HETEROCYCLES, Vol. 6, No. 7, 1977

STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. XI[*1].

NOVEL ISOMERS OF VINBLASTINE.

James P. Kutney and Brian R. Worth,

Department of Chemistry, University of British Columbia,

2075 Wesbrook Place, Vancouver, B.C.

Canada, V6T 1W5

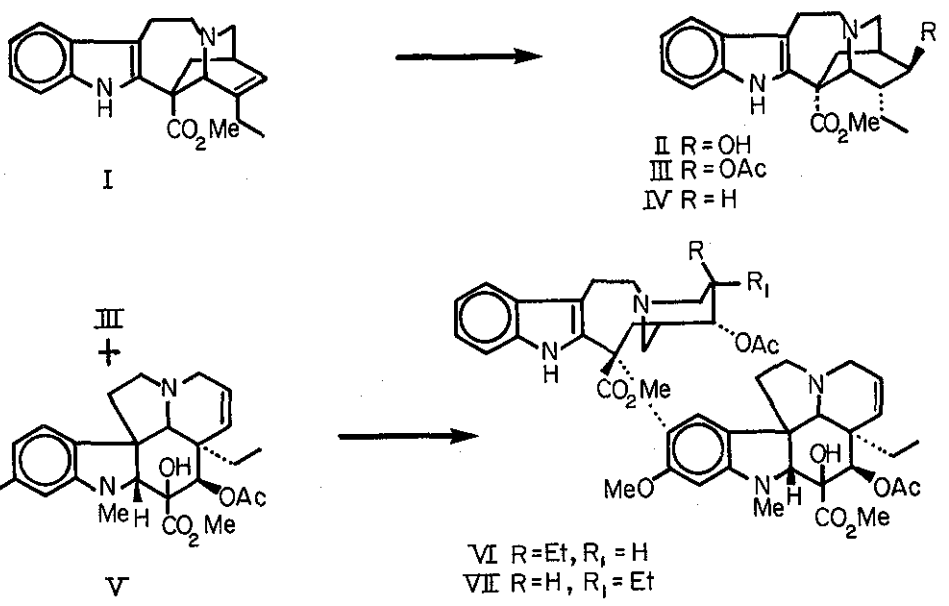
Polonovski-type coupling between 3β-acetoxydihydrocatharanthine N_b-oxide and vindoline provided 3'α-acetoxy-4'-deoxyvinblastine (VII) and 3'α-acetoxy-4'-deoxyleurosidine (VI). Hydroboration/oxidation and subsequent acetylation of 3',4'-dehydrovinblastine (VIII) gave a further isomer, 3-O-acetyl-3'β-acetoxy-4'-deoxyvinblastine (XI).

* This article is dedicated to commemorate the death of Professor Hans Schmid, an outstanding scientist and close personal friend. We will long remember his significant contributions to various areas of chemical science.

A continuing investigation of the chemistry of bisindole alkaloids in the vinblastine-vincristine family has provided syntheses of several antitumor agents, e.g. leurosine[2,3] and 3'α-hydroxy-leurosidine (previously designated as 3'α-hydroxyvinblastine)[2]. Encouraging biological data for several analogues of the natural products prompted investigations towards further examples, potentially useful in the evaluation of structure-activity relationships. The present work describes the preparation of several 3'-oxygenated isomers of vinblastine.

An earlier synthesis of leurosine[3] demonstrated the feasibility of Polonovski-type coupling between $C_{3/4}$-oxygenated catharanthine derivatives and vindoline. Thus it was also of interest to exploit further examples of this route to oxygenated "dimeric" compounds.

Hydroboration of catharanthine (I) with excess borane-methyl sulphide complex in refluxing benzene, followed by alkaline hydrogen-peroxide oxidation gave 3β-hydroxydihydrocatharanthine (II) [ms: M^+ 354; pmr: δ ($CDCl_3$) 3.94 (1H, d, J = 3.5 Hz, C_5-H), 3.62 (3H, s, $-CO_2CH_3$), 1.02 (3H, distorted triplet, J = 3 Hz, $-CH_2CH_3$)] in 48% yield. The corresponding acetate (III) (M^+ 396) had mp. 176-177°. The pmr spectrum of III showed triplet absorption at δ 4.64, J = 3.5 Hz, for C_3-H, and a doublet at δ 3.95, J = 3 Hz for C_5-H, characteristic of compounds such as dihydrocatharanthine (IV) where the ethyl group is in the α-orientation. The structure III is consistent with cis-addition of borane from the less hindered face of the quinuclidine system.

