STUDIES ON THE SYNTHESIS OF BISINDOLE ALKALOIDS. X[1].

THE SYNTHESIS OF NOVEL VINBLASTINE DERIVATIVES.

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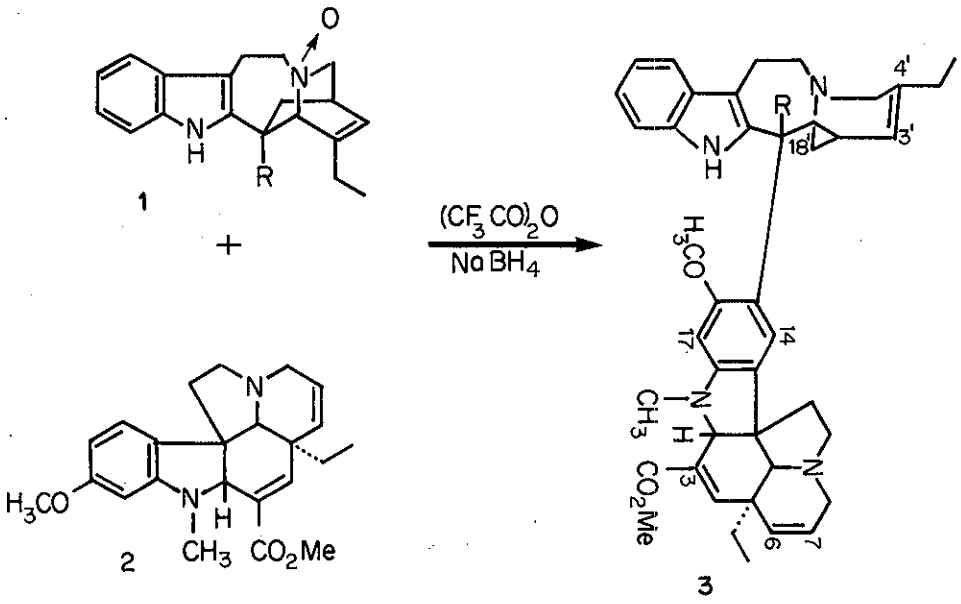
The coupling of catharanthine-N_b-oxide with various novel vindoline derivatives provides a series of novel vinblastine derivatives. These compounds provide an opportunity to evaluate the importance of the functionality in the dihydroindole unit of the bisindole system in terms of anti-tumor activity.

In the accompanying communication[1] 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 = CO_2CH_3), prepared according to our previously described procedure[2,3], with the unsaturated ester 2[1] (*dichloromethane, trifluoroacetic anhydride*, -50°C)[2,3] provided the desired dimer 3 (R = CO_2CH_3) 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, C_{14}'-H), 2.80 (m, 4H, C_4-H and C_{11}'-C_{13}'H), 3.46 (s, 1H, C_{14}-H), 3.98 (s, 1H, C_{17}-H), 4.0-4.4 (m, 3H, C_3'H, C_6-H, C_7-H), 5.76 (s, 1H, C_2-H), 6.22 (s, 6H, 2 x OCH_3), 6.38 (s, 3H, OCH_3), 7.17 (s, 3H, NCH_3), 8.96 (t, J = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 9.20 (t, J = 7.5 Hz, 3H, $CH_2\underline{CH_3}$); MS: m/e 716 (M^+, $C_{44}H_{52}N_4O_5$), 657, 536, 534, 464, 451, 393, 380, 353, 336, 277, 237)]. The points of attachment of the indole and dihydroindole units (C_{15}-C_{18}') as shown in 3, are readily seen from the PMR data (singlets at τ 3.46 and 3.98 for the C_{14} and C_{17} protons in the dihydroindole portion) and the desired natural stereochemistry at C_{18}' is evident from the CD data[4,5].

