HETEROCYCLES, Vol. 5, 1976

STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. V[1,2]. THE HYDRAZINE METHOD.

James P. Kutney*, Edwin Jahngen and Tetsuya Okutani

Department of Chemistry, University of British Columbia

2075 Wesbrook Place, Vancouver, B.C.

Canada, V6T 1W5

The hydrazine method, which involves the removal of the $C_{18'}$ ester group in a series of synthetic bisindole derivatives by means of anhydrous hydrazine, can be employed for the synthesis of a family of bisindole derivatives possessing natural stereochemistry at the important $C_{18'}$ position.

In developing various synthetic approaches for the laboratory preparation of bisindole alkaloids of the vinblastine-vincristine family, we had previously demonstrated that the "chloroindolenine approach"[3,4] does indeed provide a versatile and generally high-yielding synthesis of bisindole derivatives. Unfortunately the resultant "dimeric" products thus formed possess the incorrect (unnatural) stereochemistry at $C_{18'}$, the centre linking the two "halves" of the bisindole system. It was desirable to determine whether an inversion of stereochemistry could be achieved at this centre in a process which was generally simple and would provide the resultant products in reasonable yield. This communication describes the results which we have obtained in this direction.

During their elegant investigations on the structure elucidation of Iboga alkaloids, the Swiss group[5] were able to achieve the removal of the sterically hindered and generally unreactive ester group in these alkaloids by means of reaction with anhydrous hydrazine (Figure 1). Their mechanistic postulate for this conversion involved nucleophilic attack of the reagent onto the carbonyl centre and subsequent removal of the ester function via an intermediate (I) possessing an olefinic linkage at the carbon atom originally bearing the ester group. Subsequent regeneration of the indole system (I⟶ II) requires protonation of the relevant carbon centre thereby allowing the possibility of stereochemical alteration at this position. Application of this reaction to the bisindole series was considered in the hope that natural stereochemistry at $C_{18'}$ would be obtained in the resultant product.

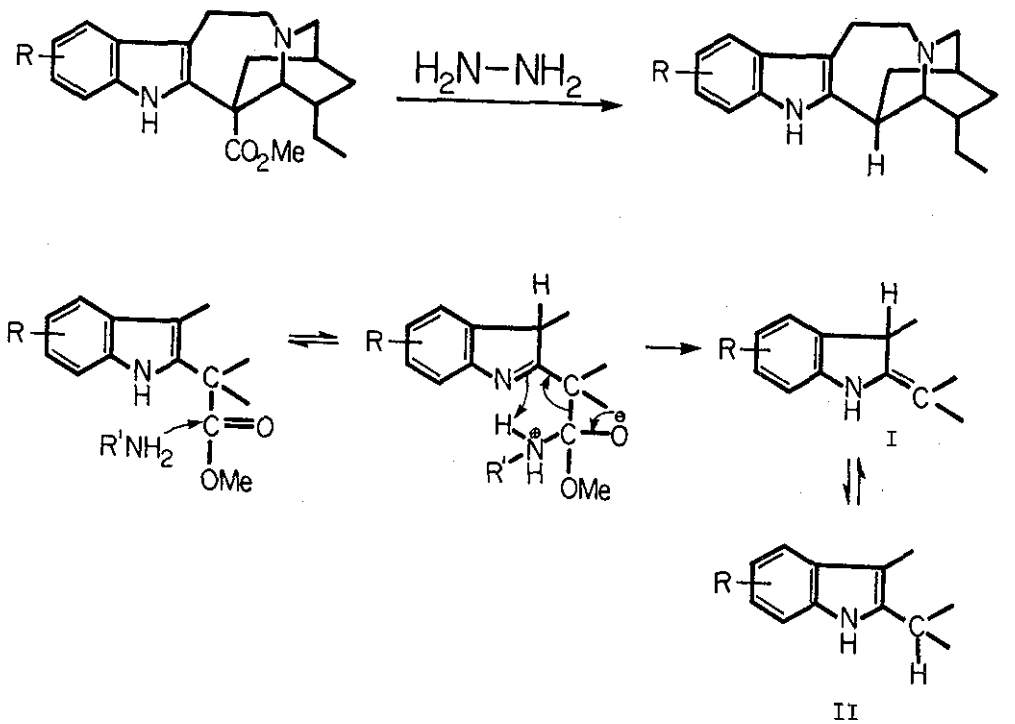

Figure 1. Decarbomethoxylation of Iboga alkaloids by the hydrazine method.

