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SYNTHESIS OF 2-HYDROXYDENDROBINE AND NOBILINE

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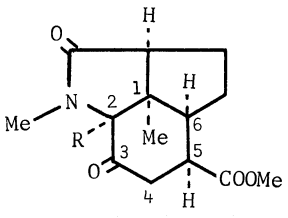
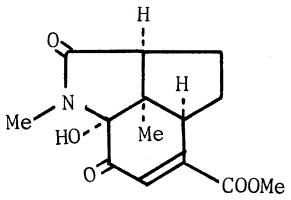
An efficient method of introducing a hydroxy group at the C-2 position of the dendrobine skeleton using a keto lactam (1) is described. By means of this method 2-hydroxydendrobine (9) was synthesized from a keto lactam (4). Further, 2-hydroxydendrobine was transformed into nobiline (10).

A number of Dendrobium alkaloids have so far been isolated and their structures elucidated[1] [e.g., a key representative, dendrobine (8)[2]]. Some of them possess an oxygen function at the C-2 position, as exemplified by 2-hydroxydendrobine (9),[3] nobiline (10),[2e,2f,4] and dendroxine (11).[5] We herein describe an efficient method of hydroxylation at the C-2 position of the dendrobine skeleton using a keto lactam (1), an intermediate of our synthesis of (±)-dendrobine,[6] and application of this method to a keto lactam (4),[7] a degraded product of natural dendrobine,[2] leading to the synthesis of 2-hydroxydendrobine (9) and nobiline (10).[8] Previously, it was shown that the direct introduction of a hydroxy group to the C-2 position without any change of the tetracyclic skeleton such as (8) by oxidation of the pyrrolidine part of dendrobine (8) via the immonium salt could not be effected: with a variety of oxidizing agents an oxygen function was exclusively introduced to the C-14 position.[5,9,10]

Bromination of the keto lactam (1) ($PyHBr_3$ - HCl - THF, room temp., 1.5 hr) followed by the treatment with water afforded a mixture, which was separated by preparative



1 : R = H
2 : R = OH



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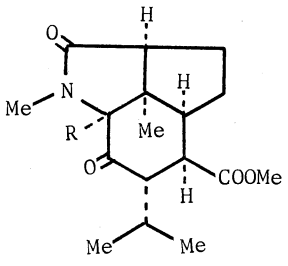
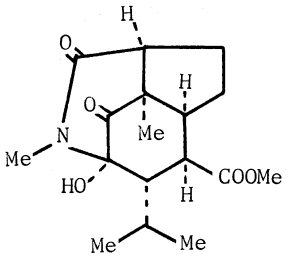


4 : R = H
5 : R = OH



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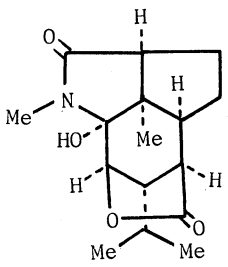
tlc [aluminum oxide, EtOAc - $CHCl_3$ (1:1)] to give the two compounds having a hydroxy group at the C-2 position, (2)[11,22] (amorphous powder, 30%) and (3)[12,22] (amorphous powder, 30%), the latter (3) being converted quantitatively to the former (2) by reduction with zinc (AcOH - DME, 80°, 40 min). The keto lactam (4) prepared from dendrobine was subjected to bromination (Br_2 - dioxane, room temp., 2 days)[13] followed by treatment with water, yielding, after preparative tlc purification [silica gel, EtOAc - $CHCl_3$ (1:1)], a hydroxy compound (5)[14,22] (amorphous powder, 75%) together with the starting compound (4) (20%). In contrast to the hydroxylation procedure described above, the standard method[15] for the base-catalyzed hydroxylation alpha to the keto group, known to be mild enough to avoid rearrangement of the intermediary hydroperoxide could not be applied to the keto lactam (4); under these conditions [O_2 - t-BuOK - $P(OEt)_3$ - DMF - THF, -78°, 20 min], the sole product isolated was a δ-lactam (6)[16] (40%), which was formed by hydroxylation at the C-2 position and the simultaneous rearrangement of the lactam nitrogen from the C-2 position to the C-3 position. It should be noted that the regioselectivity of bromination described above in the tricyclic systems such as (1) depends remarkably on the stereochemistry of substituents on the tricyclic skeleton: in the compound (4) bromination occurs exclusively at C-2 (vide ante), in the compound (1) predominantly at C-2 (vide ante), and in the C-5 epimer of (1) mainly at C-4.[17]



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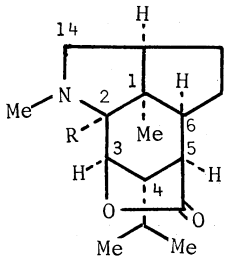
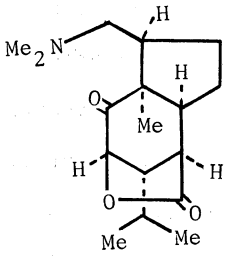
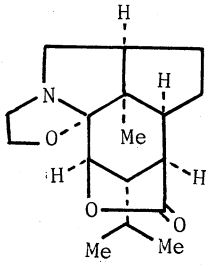


8 : R = H (dendrobine)
9 : R = OH (2-hydroxydendrobine)



10 (nobiline)



11 (dendroxine)

Reduction of (5) with zinc borohydride (DME, 0°, 1 hr) afforded a product, which, without purification, was treated with sodium hydride (DME, 0°, 1 hr) giving a lactone (7)[18,22] [mp 216 - 216.5°, 20% from (5)]. The lactone (7) was shown to be identical with the compound prepared by oxidation of 2-hydroxydendrobine[19] (CrO_3 - Py, 25°, 2 hr). Treatment of the lactone (7) with triethyloxonium tetrafluoroborate[20] (CH_2Cl_2, 25°, 20 hr) and subsequent reaction with sodium borohydride (DME, 0°, 3 hr) provided a mixture of amino compounds complexed with boron[21] together with the starting lactone (7) (75%). For the hydrolysis of the complex, the mixture was treated with acid [ether saturated with HCl - MeOH (1:1), ca. 50°, 1 hr], giving, after

preparative tlc purification [silica gel, $CHCl_3$ - MeOH (9:1)], 2-hydroxydendrobine (9) (ca. 10%) and dendrobine (8) (ca. 10%), identified by spectral and chromatographic comparison.

