

STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. X¹.

THE SYNTHESIS OF NOVEL VINBLASTINE DERIVATIVES.

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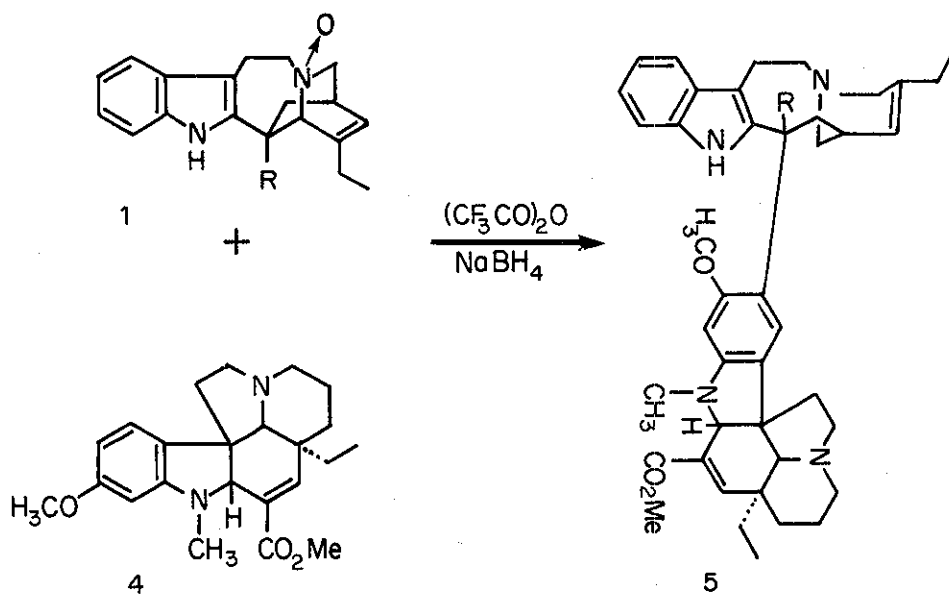
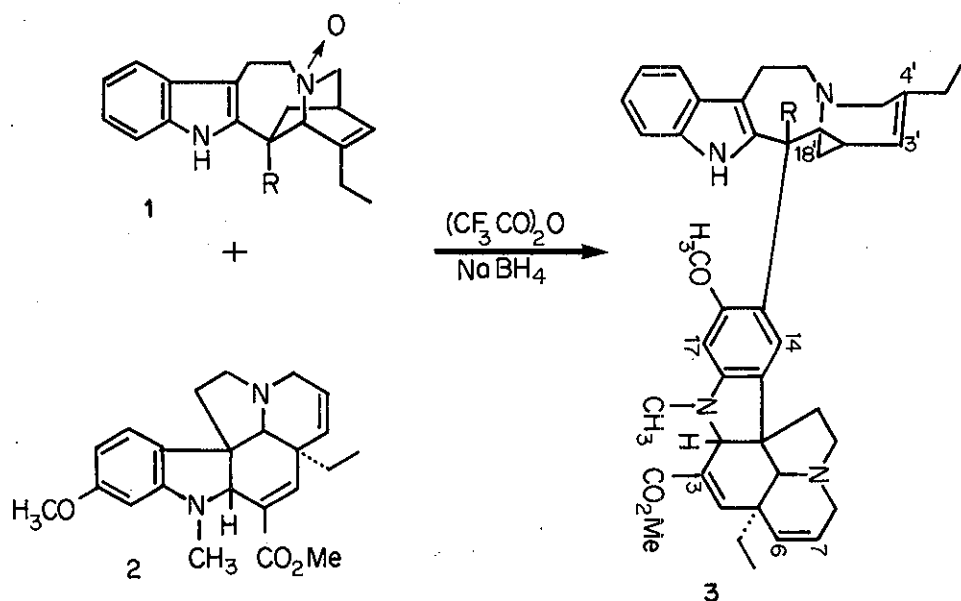
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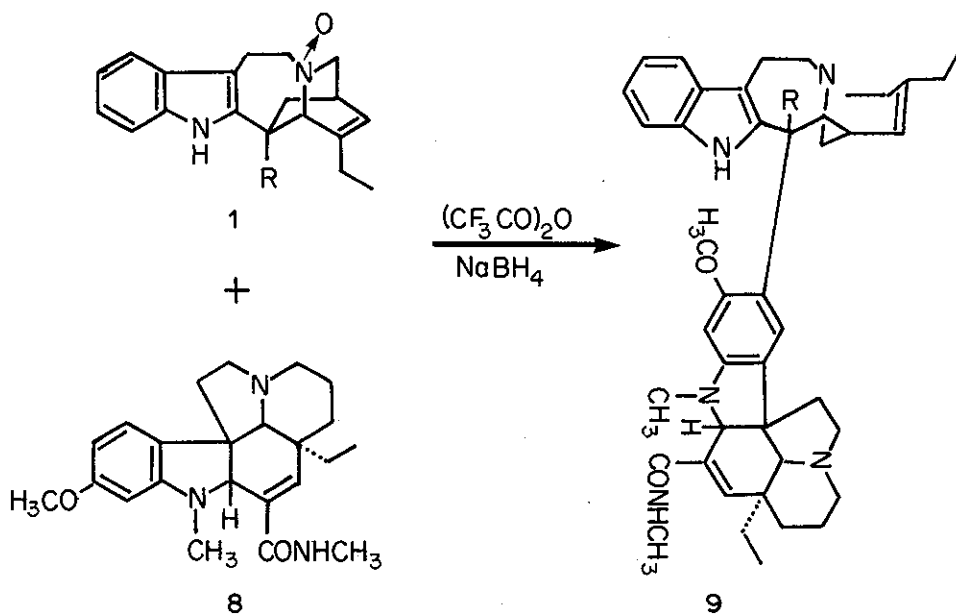
