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Transformation of Tazettine to Pretazettine¹⁾

SHIGERU KOBAYASHI, MASARU KIHARA,^{2a)} TETSURO SHINGU,^{2b)} and KEIJI SHINGU^{2c)}

*Faculty of Pharmaceutical Sciences, Tokushima University,^{2a)} School of Pharmacy,
Kobe Gakuin University,^{2b)} and Faculty of Science, Osaka University^{2c)}*

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Pretazettine (1), which shows antileukemic activity, was obtained by conversion of tazettine (2) to 3-epitazettadiol (3) [whose structure was confirmed by its cyclization to deoxypretazettine (4)], followed by manganese dioxide oxidation of 3. The transformation of 2 to 1 confirmed the stereochemistry of pretazettine (1).

Keywords—pretazettine; tazettine; 3-epitazettadiol; deoxypretazettine; deoxy-pretazettine neomethine; antileukemic activity; stereochemistry; manganese dioxide; Amaryllidaceae; NMR

We have previously reported^{3,4)} the isolation of pretazettine (1),⁵⁾ which shows anti-leukemic activity,⁶⁾ from the bulbs of *Zephyranthes carinate* HERB. and *Lycoris radiata* HERB. (Amaryllidaceae).

This paper describes the transformation of tazettine (2),⁷⁾ which was found⁵⁾ to be an extraction artifact of 1, to pretazettine (1), via 3-epitazettadiol (3), whose stereochemistry was confirmed both by its cyclization to deoxypretazettine (4) and by conversion of 4 to deoxypretazettine neomethine (5).

Reduction of tazettine (2) with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) gave two crystalline isomers, tazettadiol (6)⁸⁻¹⁰⁾ (62.7%) and a new minor product (13.5%), 3-epitazettadiol (3), C₁₈H₂₃NO₅, mp 139—141°, [α]_D²⁰ +95.0° (*c*=1.0, ethanol). The structure of 3 was deduced from spectral data. The infrared (IR) spectrum showed absorptions due to a hydroxyl group at 3440 cm⁻¹ and a double bond at 1620 cm⁻¹. The nuclear magnetic resonance (NMR) spectrum given in Table I was very similar to that of 6 and the assignment of the following signals was achieved by a nuclear magnetic double resonance (NMDR) experiment. First, monitoring the line (δ 6.67) of C-6'-H gave an NOE (intramolecular nuclear Overhauser effect) peak at δ 2.71, since irradiation at δ 2.71 (C-7a-H) gave a 17% NOE increment in the signal of C-6'-H. This irradiation at δ 2.71 reduced a multiplet at δ 5.73 (C-4-H)

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to a double doublet (the long-range coupling disappeared). Irradiation at δ 4.84 (C-7'-H) gave a 20% NOE increment in the signal (δ 6.96) of C-3'-H. Irradiation at δ 4.36 (C-3-H) reduced a double doublet at δ 2.37 of C-2-H β to a doublet.

The following mechanism has been suggested to account for formation of both **3** and **6** on hydride reduction of **2** (see Chart 2): addition of the AlH_4^- nucleophile (with the stereo-

