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STEREOCHEMISTRY OF INTERMEDIATES IN THE SYNTHESES OF DENDROBIUM ALKALOIDS

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We have carried out the studies on the syntheses of Dendrobium alkaloids and completed the synthesis of dl-dendrobine 1, recently [1] In the present paper the stereochemical aspects of the synthetic intermediates of Dendrobium alkaloids are described

1 Stereochemistry of keto ester acids (4a, 4b) From 7-methoxy-5-methyltetralone-1[2] a mixture of two stereoisomeric ketol acids, 3a and 3b (ca 8 1) was synthesized by eight steps [1] Each compound (3a, 3b) separated[1,3] was converted by three steps to the corresponding keto ester acid, 4a[1] (mp 113-114°) and 4b[4] (mp 140-143°) The stereochemical problem of these keto ester acids was the configuration of the ester group at C-5, which was settled as follows The keto ester acid 4a on treatment with pyridinium bromide perbromide in THF - ether - HCl (room temperature) followed by catalytic reduction (Pd-C/MeOH) gave a keto ester lactone 5a[4,5,6] (amorphous), which was subsequently reduced with $NaBH_4$ (DME, 0°, 1 hr), affording a dilactone 6a[4,5,7] (mp 234-236°) together with a hydroxy ester lactone 7a[4,5,8] (mp 106-106 5°) The dilactone 6a was also obtained by reduction of 5a with $Al(i\text{-}PrO)_3$ (toluene, reflux) Similarly the isomeric keto ester acid 4b was converted to a keto ester lactone 5b[4,5,9] (mp 135-136 5°) under the same conditions as employed in the transformation of 4a to 5a Reduction of 5b with $NaBH_4$ (DME, 0°, 1 hr) gave a hydroxy ester lactone 7b[4,5,10] (mp 133-134°) which was lactonized with $Al(i\text{-}PrO)_3$ (toluene, reflux), yielding a dilactone 6b[4,5,11] (mp 210-211°) In the NMR spectra of two stereoisomeric dilactones which are conformationally rigid, the signal of the C-2 proton is expected to appear at lower field in the isomer possessing cis-relationship between the C-2 hydrogen and the C-3 ethereal oxygen of the lactone ring than in the other isomer having trans-relation, from the inspection of the molecular models,

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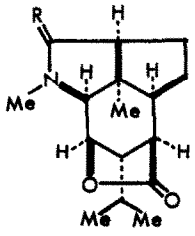
the signal of the C-2 proton was observed at δ 4 44 (1H, d, J = 4 0 Hz) in one isomer (mp 234°) and 4 28 (1H, d, J = 4 4 Hz) in the other isomer (mp 210°) Thus the stereostructures of the dilactones (mp 234° and mp 210°) were deduced to be 6a and 6b, respectively Further the following results were obtained (A) The hydroxy ester lactone 7b with the stereochemistry at C-3 established, on treatment with NaOMe in MeOH (room temperature, 15 hr) was isomerized (~ 50%) to 7a, demonstrating that the configuration of the C-3 hydroxyl of 7a is identical with that of 7b (B) Any dilactone could not be formed from the hydroxy ester lactone 7a under the conditions [Al(i-PrO)$_3$, toluene, reflux] employed for the formation of the dilactone 6b from 7b, indicating the trans-relation between the C-3 hydroxyl and the C-5 ester group in 7a and therefore establishing the configuration of the C-5 ester group of 7a as depicted and in turn that of 7b. The stereostructures of the two dilactones (6a, 6b) coupled with these findings (A and B) made it possible to establish the stereochemistry of the C-5 ester group of the keto ester lactones (5a, 5b), and consequently that of the major keto ester acid (mp 113°) and the minor one (mp 140°) as 4a and 4b, respectively

