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COUPLING OF (-)-VINDOLINE WITH (±)-EBURNAMENINE, STRUCTURE AND STEREOCHEMISTRY OF THE DIMERIC PRODUCTS

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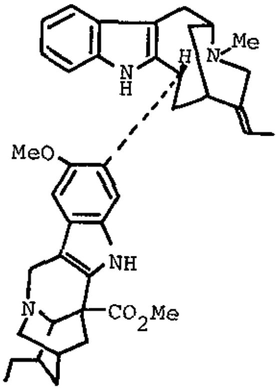
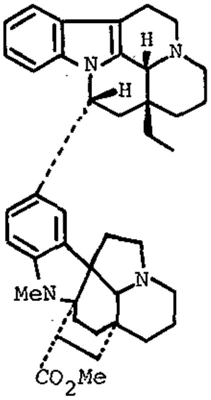
Detailed study of the coupling of (-)-vindoline with (±)-eburnamenine is described.

Although a number of coupling experiments to form the dimeric indole alkaloids, such as voacamine type(1),[1,2] pleiomutine type (2),[3,4] and vinblastine type(3),[5∿19] have been reported, all of the monomeric precursors used, but one exception[5], were optically active with natural configurations. In the exception[5], a



(1)



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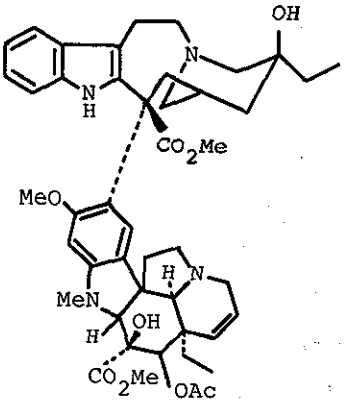
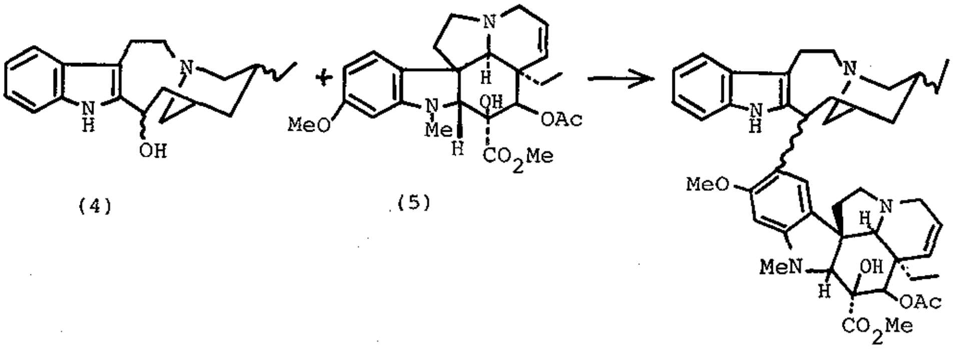


(3)

vinblastine type dimer(6) was claimed to be obtained as a stereoisomeric mixture by a coupling of synthetic (±)-dihydrocleavamine(4) and (-)-vindoline(5), however, no stereochemical assignment has been made on this compound. Since we are interested in the structure and the stereochemistry



(4)

(5)

(6)

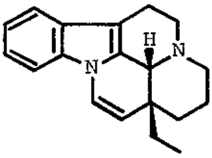
of the dimeric indole alkaloids, especially those of the dimers formed from a coupling of a optically active monomeric precursor with a racemic one, a model coupling experiment using natural (-)-vindoline(5) and synthetic (±)-eburnamenine(7) was carried out.