The synthesis of the bisindole product 5 (R = CO_2CH_3) was achieved by the reaction of 1 (R = CO_2CH_3) with the ester 4[1] 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, C_{14}'-H), 2.90-2.80 (m, 4H, C_4-H and C_{11}'-C_{13}'-H), 3.40 (s, 1H, C_{14}-H), 4.00 (s, 1H, C_{17}-H), 4.48 (d, J = 6 Hz, 1H, C_3'-H), 5.76 (s, 1H, C_2-H), 6.20 (s, 3H, OCH_3), 6.23 (s, 3H, OCH_3), 6.42 (s, 3H, OCH_3), 7.14 (s, 3H, NCH_3), 9.00 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 9.18 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$); MS: m/e 718 (M^+, $C_{44}H_{54}N_4O_5$)].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2
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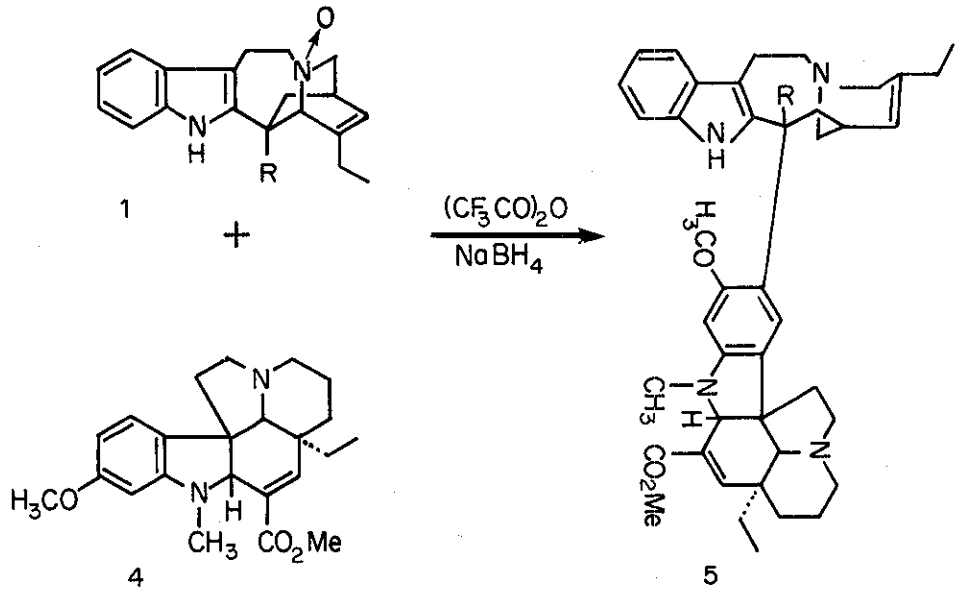
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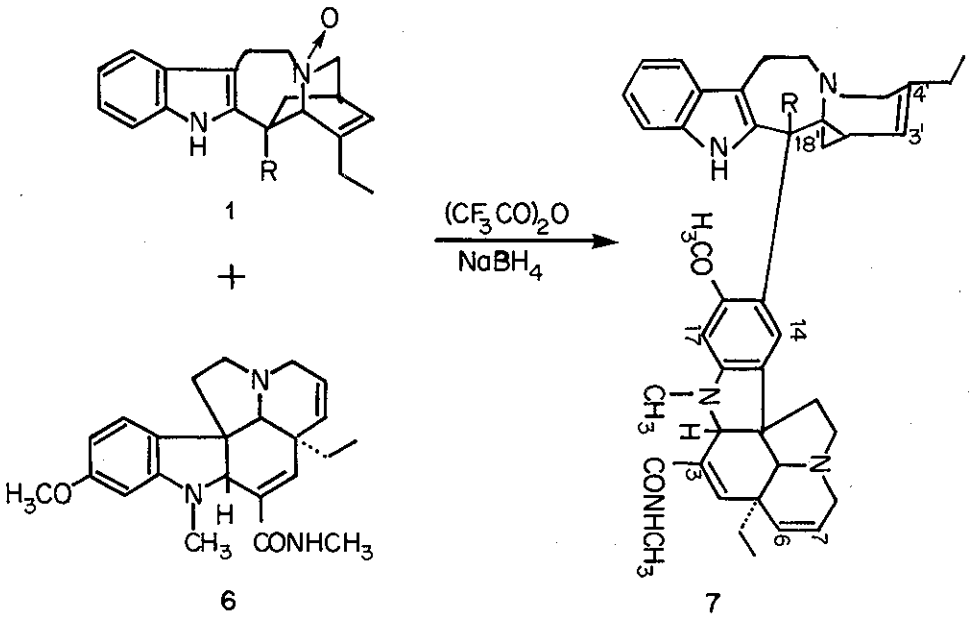
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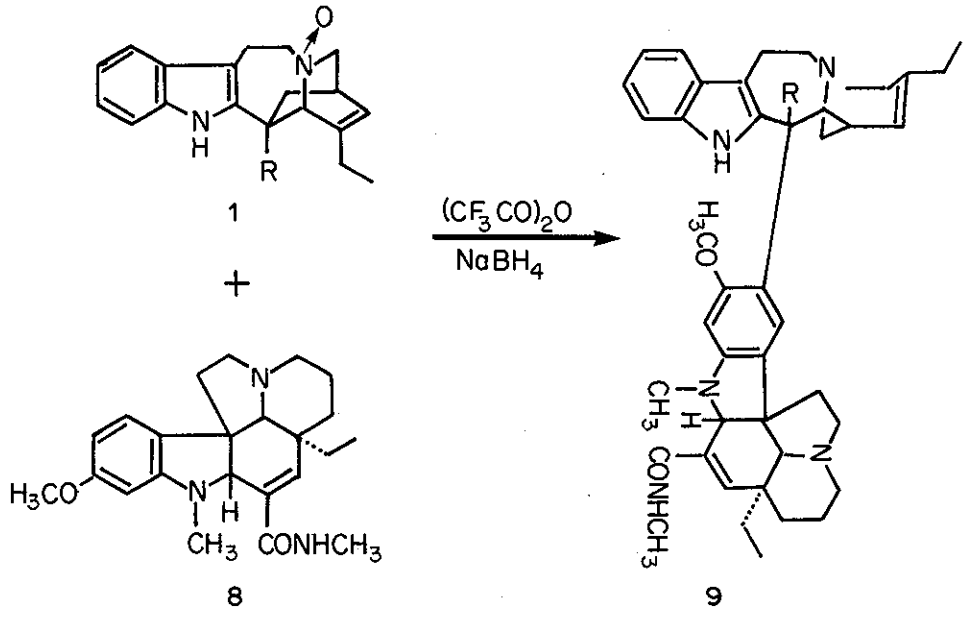
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H_3CO
CH_3 CONHCH$_3$
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$(CF_3CO)_2O$
$NaBH_4$
H_3CO
CONHCH$_3$
9