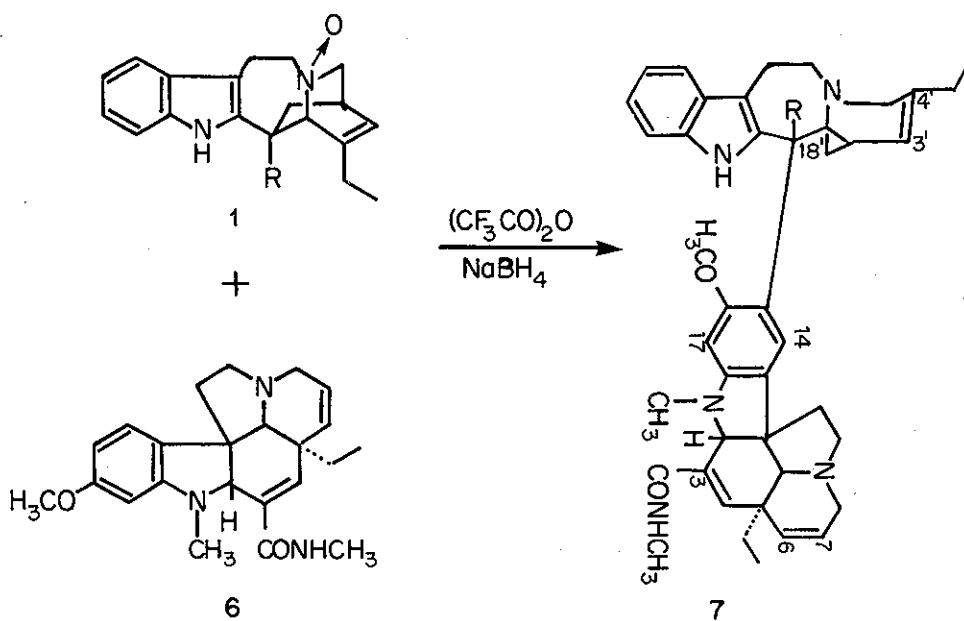
The coupling of catharanthine-N_b-oxide with various novel vindoline derivatives provides a series of novel vinblastine derivatives. These compounds provide an opportunity to evaluate the importance of the functionality in the dihydroindole unit of the bisindole system in terms of anti-tumor activity.