2-Hydroxydendrobine (9) was treated with formaldehyde and formic acid (100°, 4 hr), yielding nobiline (10)[23] (43%) and dendrobine (8) (47%), identification of which was made by spectral comparison.

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7. The keto lactam (4) (in racemic form) was also the synthetic intermediate of (±)dendrobine.[6]

8. Nobiline is also known as nobilonine.[4] For previous synthesis of nobiline from dendrobine, see ref.4.

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11. νmax ($CHCl_3$) 3450, 1730, 1690 cm^{-1}; δ ($CDCl_3$, 60 MHz) 1.24 (3H, s), 2.59 (3H, s), 3.73 (3H, s), 4.71 (1H, m, OH); m/e 281 (M^+).

12. νmax ($CHCl_3$) 3480, 1725, 1690, 1680 cm^{-1}; δ ($CDCl_3$, 60 MHz) 1.30 (3H, s), 2.59 (3H, s), 3.58 (3H, s), 6.80 (1H, d, J = 1.5 Hz); m/e 279 (M^+).

13. Since the keto lactam (4) was much less reactive than the keto lactam (1), a longer reaction time (4 days) was required for bromination of (4) under conditions employed for conversion of (1) to (2).

14. νmax ($CHCl_3$) 3480, 1735, 1715, 1690 cm^{-1}; δ ($CDCl_3$, 60 MHz) 1.07 (6H, d, J = 7.0 Hz), 1.20 (3H, s), 2.62 (3H, s), 3.74 (3H, s), 4.83 (1H, m, OH); m/e 323 (M^+). Hydroxylation at C-2 of the keto lactam (4) under similar conditions was effected independently by Y. Tsuda (Personal communication from Prof. Y. Tsuda, Showa College of Pharmaceutical Science, Tokyo).

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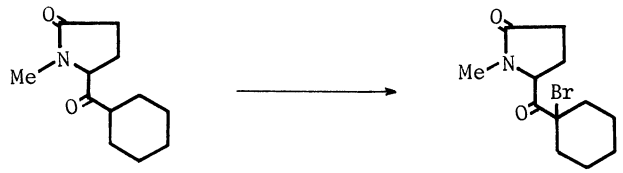
16. νmax ($CHCl_3$) 3520, 1730, 1665 cm^{-1}; δ ($CDCl_3$, 60 MHz) 0.78 (3H, d, J = 6.0 Hz), 0.83 (3H, d, J = 6.0 Hz), 1.16 (3H, s), 3.21 (3H, s), 3.70 (3H, s), 3.87 (1H, br.s, OH); m/e 323 (M^+). This compound was also obtained quantitatively by treating the hydroxy compound (5) with $Al(i\text{-}PrO)_3$ under reflux in toluene.

17. Further, bromination of the simple model compound (A) under the conditions described in the text was examined, affording exclusively a product (B). This finding shows that the regioselectivity of bromination at C-2 (carbon bearing the acylamino group) in (1) and (4) is presumably due to the steric factor(s) of the tricyclic system containing the cis-hydrindan, and is not due to the presence of the acylamino group at C-2.



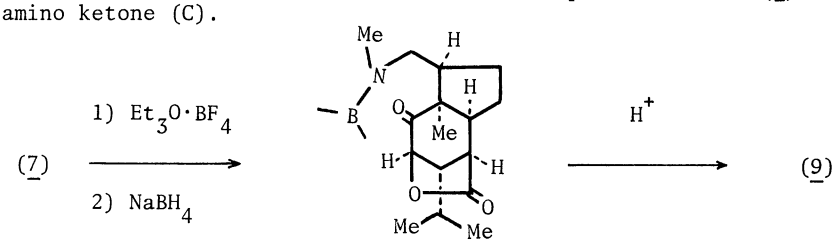
(A) (B)

18. νmax ($CHCl_3$) 3560, 3360, 1790, 1675 cm^{-1}; δ ($CDCl_3$, 60 MHz) 0.97 (3H, d, J = 7.0 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.37 (3H, s), 2.78 (3H, s), 4.58 (1H, d, J = 4.5 Hz); m/e 293 (M^+).

19. We are very grateful to Dr. K. Leander for supplying sample of 2-hydroxydendrobine.

20. R. F. Borch, Tetrahedron Lett., 61 (1968).

21. Although 2-hydroxydendrobine itself exists in the alkanolamine form (9),[3] the boron complex [νmax ($CHCl_3$) 1790 (γ-lactone), 1710 (ketone) cm^{-1}] to be led to (9) would be in the form of the amino ketone (C).



(C)

22. Elemental composition of this compound was verified by high resolution mass spectral determination on the molecular ion.

23. This transformation was also performed independently by S. Brandänge and K. Leander (Unpublished result cited in Ph. D. Dissertation of K. Leander, Univ. Stockholm).

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