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ON THE CONFIGURATION OF THE C_5-SUBSTITUENTS OF LYCOPODIUM ALKALOIDS, 8-DEOXYSERRATINIDINE, EPIDIHYDROFAWCETTIDINE, SERRATINIDINE, AND DIHYDROFAWCETTIDINE

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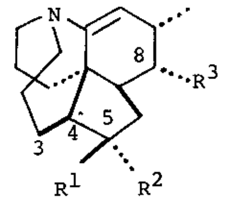
Abstract —— The configuration of the C_5-substituents of 8-deoxyserratinidine, epidihydrofawcettidine, serratinidine, and dihydrofawcettidine was determined as formulas 2, 3, 4, and 5, respectively, by ^{1}H-NMR, Brewster's benzoate rule, and an X-ray analysis of 8-deoxyserratinidine.

In previous papers, we reported the configurational establishment of the C_3-C_4 bond of fawcettidine (1)[1] and the structure elucidation of 8-deoxyserratinidine (2)[2], epidihydrofawcettidine (3)[2], and serratinidine (4)[3]. However, the configuration of the C_5-substituents of the latter three alkaloids had been left to be determined. In this communication, we describe the configurational establishment of the C_5-substituents of these alkaloids and dihydrofawcettidine (5)[3], which is a reduction product of 1 with $NaBH_4$ and is an epimer of 3 with respect to the C_5-hydroxy group.

In the ^{1}H-NMR (60 MHz) spectrum in $CDCl_3$-D_2O, the signals due to a proton geminal to a C_5-substituent were observed at δ 4.07 ($W_{1/2}$=22 Hz) in 2, at δ 3.98 ($W_{1/2}$=10 Hz) in 3, at δ 4.33 ($W_{1/2}$=24 Hz) in 4[4], and at δ 4.17 ($W_{1/2}$=20 Hz) in 5, respectively. The half-band width suggests that the C_5-substituents of 2, 4, and 5 have the same relative configuration. Since 3 and 5 possess the same absolute configuration[2,3] and have an epimeric relationship with respect to the C_5-hydroxy group as mentioned above, the Brewster's benzoate rule[5] was applied



(1) $R^1=R^2=O$, $R^3=H$

(2) $R^1=R^3=H$, $R^2=NHAc$

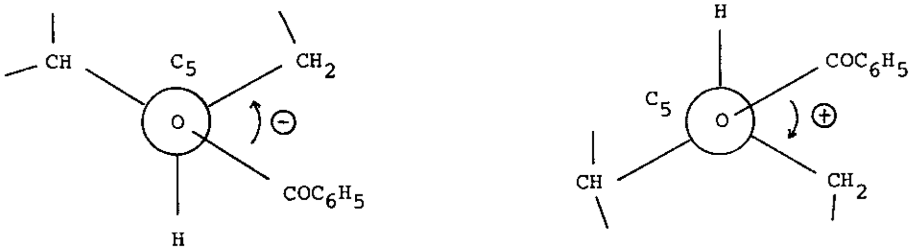
(3) $R^1=OH$, $R^2=R^3=H$

(4) $R^1=H$, $R^2=NHAc$, $R^3=OH$

(5) $R^1=R^3=H$, $R^2=OH$

(6) $R^1=OCOC_6H_5$, $R^2=R^3=H$

(7) $R^1=R^3=H$, $R^2=OCOC_6H_5$



(6) (7)

Chart 1

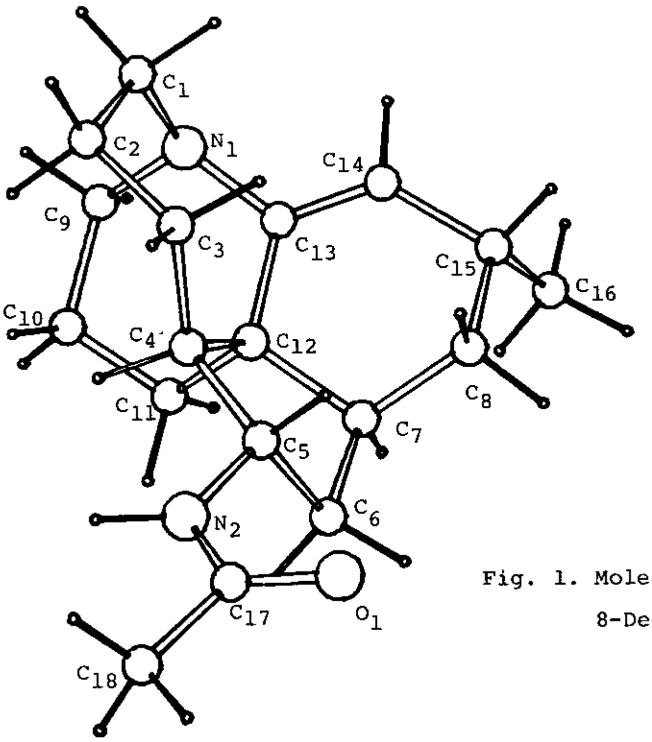


Fig. 1. Molecular Structure of 8-Deoxyserratinidine (2)