In the accompanying communication¹ we presented a series of investigations which provided efficient synthetic pathways to various novel vindoline derivatives. We would now like to describe our studies in which such derivatives are employed in the syntheses of several novel vinblastine derivatives.

The coupling of catharanthine N-oxide (1, R = CO₂CH₃), prepared according to our previously described procedure^{2,3}, with the unsaturated ester 2¹ (dichloromethane, trifluoroacetic anhydride, -50°C)^{2,3} provided the desired dimer 3 (R = CO₂CH₃) in 37% yield [IR: 1720, 1700 (sh) cm⁻¹; UV: λ (ε): 263 (25222), 287 (18575), 295 (17353), 311 (9520) nm; CD: λ (Δε): 222 (+12.2), 208 (-22.0) nm; PMR: τ 1.93 (s, 1H, NH), 2.46 (m, 1H, C₁₄'-H), 2.80 (m, 4H, C₄-H and C₁₁'-C₁₃'H), 3.46 (s, 1H, C₁₄-H), 3.98 (s, 1H, C₁₇-H), 4.0-4.4 (m, 3H, C₃'H, C₆-H, C₇-H), 5.76 (s, 1H, C₂-H), 6.22 (s, 6H, 2 x OCH₃), 6.38 (s, 3H, OCH₃), 7.17 (s, 3H, NCH₃), 8.96 (t, J = 7.5 Hz, 3H, CH₂CH₃), 9.20 (t, J = 7.5 Hz, 3H, CH₂CH₃); MS: m/e 716 (M⁺, C₄₄H₅₂N₄O₅), 657, 536, 534, 464, 451, 393, 380, 353, 336, 277, 237]. The points of attachment of the indole and dihydroindole units (C₁₅-C₁₈') as shown in 3, are readily seen from the PMR data (singlets at τ 3.46 and 3.98 for the C₁₄ and C₁₇ protons in the dihydroindole portion) and the desired natural stereochemistry at C₁₈' is evident from the CD data^{4,5}.

The synthesis of the bisindole product 5 (R = CO₂CH₃) was achieved by the reaction of 1 (R = CO₂CH₃) with the ester 4¹ in the above described manner. This substance, obtained in 30% yield, was assigned the structure and stereochemistry indicated on the basis of the following spectral data [IR: 1720 cm⁻¹; UV: λ (ε): 268 (20520), 284 (16150), 292 (13650), 313 (7330) nm; CD: λ (Δε): 222 (+14.0), 207 (-17.4) nm; PMR: τ 1.96 (s, 1H, NH), 2.48 (m, 1H, C₁₄'-H), 2.90-2.80 (m, 4H, C₄-H and C₁₁'-C₁₃'-H), 3.40 (s, 1H, C₁₄-H), 4.00 (s, 1H, C₁₇-H), 4.48 (d, J = 6 Hz, 1H, C₃'-H), 5.76 (s, 1H, C₂-H), 6.20 (s, 3H, OCH₃), 6.23 (s, 3H, OCH₃), 6.42 (s, 3H, OCH₃), 7.14 (s, 3H, NCH₃), 9.00 (t, J = 7 Hz, 3H, CH₂CH₃), 9.18 (t, J = 7 Hz, 3H, CH₂CH₃); MS: m/e 718 (M⁺, C₄₄H₅₄N₄O₅)].





Vinblastine amides have been shown to possess important biological activity⁶ and it was of considerable interest to prepare several novel amide derivatives in which ring C of the dihydroindole unit in the bisindole structure lacks the normal oxygen functionality. Biological evaluation of such substances would reveal whether such functions are required to maintain a high level of anti-tumor activity. For this purpose the vindoline amide derivatives described in the accompanying publication¹, were utilized in the preparation of the novel bisindole products 7 and 9 (R = CO₂CH₃).