In our initial investigations we repeated an already published[6] reaction in which vinblastine (III) is treated with hydrazine in a manner similar to that described by the Swiss group (Figure 2). The isolated product (82% yield) was evaluated in terms of its stereochemistry at $C_{18'}$ by the CD method[7] developed earlier [λ_{max}^{MeOH} ($\Delta\varepsilon$): 210 (-1.3), 229 (+6.0), 254 (-0.3), 276 (+1.5) nm] and there was no doubt that the natural stereochemistry was maintained as shown in IV.

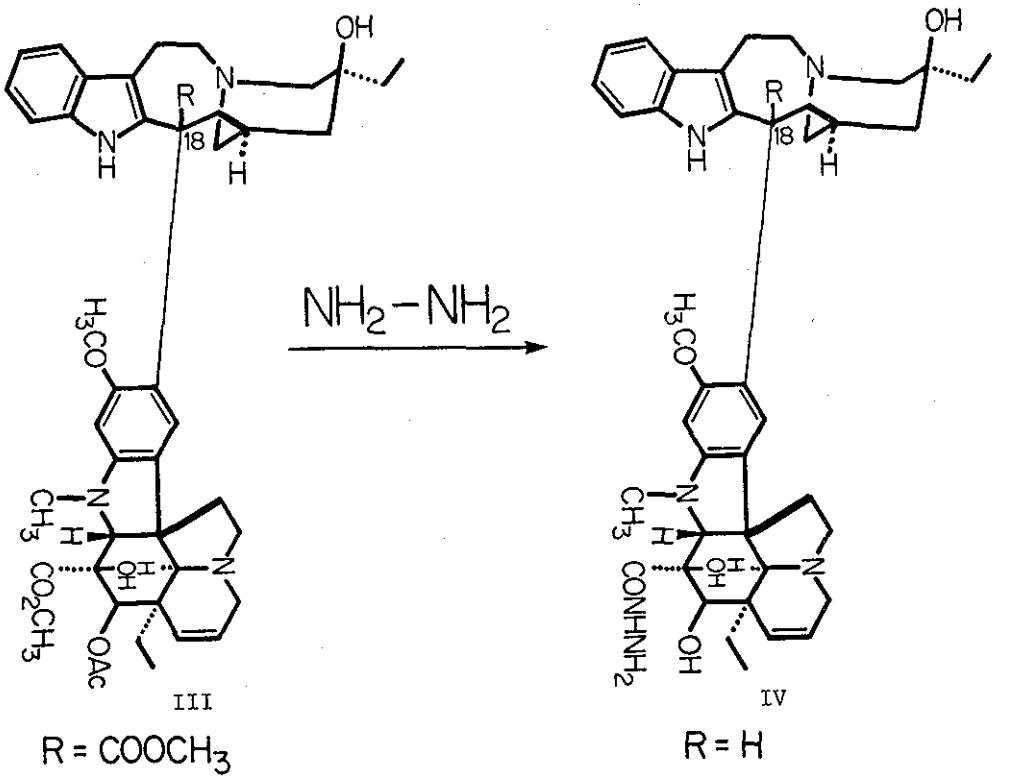

Figure 2. Decarbomethoxylation of vinblastine (III) by the hydrazine method.

Attention was then directed to the stereochemical course followed in the synthetic 18'-epi bisindole derivatives obtained from the chloroindolenine approach[3,4]. Thus 18'-decarbomethoxy-18'-epi-4'-deoxo-4'-epivinblastine (V) was reacted with refluxing hydrazine for 82 hours. The isolated crystalline product (73% yield) was identical with the known

dimer hydrazide derivative (VI, Figure 3) prepared via the chloroindolenine method[3,4]. It was thus clear that the dimer lacking a carbomethoxy group at $C_{18'}$ was stable at this centre during the hydrazine reaction.

