

TRANSFORMATION OF TAZETTINE TO PRETAZETTINE

Shigeru Kobayashi* and Masaru Kihara

Faculty of Pharmaceutical Sciences, University of Tokushima

Shomachi, Tokushima 770, Japan

Tetsuro Shingu

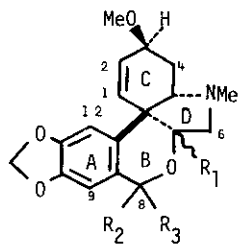
School of Pharmacy, Kobe Gakuin University

Ikawadani, Tarumi-ku, Kobe 673, Japan

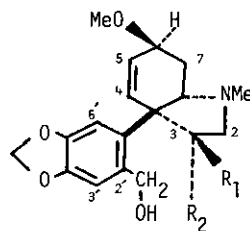
Abstract — Transformation of tazettine (2) to pretazettine (1) having antileukemic activity is described. This transformation confirmed the stereochemistry of pretazettine (1).

Pretazettine (1), an unstable base of Amaryllidaceae alkaloids, is interesting because of its antileukemic activity². The base was found¹ to be easily converted to tazettine (2), 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), C₁₈H₂₃NO₅, mp 139-141°, [α]_D²⁰ +95.0° (EtOH), ν_{max} (KBr) 3440 (OH), 1620 (C=C), δ (CDCl₃) 6.96 (1H, s, H-3'), 6.67 (1H, s, H-6'), 5.90 (2H, s, OCH₂O), 5.89 (1H, m, H-5), 5.73 (1H, td, J₄₋₅=11, J₄₋₆=2, J_{4-7a}=2 Hz, H-4), 4.84 and 4.72 (each 1H, d, J=12 Hz, AB type of ArCH₂OH), 4.36 (1H, m, H-3), 3.93 (1H, m, H-6), 3.37 (3H, s, OCH₃), and 2.31 (3H, s, NCH₃).



- 1: R₁ = H, R₂ = OH, R₃ = H
- 2: R₁ = OH, R₂ = R₃ = H
- 4: R₁ = H, R₂ = R₃ = H
- 6: R₁ = H, R₂ = R₃ = H
- 7: R₁ = H, R₂, R₃ = 0
- 8: R₁ = H, R₂ = OH, R₃ = H
- 9: R₁ = H, R₂, R₃ = 0



- 3: R₁ = H, R₂ = OH
- 5: R₁ = OH, R₂ = H

The formations of $\mathfrak{5}$ and $\mathfrak{3}$ indicate that the hydride reduction of $\mathfrak{2}$ 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 $\mathfrak{5}$ as a major product, and that from the hindered side gives $\mathfrak{3}$ as a minor product. The configuration of C-3 in $\mathfrak{5}$ and $\mathfrak{3}$ was also confirmed by cyclization reactions of these compounds.

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

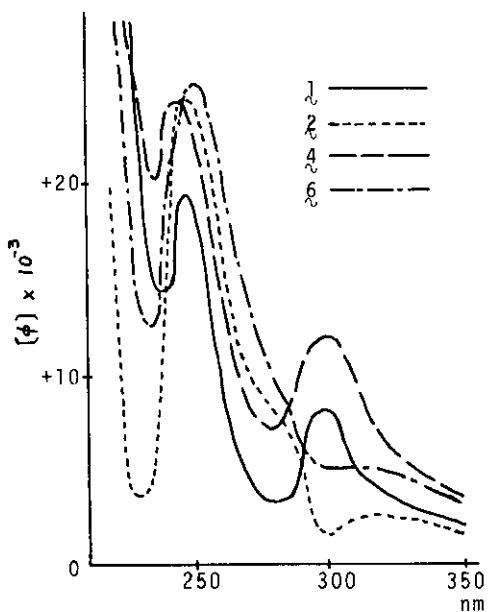


Fig. 1
ORD Spectra of $\mathfrak{1}$, $\mathfrak{2}$, $\mathfrak{4}$, and $\mathfrak{6}$ in MeOH

