinctly separated, showing that the two substances were not identical. Clearly under the conditions employed, catharanthine undergoes an isomerization at one of the three asymmetric centres present in the molecule. This isomerization probably occurs at C-20, and a possible mechanism is presented in Scheme 1. Dreiding models of 20-isocatharanthine were found to be highly strained which would account for its instability and the isomerization to catharanthine. When the same isomerization was however attempted using sodamide or sodium hydride no reaction with catharanthine was observed.



It has previously been reported [9] that in contrast to dihydrocatharanthine, catharanthine does not undergo decarboxylation readily on saponification and treatment with acid. We have found that catharanthine can be decarbomethoxylated smoothly in one step if it is dissolved in

* Part VIII: Atta-ur-Rahman, Anwer Basha, Nighat Waheed, and Maryam Ghazala, Z. Naturforsch. **31b**, 1416 (1976).

Requests for reprints should be sent to Dr. Atta-ur-Rahman, Husein Ebrahim Jamal Post Graduate Institute of Chemistry, University of Karachi, *Karachi-32*, Pakistan.

dioxan, acidified with a few drops of glacial acetic acid and hydrogen sulphide is bubbled into the solution at 20 °C. The conversion is slow at room temperature (50% in 24 hours), but the reaction proceeds cleanly without any side products being visible. Yields are over 90% based on unrecovered catharanthine.

An investigation of the life-time of catharanthine in refluxing glacial acetic acid has been carried out to throw light on the highly controversial results of Scott [10, 11] on the biosynthesis of indole alkaloids. Scott has claimed yields of 12% catharanthine after refluxing it in glacial acetic acid for 16 hours, 9% after 34 hours and 5% after 72 hours. G. F. Smith and co-workers, on the other hand, claim yields of less than 1% catharanthine after refluxing it in glacial acetic acid for one hour [12]. We have found that the yields of catharanthine are variable depending on the temperature of the external bath and the scale on which the reaction is carried out. On average we have obtained less than 4% catharanthine after refluxing it in glacial acetic acid for 12–16 hours. Our results are thus in broad agreement with those of G. F. Smith and co-workers [13].

It would be relevant to emphasize that the dramatic developments in the field of synthesis of binary Vinca alkaloids by the French group and ourselves [6–8] are partly a result of the novel biosynthetic hypothesis proposed by us in 1971 [5] suggesting that vinblastine and vincristine could biosynthetically arise directly from catharanthine (and vindoline) instead of tetracyclic precursors as envisaged by other workers in the field. Our hypothesis has been subsequently confirmed [14] by labelling experiments, and duly acknowledged by Potier and co-workers [15].

[1] J. Harley-Mason, Atta-ur-Rahman, and J. A. Beisler, Chem. Commun. **1966**, 743.
[2] J. Harley-Mason and Atta-ur-Rahman, Chem. Commun. **1967**, 208.
[3] J. Harley-Mason and Atta-ur-Rahman, Chem. Commun. **1967**, 1048.
[4] J. Harley-Mason and Atta-ur-Rahman, Chem. Ind. **52**, 1845 (1968).
[5] Atta-ur-Rahman, Pak. J. Sci. Ind. Res. **14(6)**, 487 (1971).
[6] Atta-ur-Rahman, Nighat Waheed, and Maryam Ghazala, Z. Naturforsch. **31b**, 264 (1976).
[7] Atta-ur-Rahman, Anwer Basha, and Maryam Ghazala, Tetrahedron Lett. **27**, 2351 (1976).
[8] Atta-ur-Rahman, Anwer Basha, Nighat Waheed, and Maryam Ghazala, Z. Naturforsch. **31b**, 1416 (1976).
[9] M. Gorman, N. Neuss, and N. J. Cone, J. Am. Chem. Soc. **87**, 93 (1965).
[10] A. A. Qureshi and A. I. Scott, Chem. Commun. **1968**, 945.
[11] A. A. Qureshi and A. I. Scott, Chem. Commun. **1968**, 947.
[12] R. T. Brown, J. S. Hill, G. F. Smith, K. S. J. Stapleford, J. Poisson, M. Muquet, and N. Kunesch, Chem. Commun. **1969**, 1475.
[13] R. T. Brown, J. S. Hill, G. F. Smith, and K. S. J. Stapleford, Tetrahedron Lett. **27**, 5217 (1971).
[14] P. E. Daddona and C. R. Hutchinson, J. Am. Chem. Soc. **96**, 6806 (1974).
[15] N. Langlois, F. Gueritte, Y. Langlois, and P. Potier, J. Am. Chem. Soc. **98**, 7017 (1976).

Satz und Druck: Allgäuer Zeitungsverlag GmbH, Kempten