Reaction of 1 (R = CO₂CH₃) with the unsaturated amide 6 (dichloromethane, trifluoroacetic anhydride, -50°C) provided the desired bisindole 7 (R = CO₂CH₃) in 36% yield [IR: 1720, 1660 cm⁻¹; UV: λ (ε): 267 (23719), 287 (18055), 296 (14868), 312 (9204) nm; CD: λ (Δε): 222 (+14.1), 207.5 (-28.2) nm; PMR: τ 1.93 (s, 1H, NH), 2.50 (m, 1H, C₁₄'-H), 2.82 (m, 3H, C₁₁'-C₁₃'-H), 3.38 (s, 1H, C₁₄-H), 3.64 (s, 1H, C₄-H), 3.97 (s, 1H, C₁₇-H), 4.0-4.5 (m, 3H, C₃'-H, C₆-H, C₇-H), 5.76 (s, 1H, C₂-H), 7.10 (d, J = 6 Hz, 3H, NHCH₃), 7.12 (s, 3H, NCH₃), 8.98 (t, J = 7.5 Hz, 3H, CH₂CH₃), 9.17 (t, J = 7 Hz, 3H, CH₂CH₃); MS: m/e 715 (M⁺, C₄₄H₅₃N₅O₄)].

In a similar manner, the coupling of catharanthine N-oxide (1, R = CO₂CH₃) with the amide 8 afforded the bisindole derivative 9 (R = CO₂CH₃) in 22% yield [IR: 1720, 1660 cm⁻¹; UV: λ (ε): 261 (17637), 287 (12934), 296 (11758), 312 (8466) nm; PMR: τ 1.98 (s, 1H, NH), 2.48 (m, 1H, C₁₄'-H), 2.94 (m, 3H, C₁₁'-C₁₃'-H), 3.40 (s, 1H, C₁₄-H), 3.80 (s, 1H, C₄-H), 4.02 (s, 1H, C₁₇-H), 4.50 (m, 1H, C₃'-H), 5.73 (s, 1H, C₂-H), 6.24 (s, 3H, OCH₃), 6.43 (s, 3H, OCH₃), 7.10 (d, J = 6Hz, 3H, NHCH₃), 7.13 (s, 3H, NCH₃), 9.01 (t, J = 7 Hz, 3H, CH₂CH₃), 9.14 (t, J = 7 Hz, 3H, CH₂CH₃); MS: m/e 717 (M⁺, C₄₄H₅₅N₅O₄)].

The four novel vinblastine derivatives described above are presently undergoing extensive biological evaluation. Results of these experiments will be presented later.

Acknowledgement: Financial aid from the National Research Council of Canada and from Contract N01-CM-23223, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, is gratefully acknowledged. We would also like to thank the Lilly Research Laboratories, Indianapolis, Indiana, for generous supplies of vindoline and catharanthine.

References

1. For Part IX, see J.P. Kutney, K.K. Chan, W.B. Evans, Y. Fujise, T. Honda, F.K. Klein and J.P. de Souza, Heterocycles, 1977, 5,
2. J.P. Kutney, A.H. Ratcliffe, A.M. Treasurywala and S. Wunderly, Heterocycles, 1975, 3, 639.
3. J.P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A.H. Ratcliffe, A.M. Treasurywala and S. Wunderly, Helv. Chim. Acta, 1976, 59, 2858.
4. J.P. Kutney, D.E. Gregonis, R. Imhof, I. Itoh, E. Jahngen, A.I. Scott and W.K. Chan, J. Amer. Chem. Soc., 1975, 97, 5013.
5. Satisfactory elemental analyses and/or high resolution mass measurements were obtained on all compounds reported.
6. M.J. Sweeney, G.J. Cullinan, G.A. Poore and K. Gerzon, Proc. Tenth Annual Meeting, Amer. Soc. Clin. Oncology, 1974, March 15; U.S. Patent 539,681, Chem. Abstr., 1976, 85, 192965t.

Received, 4th February, 1977