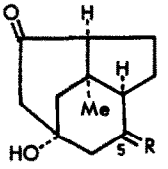
2 Stereochemistry of the intermediates (9a, 11) and keto ester lactams (13a, 13b)
The keto ester acid 4a was originally converted to the two keto ester lactams (13a, 13b) by the following sequence,[1] 4a → imidazolide → hydroxy lactam ester 9a → bromide 11 → keto ester lactams, 13a and 13b In this sequence of reactions it was proved that no epimerization occurred at C-5 during the conversion of 4a to 11 from the following evidence 1) the isomer, 4b on treatment of its imidazolide with aqueous $MeNH_2$ was converted to the keto ester amide 8[4,5,12] (amorphous), which afforded under acidic conditions a hydroxy lactam ester 9b[4] (amorphous), the C-5 epimer of 9a, ii) bromination (pyridinium bromide perbromide - THF, room temperature) of a hydroxy lactam acid 10[13] (amorphous) prepared from 9a gave a corresponding bromide 12 (amorphous) which yielded 11 by diazomethane
The original method[1] for dehydrobromination of 11 consisted of refluxing with NaH in DME followed by neutralization with anhydrous oxalic acid to give two epimers [13a, 13b (ca 5 1)], the major one of which showed the larger Rf value in tlc In contrast to these vigorous conditions[1] which destroyed the asymmetry at C-5 of 11 during the reaction (11 → 13), it was found that the conditions (5% aqueous NaOH - THF, room temperature) mild enough to retain the configuration of the C-5 ester group of 11 could be applied to the conversion of 11 to 13a (~ 70%), both 11 and 12 were converted under the mild conditions described above to a keto acid

lactam 14, which was then led by diazomethane to the epimer (13a) with the larger Rf value in tlc. Thus the stereochemistry of the major isomer and minor one obtained by dehydrobromination of 11 with NaH (DME, reflux) was established to be 13a and 13b, respectively.

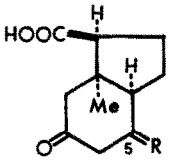
Further independent evidence confirming the configuration of the C-5 ester group of the keto



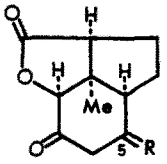
1, R=H_2
2, R=O



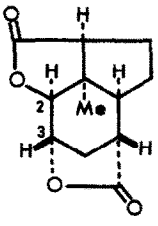
3a, R=
3b, R=



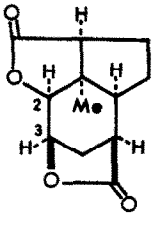
4a, R=
4b, R=



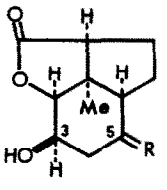
5a, R=
5b, R=



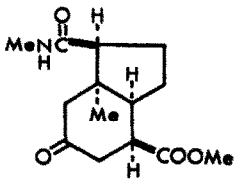
6a



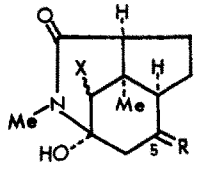
6b



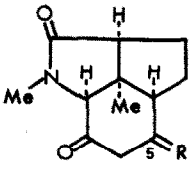
7a, R=
7b, R=



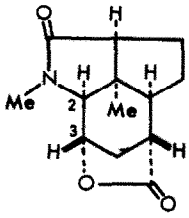
8



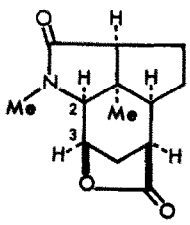
9a, X=H, R=
9b, X=H, R=
10, X=H, R=
11, X=Br, R=
12, X=Br, R= 



13a, R=
13b, R=
14, R=



15a



15b

ester lactams (13a, 13b) was obtained Reduction of 13a and 13b with Al(i-PrO)$_3$ (toluene, reflux) gave the corresponding lactam lactones, 15a[4,5,14] (mp 168-169 5°) and 15b[4,5,15] (amorphous), respectively Since the signal due to the C-2 proton appeared at δ 3 56 (1H, d, J = 4 0 Hz) in the crystalline lactam lactone and 3 28 (1H, d, J = 4.5 Hz)[16] in the amorphous one, the C-2 hydrogen in the crystalline isomer was shown to be cis to the C-3 ethereal oxygen of the lactone ring Based on these NMR spectral data, the stereochemistry of the major isomer of the keto ester lactams was shown to be 13a.