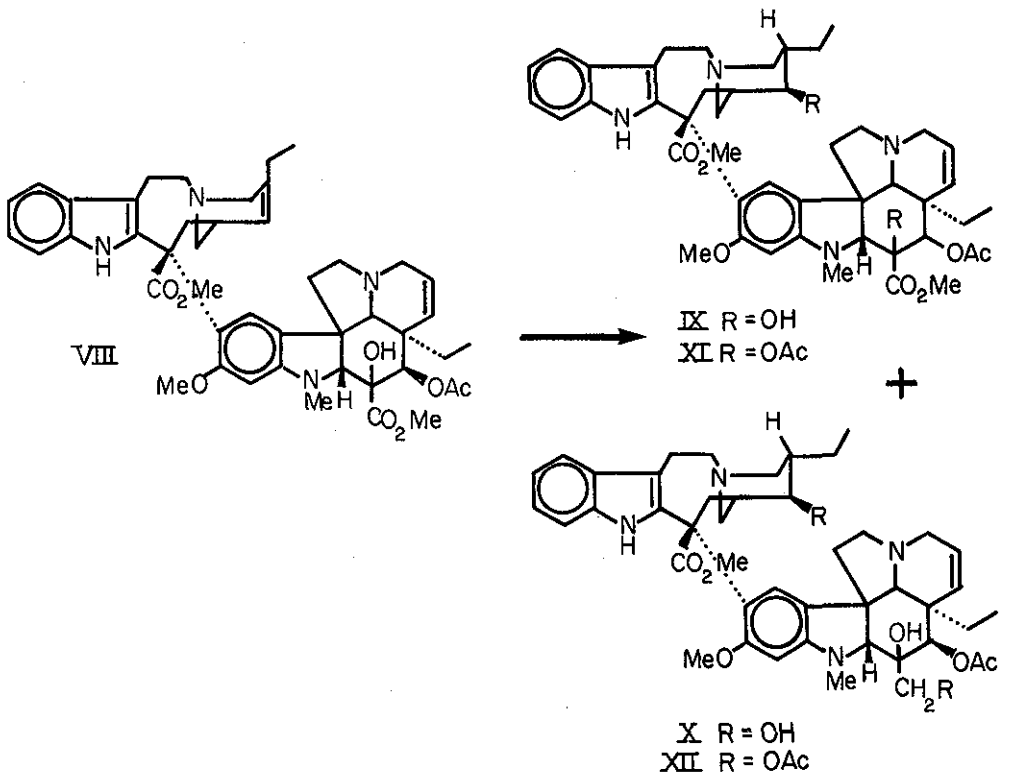


Coupling of III with vindoline in the usual manner[4,5] ((i) mCPBA, CH_2Cl_2, -20°; (ii) vindoline, TFAA, -50°; (iii) $NaBH_4$, EtOH) afforded a mixture of VI and VII: [ms: M^+ 852; pmr: δ ($CDCl_3$) 8.13 (1H, bs, -NH), 6.49 (1H, s, C_{17}-H), 6.12 (1H, s, C_{14}-H), 5.90 (1H, dd, J=10, 4 Hz, C_7-H), 5.39 (1H, s, C_4-H), 5,30 (1H, d, J = 10 Hz, C_6-H), 4.72 (1H, bs, $C_{3'}$-H). 4.14 (1H, bs, D_2O exchangeable, -OH), 3.77 (3H, s, $-OCH_3$, for both isomers), 3.82, 3.80, 3.70 and 3.64 (½ x 3H, s, $-OCH_3$), 2.62 (3H, s, $-NCH_3$), 2.06 (3H, s, $-OCOCH_3$), 2.00 (3H, s, $-OCOCH_3$), 0.86 (3H, two overlapping triplets, $C_{4'}$-CH_2CH_3), 0.65 (3H, t, $-CH_2CH_3$)].

