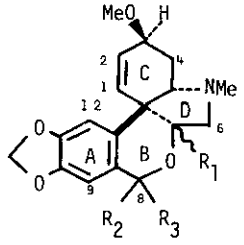
TRANSFORMATION OF TAZETTINE TO PRETAZETTINE

Shigeru Kobayashi* and Masaru Kihara
Faculty of Pharmaceutical Sciences, University of Tokushima
Shomachi, Tokushima 770, Japan
Tetsuro Shingu
School of Pharmacy, Kobe Gakuin University
Ikawadani, Tarumi-ku, Kobe 673, Japan

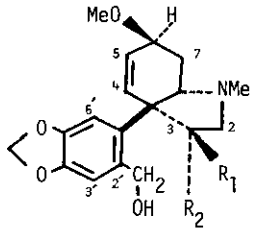
Abstract —— Transformation of tazettine (2) to pretazettine (1) having antileukemic activity is described. This transformation confirmed the stereochemistry of pretazettine (1).

Pretazettine (1)[1], an unstable base of Amaryllidaceae alkaloids, is interesting because of its antileukemic activity[2]. The base was found[1] to be easily converted to tazettine (2)[3], one of the most widely-distributed alkaloids in this family, during extraction of 1 from these plants in the usual way. In this paper we report the transformation of 2 to 1, via 3-epitazettadiol (3), whose structure was confirmed by its cyclization to deoxypretazettine (4).

Reduction of 2 with lithium aluminum hydride gave tazettadiol (5)[4,5] (62.7%) and a new minor product (13.5%), 3-epitazettadiol (3), $C_{18}H_{23}NO_5$, mp 139-141°, $[\alpha]_D^{20}$ +95.0°(EtOH), ν_{max}(KBr) 3440(OH), 1620(C=C), δ ($CDCl_3$) 6.96(1H, s, H-3'), 6.67(1H, s, H-6'), 5.90(2H, s, OCH_2O), 5.89(1H, m, H-5), 5.73(1H, td, J_{4-5}=11, J_{4-6}=2, J_{4-7a}=2 Hz, H-4), 4.84 and 4.72(each 1H, d, J=12 Hz, AB type of $ArCH_2OH$), 4.36(1H, m, H-3), 3.93(1H, m, H-6), 3.37(3H, s, OCH_3), and 2.31(3H, s, NCH_3).



1: R_1= ◄H, R_2=OH, R_3=H
2: R_1= ····OH, R_2=R_3=H
4: R_1= ◄H, R_2=R_3=H
6: R_1= ····H, R_2=R_3=H
7: R_1= ◄H, R_2,R_3=O
8: R_1= ····H, R_2=OH, R_3=H
9: R_1= ····H, R_2,R_3=O



3: R_1=H, R_2=OH
5: R_1=OH, R_2=H

The formations of 5 and 3 indicate that the hydride reduction of 2 proceeds via the keto-alcohol intermediate, which, however, has never been detected. Addition of AlH_4^- nucleophile to the carbonyl function of the intermediate with stereochemical restraints of the β-bonded phenyl group gives 5 as a major product, and that from the hindered side gives 3 as a minor product. The configuration of C-3 in 5 and 3 was also confirmed by cyclization reactions of these compounds.

Cyclization of 3 with 3% sulfuric acid (at 100° for 1.5 hr) gave deoxypretazettine (4), (44.4%), mp 112-113°, $[\alpha]_D^{21}$ +307.0°(EtOH), δ ($CDCl_3$), 6.77(1H, s, H-12), 6.48(1H, s, H-9), 5.89(2H, s, OCH_2O), 3.86(1H, dd, $J_{6a-6\alpha}$=11, $J_{6a-6\beta}$=8 Hz, H-6a), 3.41(3H, s, OCH_3), 2.94(1H, dd, $J_{6\alpha-6a}$=11, $J_{6\alpha-6\beta}$=10 Hz, H-6α), 2.92(1H, m, H-4a), 2.62(1H, dd, $J_{6\beta-6\alpha}$=10, $J_{6\beta-6a}$=8 Hz, H-6β), and 2.48(3H, s, NCH_3). The ORD and CD curves of 4 are similar to those of 1 (see Fig. 1 and 2) and are significantly different from those of 2 and deoxytazettine (6)[4,5] (a similar cyclization product of 5). Furthermore, 1 and 4 show positive Cotton effects centered at 290 nm, but 2 and 6 show negative Cotton effects. These facts indicate that 6 has the same configuration as 2, while 4 is epimeric at C-6a and has the same configuration as pretazettine 1.