in order to assume the configuration of the C_5-substituents of both compounds. Then, 3 and 5 were benzoylated to give benzoylepidihydrofawcettidine (6)[6] and benzoyldihydrofawcettidine (7)[6], respectively. The Brewster's benzoate rule was applied to 3 and 6 $[\Delta[M]_D^{20}-32.3° = [M]_D^{20}+333.5°(\text{benzoate}) - [M]_D^{20}+365.8°(\text{OH})]$, and to 5 and 7 $[\Delta[M]_D^{20}+176.2° = [M]_D^{20}+496.3°(\text{benzoate}) - [M]_D^{20}=320.1°(\text{OH})]$. As can be seen from the Newman's projections of the surroundings of the bond between O and C_5 of 6 and 7 in chart 1, benzoylepidihydrofawcettidine, which shows a negative $\Delta[M]_D$, can be represented by formula 6, and benzoyldihydrofawcettidine, which shows a positive $\Delta[M]_D$, can be represented by formula 7. These assumptions were also supported by the results derived from the benzoate sector rule[7] applied to 6 and 7.[8] Therefore, the stereostructures of 8-deoxyserratinidine, serratinidine, and dihydrofawcettidine can be represented by formulas 2, 4, and 5, respectively, since these three bases possess the same configuration with respect to the C_5-substituent.

Next, in order to confirm these assumptions, 8-deoxyserratinidine (2) was subjected to an X-ray analysis. Compound (2) crystallized from ether in the monoclinic, space group $P2_1$, with two molecules per unit cell of dimensions a=12.783(3), b=9.364(2), c=7.326(2) Å, β=104.96(2)°, Z=2, and Dx=1.131 g/cm^3. A total of 1017 unique reflections having Fo>3σ(Fo) were measured on a Rigaku AFC-5 diffractometer using CuKα radiation. The structure was solved by the direct method using the program MULTAN-78[9] and refined by the full-matrix least-squares method to R=0.066. The molecular structure of 2 so derived is depicted in Fig. 1, proving the above-mentioned assumptions. Consequently, the stereostructures of 8-deoxyserratinidine, epidihydrofawcettidine, serratinidine, dihydrofawcettidine can be definitely represented by formulas 2, 3, 4, and 5, respectively.

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3) H. Ishii, B. Yasui, R. Nishino, T. Harayama, and Y. Inubushi, *Chem. Pharm. Bull.*, 1970, **18**, 1880.

4) In our previous paper[3], the relative configurational establishment of the C_3-C_4 bond and the C_5-NHAc group of serratinidine (4) had been left behind. However, it seems reasonable to assume that the C_3-C_4 bond of 4 possesses the same configuration as that of 1, since fawcettidine (1), the stereostructure of which has been recently determined[1], and 4 were derived from serratinine via the reductive product of the same type of enolate[3](a reductive fission of the C_4-N bond of serratinine).

5) a) J. H. Brewster, *Tetrahedron*, 1961, **13**, 106. b) J. H. Brewster, *J. Amer. Chem. Soc.*, 1959, **81**, 5475, 5483, 5493.

6) Benzoylepidihydrofawcettidine (6) : m/e 351 (M^+). IR ($CHCl_3$), ν 1710, 1660, 1602, 1586. ^1H-NMR (60 MHz in $CDCl_3$), δ 1.01 (3H, d, J=7 Hz, $>CH-CH_3$), 5.08 (1H, m, $W_{1/2}$=9 Hz, -CH-OCO), 5.53 (1H, d, J=3 Hz, olefinic proton), 7.33-8.20 (5H, m, aromatic protons). $[\alpha]_D^{20}$=+95.0° (c=1.0) in EtOH. Benzoyldihydrofawcettidine (7) : m/e 351 (M^+). IR ($CHCl_3$), ν 1705, 1658, 1600, 1581. ^1H-NMR (60 MHz in $CDCl_3$), δ 1.00 (3H, d, J=7 Hz, $>CH-CH_3$), 5.33 (1H, m, $W_{1/2}$=20 Hz, -CH-OCO), 5.55 (1H, d, J=2 Hz, olefinic proton), 7.34-8.20 (5H, m, aromatic protons). $[\alpha]_D^{20}$=+141.4° (c=0.99) in EtOH.

7) N. Harada, H. Ohashi, and K. Nakanishi, *J. Amer. Chem. Soc.*, 1968, **90**, 7349.

8) The CD data [θ](nm) in MeOH. 3 : +43800 (231) ($c=1.74\times10^{-3}M$), 5 : +56900 (233) ($c=1.86\times10^{-3}M$), 6 : +47900 (230) ($c=0.99\times10^{-3}M$), 7 : +56400 (235) ($c=0.99\times10^{-3}M$). Details will be discussed in a full paper.

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