An alternative route to 3'-oxygenated isomers was available through direct functionalisation of 3',4'-dehydrovinblastine (VIII). Hydroboration/oxidation of VIII gave a mixture of 3'β-hydroxy-4'-deoxyvinblastine (IX) [pmr: δ ($CDCl_3$) 7.90 (1H, bs, -NH), 6.47 (1H, s, C_{17}-H), 6.04 (1H, s, C_{14}-H), 5.82 (1H, dd, J = 10, 4 Hz, C_7-H), 5.40 (1H, s, C_4-H), 5.26 (1H, d, J = 10 Hz, C_6-H), 3.74 (3H, s, $-OCH_3$), 3.72 (3H, s, $-OCH_3$), 3.69 (1H, s, C_2-H), 3.53 (3H, s, $-OCH_3$), 2.64 (3H, s, $-NCH_3$), 2.02 (3H, s, $-OCOCH_3$), 0.90 (3H, t, J = 7.5 Hz, $-CH_2CH_3$), 0.74 (3H, t, J = 7 Hz, $-CH_2CH_3$)] and X [pmr: δ ($CDCl_3$) 7.85 (1H, bs, -NH), 6.52 (1H, s, C_{17}-H), 6.19 (1H, s, C_{14}-H), 5.93 (1H, dd, J = 10, 4 Hz, C_7-H), 5.52 (1H, d, J = 10 Hz, C_6-H), 5.00 (1H, s, C_4-H), 3.83 (3H, s, $-OCH_3$), 3.62 (3H, s, $-OCH_3$), 3.56 (1H, s, C_2-H), 3.06 (3H, s, $-NCH_3$), 2.15 (3H, s, $-OCOCH_3$), 0.98 (3H, t, J = 7.5 Hz, $-CH_2CH_3$), 0.84 (3H, t, J = 7 Hz, $-CH_2CH_3$)].

Acetylation of IX with acetic anhydrine-pyridine gave XI [ms: m/e, M^+ 894; pmr: δ ($CDCl_3$) 8.24 (1H, bs, -NH), 6.46 (1H, s, C_{17}-H), 6.12 (1H, s, C_{14}-H), 5.90 (1H, dd, J = 10, 4 Hz, C_7-H), 5.40 (1H, s, C_4-H), 5.33 (1H, d, J = 10 Hz, C_6-H), 4.26 (1H, d, J = 9 Hz, C_3'-H), 4.06 (1H, s, C_2-H), 3.86 (3H, s, $-OCH_3$), 3.74 (3H, s, $-OCH_3$), 3.62 (3H, s, $-OCH_3$), 2.80 (3H, s, $-NCH_3$), 2.06 (3H, s, $-OCOCH_3$), 1.96 (3H, s, $-OCOCH_3$), 1.77 (3H, s, $-OCOCH_3$), 0.92 (3H, t, J = 7.5 Hz, $-CH_2CH_3$), 0.67 (3H, s, $-CH_2CH_3$)].

Similarly X provided the acetate XII [ms: m/e M^+ 866; pmr: δ ($CDCl_3$) 6.48 (1H, s, C_{17}-H), 6.18 (1H, s, C_{14}-H), 5.90 (1H, dd, J = 10, 4 Hz, C_7-H), 5.46 (1H, d, J = 10 Hz, C_6-H), 5.02 (1H, s, C_4-H), 4.28 (1H, d, J = 9 Hz, C_3'-H), 4.24 and 4.00 (2H, 2d, J_{AB} = 12 Hz, CH_2OAc), 3.89 and



3.54,2 x (3H, s $-OCH_3$), 2.89 (3H, s, $-NCH_3$), 2.17, 2.12 and 1.81, 3x (3H, s, $-OCOCH_3$)].

In the pmr spectra of the acetates XI and XII the doublets with J = 9 Hz, assigned to C_3'-H, are consistent with cis-addition of borane and subsequent formation of products in which the ethyl and hydroxyl groups are equatorial.

Thus anti-Markovnikov hydration of catharanthine and subsequent coupling with vindoline provided dimeric compounds bearing 3'α-oxygen function. On the other hand, direct hydroboration/oxidation of 3',4'-dehydrovinblastine afforded a 3'β-oxygenated derivative.

In conclusion, these studies have provided synthetic routes to three of the four possible 3'-hydroxy bisindoles. These compounds will be valuable in future studies concerned with structure-activity relationships in this area of cancer chemotherapy.

Acknowledgement:

Financial aid from the National Research Council of Canada and from Contract NO1-CM-23223, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, is gratefully acknowledged. The authors also wish to thank the Lilly Research Laboratories, Indianapolis, Indiana, for generous gifts of catharanthine and vindoline.

References

1. For Part X, see J.P. Kutney, W.B. Evans and T. Honda, Heterocycles, 1977, 6, 443.
2. J.P. Kutney, J. Balsevich, G.H. Bokelman, T. Hibino, I. Itoh and A.H. Ratcliffe, Heterocycles, 1976, 4, 997.
3. J.P. Kutney and B.R. Worth, Heterocycles, 1976, 4, 1777.
4. J.P. Kutney, A.H. Ratcliffe, A.M. Treasurywala and S. Wunderly, Heterocycles, 1975, 3, 639.
5. J.P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A.H. Ratcliffe, A.M. Treasurywala and S. Wunderly, Helv. Chim. Acta, 1976, 59, 2858.

Received, 11th May, 1977