An equimolar of (-)-vindoline(5)[20] and (±)-eburnamenine(7)[21] was refluxed in 1.5 % methanolic hydrogen chloride[1] for 3 hr under nitrogen to promote dimerization. Upon a chromatographic separation using silica gel, the reaction provided a 77 % total yield of two stereoisomeric dimers in 3:4 ratio which were assigned to 10($[\alpha]_D^{17}$ -196.7°; m.p. 237-238°; ν_{max}^{Nujol} 1730, 1605, 1230, 1038 cm^{-1}; m/e 734(M^+), 575, 467, 282, 252, 240, 214, 210, 198, 197, 180, 149, 135, 122, 121, 107; δ^{CDCl_3} 0.48(3H, t, J=7.5 Hz), 0.86(3H, t, J=7.5 Hz), 2.08(3H, s), 2.80(3H, s), 3.80(3H, s), 3.92(3H, s), 5.25(1H, br.d, J=10 Hz), 5.40(1H, s), 5.50(1H, dd, J=5 and 11 Hz), 5.85(1H, dd, J=4 and 10 Hz), 6.17(1H, s), 6.65(1H, s)) and 11($[\alpha]_D^{17}$-3.5°; m.p. 187-188°; ν_{max}^{Nujol} 1730, 1605, 1220, 1036 cm^{-1}; m/e 734(M^+), 575, 467, 282, 252, 214, 198, 149, 135, 122, 121, 107; δ^{CDCl_3} 0.89(6H, t, J=7.5 Hz), 2.09(3H, s), 2.80(3H, s), 3.83(3H, s), 3.98(3H, s), 5.20(1H, br.d, J=10 Hz), 5.40(1H, s), 5.60(1H, dd, J=5 and 11 Hz), 5.76(1H, dd, J=4 and 10 Hz), 6.24(1H, s), 6.70(1H, s)), respectively.

The point of attachment of the vindoline and the eburnamine units(C_{15}-C_{16}) are concluded from the PMR data which exhibit two singlets due to C_{14} and C_{17} protons of the vindoline portion (δ 6.17 and δ 6.65 in the former and δ 6.24 and δ 6.70 in the latter) and a doublet of doublets due to C_{16} proton of the eburnamine portion(δ 5.50 in the former and δ 5.60 in the latter). Stereochemistry of the attaching point in each of the dimers is also concluded from the PMR data in which C-16 proton of the eburnamine portion gave rise to a doublet of doublets with coupling constants J=5 and 11 Hz(δ 5.50 in the former and δ 5.60 in the latter), respectively, and such splittings are consistent only with axial-equatrial and axial-axial couplings just as observed in the PMR spectrum of eburnamine(8).[3,22]
This observation, therefore, led to the conclusion that each of the dimers must have the alternative one of two structures, (10) and (11), of which C-16 proton in eburnamine portion being

axial in either isomer.

The remaining problem, a determination of the combination of the dimers, was clarified by the following experiments. Treatment of each dimer with tin powder in refluxing 4N hydrochloric acid[3] afforded dihydroeburnamenines[3](9 and its antipode), respectively, which are consisten with each other in all respects except showing the opposite CD curves. Since the product formed from the former showed the same CD curve as that of natural origin (9), the combination as well as the absolute stereochemistry coud be



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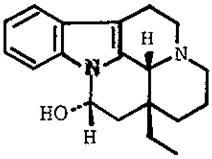

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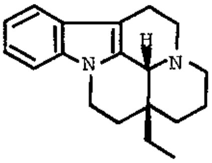

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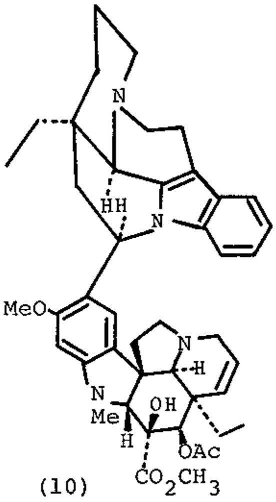

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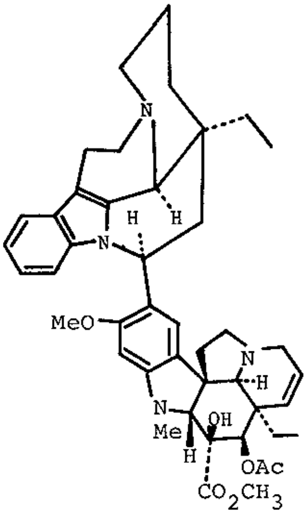

(11)

deduced to be 10 and the latter consequently could be depicted as 11.

Further structural confirmation of the dimers was accomplished by using (-)-vindoline(5) and optical active eburnamenine(7), prepared from naturally occurring (-)-eburnamine(8)[23] by heating with acetic acid[24]. Thus, (-)-vindoline(5) was refluxed with one molar equivalent of optical active eburnamenine (7) in 1.5 % methanolic hydrogen chloride as above expecting to form the dimer(10) as a sole product. As we expected, the dimer (10) was obtained in excellent yield(80 %), but surprisingly the other dimer(11) which could not be allowable to form from the natural-natural combination was also obtained in 5 % yield. This very improvable outcome may account for the presence of an alternative enantiomer in the plant, since a presence of both enantiomers is not rare in the indole alkaloids.[25]

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