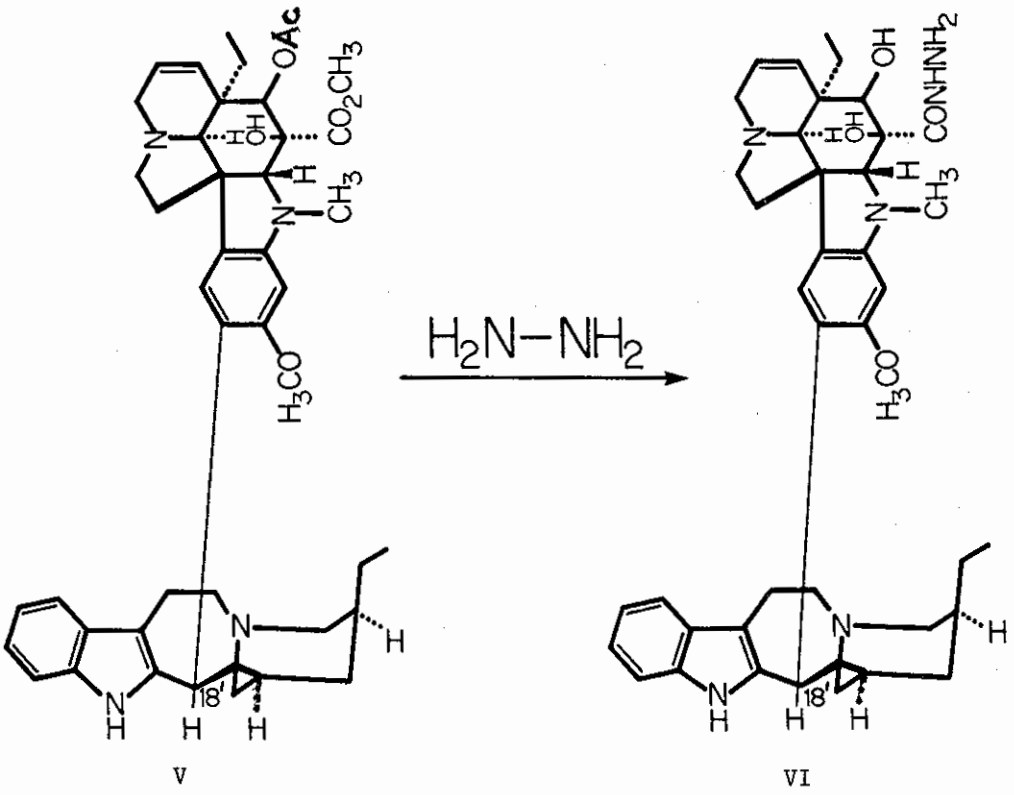

Figure 3. Reaction of 18'-decarbomethoxy-18'-epi-4'-deoxo-4'-epivinblastine (V) with anhydrous hydrazine.

When the $C_{18'}$-epi carbomethoxy series was exposed to the hydrazine reaction, interesting results were obtained (Figure 4). Thus 18'-epi-4'-deoxo-4'-epidihydrovinblastine (VII), upon reaction with refluxing hydrazine, provides two products, both of which lack the $C_{18'}$ ester group. The major component (44% yield) exhibited the following spectroscopic data [MS: m/e 738 (M^+, $C_{43}H_{58}N_6O_5$), 577, 278, 124; NMR (δ): 6.93 (s, 1H), 6.00 (s, 1H), 5.51 (d, 1H, $C_{18'}H$), 4.52 (s, 1H, AcOCH), 4.85 (s, 3H, OCH_3), 2.74 (s, 3H, NCH_3), 1.95 (s, 3H, $OCOCH_3$), 0.90 (t, 3H, $\underline{CH_3}CH_2$-), 0.75 (t, 3H, $\underline{CH_3}CH_2$); CD (λ,Δε): 210 (-2.3), 228 (+3.8), 268 (+1.9), 292 (+0.7), 305 (-1.1)] and could be readily assigned the structure VIII with natural stereochemistry at $C_{18'}$.

The minor component (10% yield) isolated from the above reaction was the 18'-epi isomer (IX) [MS: m/e 738 (M^+, $C_{43}H_{58}N_6O_5$), 149, 138, 124; NMR (δ): 6.65 (s, 1H), 6.10 (s, 1H), 4.5 (d, 1H, $C_{18'}H$), 4.50 (s, 1H, AcOCH), 3.91 (s, 3H, OCH_3), 2.75 (s, 3H, NCH_3), 1.87 (s, 3H, $OCOCH_3$), 0.97 (t, 3H, $\underline{CH_3}CH_2$-), 0.72 (t, 3H, $\underline{CH_3}CH_2$-); CD (λ,Δε): 211 (-0.3), 223 (-5.3), 258 (+2.7).

In summary it was now evident that the hydrazine method can be employed in the synthesis of 18'-decarbomethoxy vinblastine derivatives with the desired stereochemistry at the important centre linking the indole and dihydroindole units. The application of this method to the synthesis of other bisindole derivatives is presently under study.

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.