REFERENCES AND FOOTNOTES

1 K Yamada, M Suzuki, Y Hayakawa, K Aoki, H Nakamura, H Nagase, and Y Hirata, J Amer Chem Soc , 94, 8278 (1972)

2 L. Ruzicka and L Sternbach, Helv. Chim Acta, 23, 355 (1940)

3 Separation of two stereoisomers could conveniently performed in the stage of keto ester acids (4a, 4b)

4 Satisfactory elemental analysis and/or high resolution mass spectral data for this compound was obtained

5 The NMR spectrum was taken in $CDCl_3$ at 60 MHz, and the IR spectrum in $CHCl_3$

6 νmax 1783, 1720 cm^{-1}, δ 1 35 (3H, s), 3 72 (3H, s), 4 28 (1H, s), m/e 252 (M^+)

7 νmax 1785 cm^{-1}, δ 1 36 (3H, s), 4 44 (1H, d, J = 4 0 Hz), 5 00 (1H, m), m/e 222 (M^+)

8 νmax 3600-3400, 1775, 1732 cm^{-1}, δ 1 36 (3H, s), 3 74 (3H, s), 4 00 (1H, m), 4 42 (1H, d, J = 3 0 Hz), m/e 254 (M^+)

9 νmax 1785, 1735 cm^{-1}, δ 1 46 (3H, s), 3 73 (3H, s), 4 21 (1H, s), m/e 252 (M^+)

10 νmax 3600-3400, 1778, 1735 cm^{-1}, δ 1 33 (3H, s), 3 70 (3H, s), 3 75 (1H, m), 4 73 (1H, d, J = 3 5 Hz), m/e 254 (M^+)

11 νmax 1788 cm-1, δ 1 40 (3H, s), 4 28 (1H, d, J = 4 4 Hz), 4 90 (1H, m), m/e 222 (M^+)

12 νmax 3460, 1733, 1715, 1668, 1518 cm^{-1}, δ 1 14 (3H, s), 2 80 (3H, d, J = 4 5 Hz), 3 70 (3H, s), ca 5 5 (1H, m), m/e 267 (M^+)

13 It was confirmed that no epimerization occurred at C-5 of 9a during the hydrolysis by the following evidence Hydrolysis (5% aqueous NaOH - THF, room temperature) of 9a gave 10 which regenerated 9a by diazomethane

14 νmax 1785, 1675 cm^{-1}, δ 1 31 (3H, s), 2 83 (3H, s), 3 56 (1H, d, J = 4 0 Hz), 5 00 (1H, m), m/e 235 (M^+)

15 νmax 1790, 1675 cm^{-1}, δ 1 40 (3H, s), 2 85 (3H, s), 3 28 (1H, d, J = 4 5 Hz), 4 87 (1H, m), m/e 235 (M^+)

16 The chemical shift of the signal due to the C-2 proton of oxodendrobine 2[17] was δ 3 28 (1H, d, J = 4 5 Hz) which is the same value as this

17 S Yamamura and Y Hirata, Tetrahedron Lett , 79 (1964), T Onaka, S Kamata, T Maeda, Y Kawazoe, M Natsume, T Okamoto, F Uchimaru, and M Shimizu, Chem Pharm Bull , 12, 506 (1964), Y Inubushi, Y Sasaki, Y Tsuda, B Yasui, T Konita, J Matsumoto, E Katarao, and J Nakano, Tetrahedron, 20, 2007 (1964)