Vinblastine amides have been shown to possess important biological activity[6] 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 publication[1], were utilized in the preparation of the novel bisindole products 7 and 9 (R = CO_2CH_3).

Reaction of 1 (R = CO_2CH_3) with the unsaturated amide 6 (dichloromethane, trifluoroacetic anhydride, -50°C) provided the desired bisindole 7 (R = CO_2CH_3) 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, $C_{14'}$-H), 2.82 (m, 3H, $C_{11'}$-$C_{13'}$-H), 3.38 (s, 1H, C_{14}-H), 3.64 (s, 1H, C_4-H), 3.97 (s, 1H, C_{17}-H), 4.0-4.5 (m, 3H, $C_{3'}$-H, C_6-H, C_7-H), 5.76 (s, 1H, C_2-H), 7.10 (d, J = 6 Hz, 3H, $NHCH_3$), 7.12 (s, 3H, NCH_3), 8.98 (t, J = 7.5 Hz, 3H, CH_2CH_3), 9.17 (t, J = 7 Hz, 3H, CH_2CH_3); MS: m/e 715 (M^+, $C_{44}H_{53}N_5O_4$)].

In a similar manner, the coupling of catharanthine N-oxide (1, R = CO_2CH_3) with the amide 8 afforded the bisindole derivative 9 (R = CO_2CH_3) 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, $C_{14'}$-H), 2.94 (m, 3H, $C_{11'}$-$C_{13'}$H), 3.40 (s, 1H, C_{14}-H), 3.80 (s, 1H, C_4-H), 4.02 (s, 1H, C_{17}-H), 4.50 (m, 1H, $C_{3'}$-H), 5.73 (s, 1H, C_2-H), 6.24 (s, 3H, OCH_3), 6.43 (s, 3H, OCH_3), 7.10 (d, J = 6Hz, 3H, $NHCH_3$), 7.13 (s, 3H, NCH_3), 9.01 (t, J = 7 Hz, 3H, CH_2CH_3), 9.14 (t, J = 7 Hz, 3H, CH_2CH_3); MS: m/e 717 (M^+, $C_{44}H_{55}N_5O_4$)].

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

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