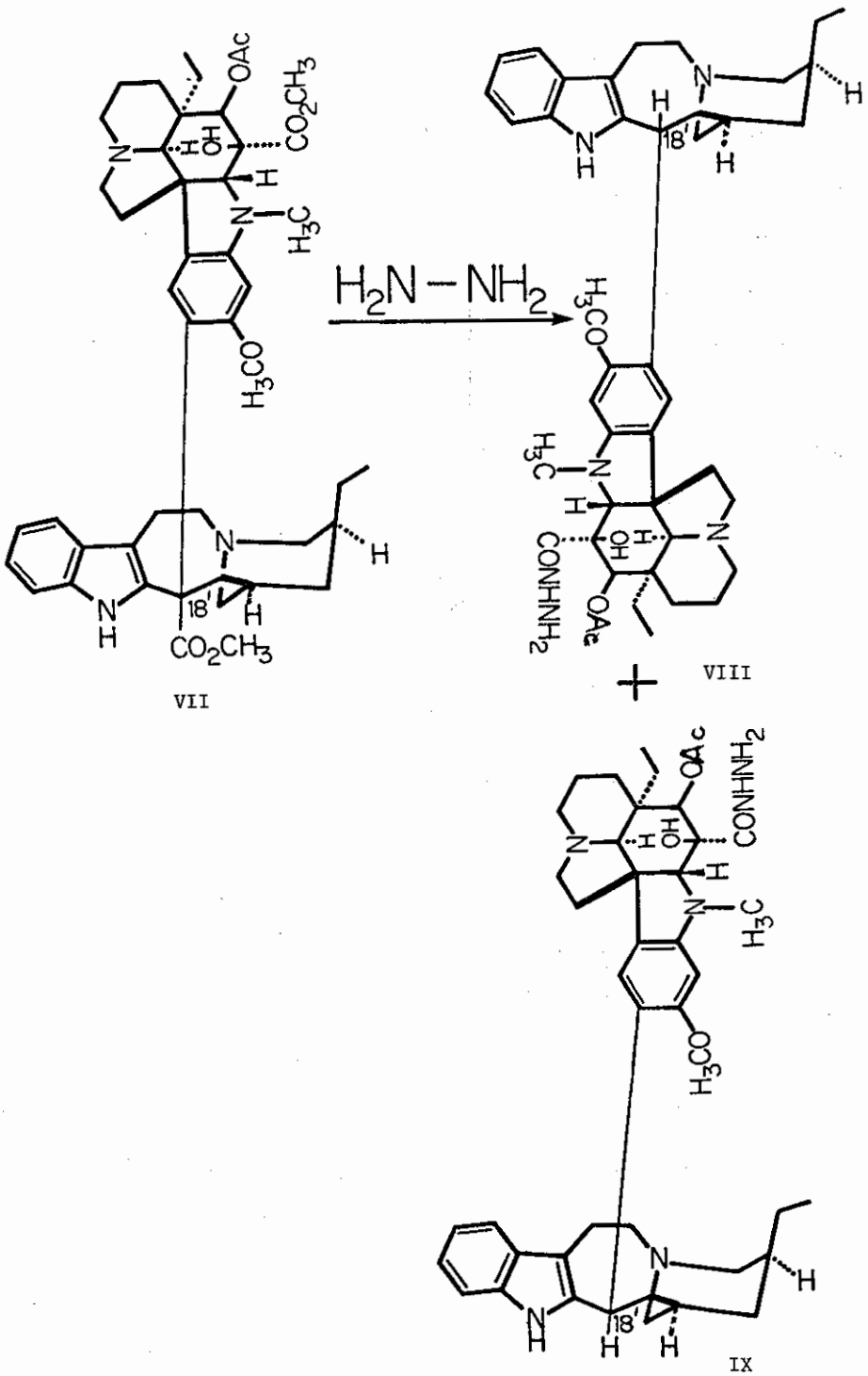

Figure 4. Isomerization of the $C_{18'}$ unnatural stereochemistry bisindole derivatives to the $C_{18'}$ natural series.

References

1. For Part IV, see J. P. Kutney, G. H. Bokelman, M. Ichikawa, E. Jahngen, A. V. Joshua, P. Liao and B. R. Worth, Heterocycles, 1976, 4, in press.
2. These results were presented, in part, at the Sixth International Symposium on Natural Products, Kingston, Jamaica, January, 1976, and at the European Symposium on Bioorganic Chemistry, Gregynog, Wales, May 1976.
3. J. P. Kutney, J. Beck, F. Bylsma and W. J. Cretney, J. Amer. Chem. Soc., 1968, 90, 4504.
4. J. P. Kutney, J. Beck, F. Bylsma, J. Cook, W. J. Cretney, K. Fuji, R. Imhof, and A. M. Treasurywala, Helv. Chim. Acta, 1975, 58, 1690.
5. U. Renner, D. A. Prins and W. G. Stoll, ibid., 1959, 42, 1572.
6. N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Buchi and R. E. Manning, J. Amer. Chem. Soc., 1964, 86, 1440.
7. J. P. Kutney, D. E. Gregonis, R. Imhof, I. Itoh, E. Jahngen, A. I. Scott and W. K. Chan, ibid., 1975, 97, 5013.

Received, 21st June, 1976