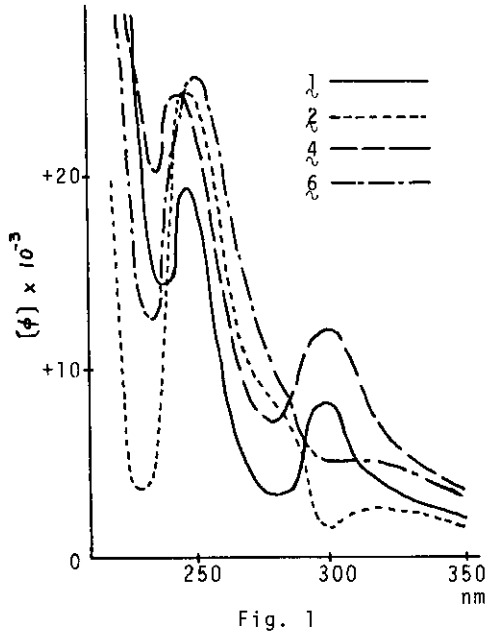


Fig. 1

ORD Spectra of 1, 2, 4, and 6 in MeOH

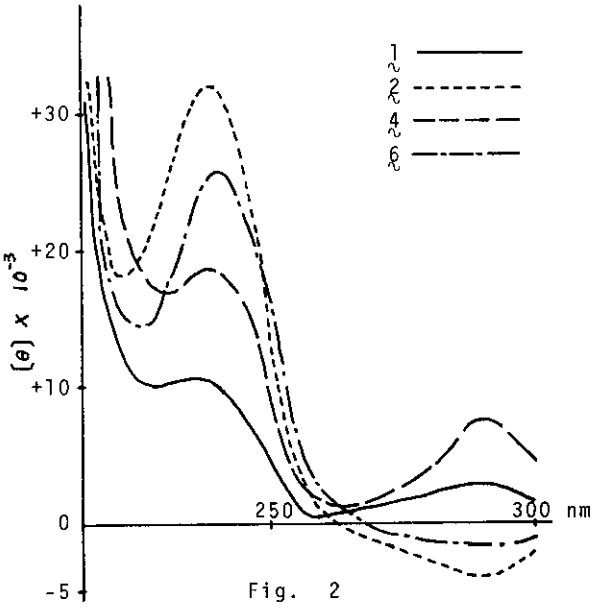


Fig. 2

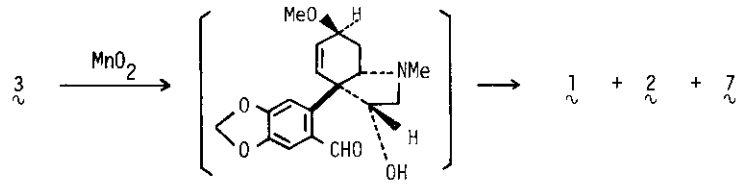
CD Spectra of 1, 2, 4, and 6 in MeOH

These conclusions are also supported by nmr studies of 4 and 6: the fact that the coupling constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in 4 are larger than those[4] in 6 (see Table 1) indicates a B/D trans configuration in 4 and a B/D cis configuration in 6. Therefore, the configuration at C-3 of the diols 5 and 3 are S- and R-configurations, respectively, since no epimerization occurred during cyclization of 3 to 4 : protonation at the benzyl hydroxy group in 3 and 5 gave the corresponding benzyl cations, on which nucliophilic attack of the secondary hydroxyl function at C-3 afforded 4 and 6, respectively. The above conclusion was supported by conversion of 3 to pretazettine (1).

Table 1. Coupling Constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in 1, 4, and 6-9 (Hz).

	1	4	7	6	8	9
$J_{6a-6\alpha}$	11	11	11	5	5	4
$J_{6a-6\beta}$	8	8	8	3	1	1

Oxidation of 3 with manganese dioxide (in $CHCl_3$ at room temperature) gave three products, pretazettine (1)[1,6] [amorphous, 29.5%, HCl salt mp 223-224°, picrate mp 203-204°(dec.)], 3-epimacronine (7)[1c,7] (mp 125-127°, 21.6%), and 2[3,4,6] (mp 202-203°, 9.4%). The bases 1 and 2 were identified by comparison with authentic samples[4,6]. Compound 7 is an oxidation product of 1, whereas 2 should be a secondary product from 1.



On the other hand, oxidation of 5 with manganese dioxide gave 6a-epipretazettine (8)[1b,7] (amorphous, 35.2%), $[\alpha]_D^{27}$ +234.0°(EtOH), and a new product, 6a-epi-3-epimacronine (9)(mp 105-108°, 20.4%), $C_{18}H_{19}NO_5$, ν_{max}(KBr) 1720(C=O), 1620(C=C), δ ($CDCl_3$) 7.54(1H, s, H-9), 6.87(1H, s, H-12), 6.21(1H, td, J_{2-1}=11, J_{2-3}=2, J_{2-4}=1 Hz, H-2), 6.02(2H, s, OCH_2O), 5.36(1H, td, J_{1-2}=11, J_{1-3}=2, J_{1-4a}=2 Hz, H-1),

4.69(1H, dd, $J_{6a-6\alpha}$=4, $J_{6a-6\beta}$=1 Hz, H-6a), 4.14(1H, m, H-3), 3.52(1H, dd, $J_{6\alpha-6\beta}$=12, $J_{6\alpha-6a}$=4 Hz, H-6α), 3.44(3H, s, OCH_3), 2.98(1H, m, H-4a), 2.86(1H, dd, $J_{6\beta-6\alpha}$=12, $J_{6\beta-6a}$=1 Hz, H-6β), 2.50(3H, s, NCH_3), 2.24(1H, m, H-4α), and 1.51(1H, td, $J_{4\beta-4\alpha}$=14, $J_{4\beta-3}$=10, $J_{4\beta-4a}$=2 Hz, H-4β). As shown in Table 1, the coupling constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in these oxidation products (1, 7, 8, and 9) indicate that the configurations at C-6a in 1 and 7 are the same as that (R-configuration) at C-3 in 3.

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7. Each compound was identified by comparison of its physical data with those in the literature.

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