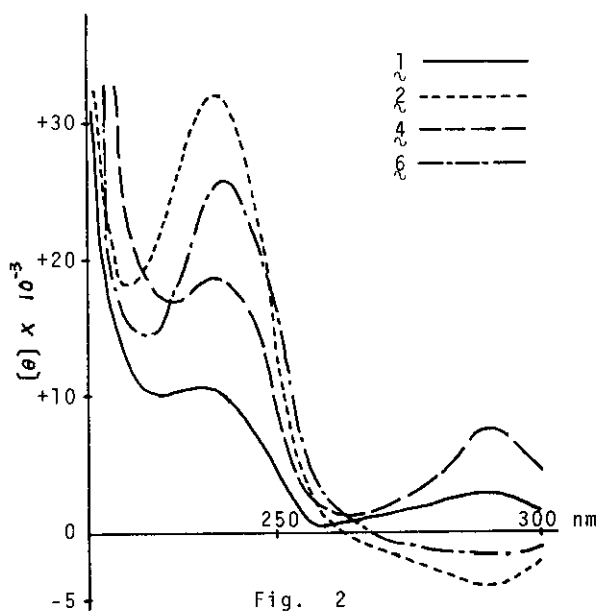


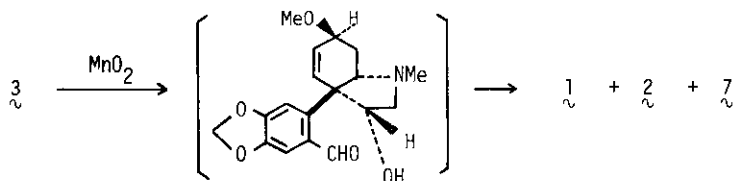
Fig. 2
CD Spectra of $\mathfrak{1}$, $\mathfrak{2}$, $\mathfrak{4}$, and $\mathfrak{6}$ in MeOH

These conclusions are also supported by nmr studies of $\underline{4}$ and $\underline{6}$: the fact that the coupling constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in $\underline{4}$ are larger than those⁴ in $\underline{6}$ (see Table 1) indicates a B/D trans configuration in $\underline{4}$ and a B/D cis configuration in $\underline{6}$. Therefore, the configuration at C-3 of the diols $\underline{5}$ and $\underline{3}$ are S- and R-configurations, respectively, since no epimerization occurred during cyclization of $\underline{3}$ to $\underline{4}$: protonation at the benzyl hydroxy group in $\underline{3}$ and $\underline{5}$ gave the corresponding benzyl cations, on which nucleophilic attack of the secondary hydroxyl function at C-3 afforded $\underline{4}$ and $\underline{6}$, respectively. The above conclusion was supported by conversion of $\underline{3}$ to pretazettine ($\underline{1}$).

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

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

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



On the other hand, oxidation of $\underline{5}$ with manganese dioxide gave 6a-epipretazettine ($\underline{8}$)^{1b,7} (amorphous, 35.2%), $[\alpha]_D^{27} +234.0^\circ$ (EtOH), and a new product, 6a-epi-3-epimacronine ($\underline{9}$) (mp 105-108°, 20.4%), $\text{C}_{18}\text{H}_{19}\text{NO}_5$, 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, $J_{6\alpha-6\alpha}=4, J_{6\alpha-6\beta}=1$ Hz, H-6a), 4.14 (1H, m, H-3), 3.52 (1H, dd, $J_{6\alpha-6\beta}=12, J_{6\alpha-6\alpha}=4$ Hz, H-6 α), 3.44 (3H, s, OCH₃), 2.98 (1H, m, H-4a), 2.86 (1H, dd, $J_{6\beta-6\alpha}=12, J_{6\beta-6\alpha}=1$ Hz, H-6 β), 2.50 (3H, s, NCH₃), 2.24 (1H, m, H-4 α), and 1.51 (1H, td, $J_{4\beta-4\alpha}=14, J_{4\beta-3}=10, J_{4\beta-4\alpha}=2$ Hz, H-4 β). As shown in Table 1, the coupling constants of $J_{6\alpha-6\alpha}$ and $J_{6\alpha-6\beta}$ 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.

ACKNOWLEDGMENTS

We wish to express our thanks to President S. Uyeo, Shizuoka College of Pharmacy, for encouragement and to Assistant Professor K. Shingu, Osaka University, for helpful advice and measurement of CD spectra.

REFERENCES AND FOOTNOTES

1. (a) W.C. Wildman and D.T. Bailey, J. Am. Chem. Soc., 1967, 89, 5514; (b) idem, ibid., 1969, 91, 150; (c) idem, J. Org. Chem., 1968, 33, 3749.
2. (a) E. Furusawa, N. Suzuki, S. Furusawa, and J.Y.B. Lee, Proc. Soc. Exp. Biol. Med., 1975, 149, 771; (b) E. Furusawa, N. Suzuki, S. Tani, S. Furusawa, G.Y. Ishioka, and J. Motobu, ibid., 1973, 143, 33; (c) E. Furusawa, S. Furusawa, S. Tani, H. Irie, K. Kitamura, and W.C. Wildman, Chem. Pharm. Bull. (Tokyo), 1976, 24, 336.
3. This alkaloid has been reviewed by J.W. Cooks and J.D. London, and W.C. Wildman in R.H.F. Manske "The Alkaloids", Vol. II (1952), VI (1960), and XI (1968), Academic Press, Inc., New York.
4. S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, Chem. Pharm. Bull. (Tokyo), 1976, 24, 716.
5. T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, J. Chem. Soc., 1956, 4749.
6. S. Kobayashi, S. Takeda, H. Ishikawa, H. Matsumoto, M. Kihara, T. Shingu, A. Numata, and S. Uyeo, Chem. Pharm. Bull. (Tokyo), 1976, 24, 1537.
7. Each compound was identified by comparison of its physical data with those in the literature.

Received, 21st September, 1979