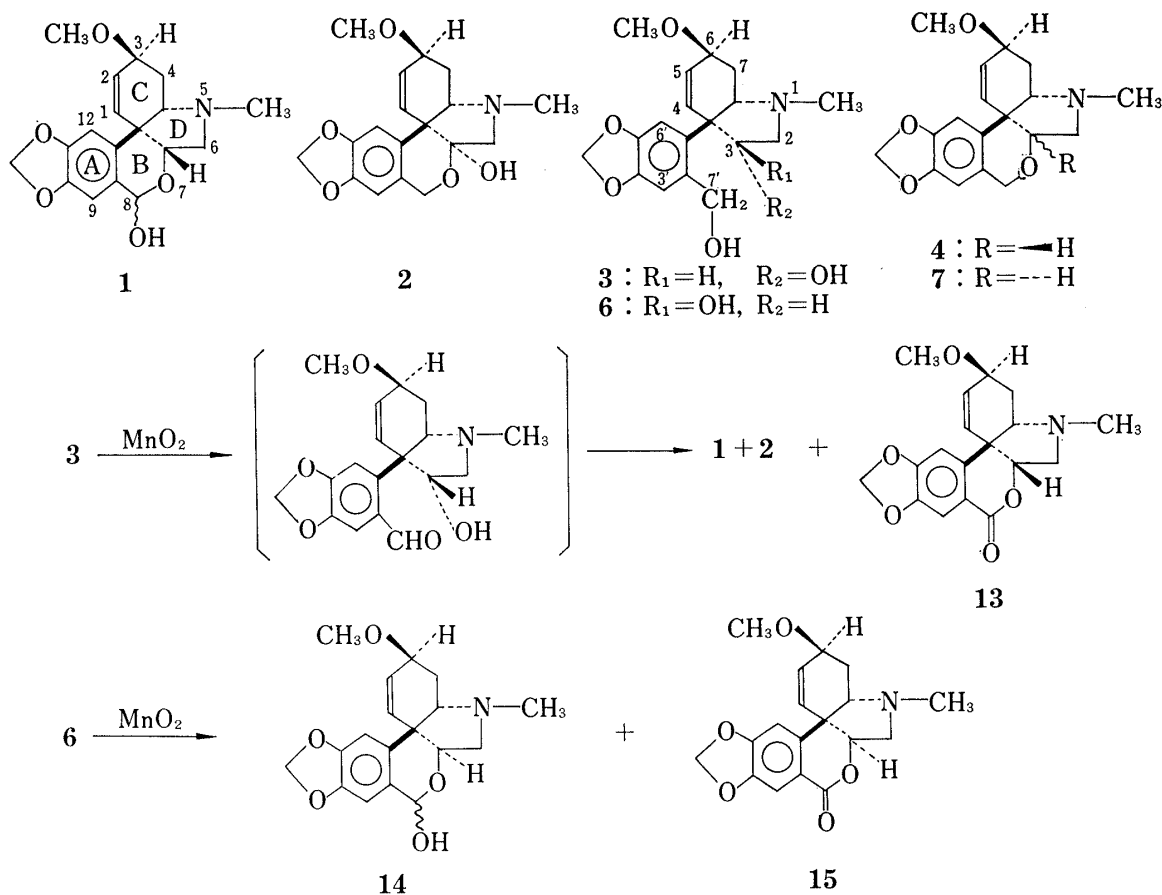


Chart 1

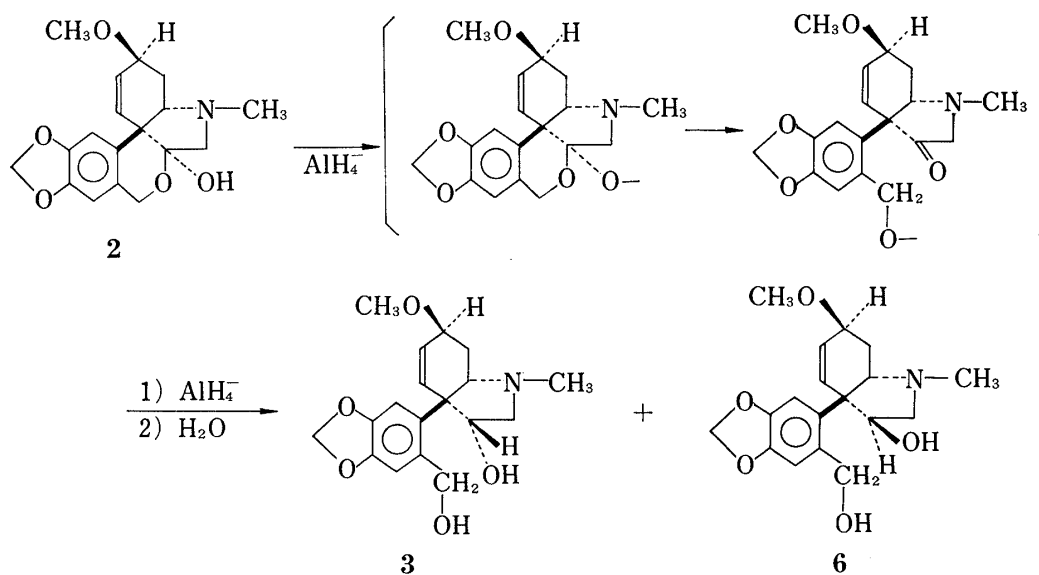


Chart 2

TABLE I. NMR Data for 3-Epipretazettadiol (3) and Tazettadiol (6) (CDCl₃, δ)^{a)}

Compd.	C-6'-H	C-3'-H	C-4-H	C-5-H	OCH ₂ O	C-7'H ₂	C-6-H	C-3-H
3	6.67	6.96	5.73 (m, $J_{4-5}=11$, $J_{4-6}=2$, $J_{4-7\alpha}=2$)	5.94 (m, $J_{5-4}=11$)	5.90	4.84 (d, $J=12$) 4.72 (d, $J=12$)	3.93 (m, $J_{6-7\beta}=10$, $J_{6-7\alpha}=5$)	4.36 (dd, $J_{3-2\beta}=6$, $J_{3-2\alpha}=1$)
6 ^{b)}	6.79	6.87	5.80 (br s)	5.80 (br s)	5.92	4.78 (d, $J=12$) 4.54 (d, $J=12$)	3.89 (m, $J_{6-7\beta}=10$, $J_{6-7\alpha}=6$)	4.36 (dd, $J_{3-2\alpha}=6$, $J_{3-2\beta}=5$)

Compd.	C-2		OCH ₃	NCH ₃	C-7a-H	C-7	
	H α	H β				H α	H β
3	2.96 (dd, $J_{2\alpha-2\beta}=10$, $J_{2\alpha-3}=1$)	2.37 (dd, $J_{2\beta-2\alpha}=10$, $J_{2\beta-3}=6$)	3.37	2.31	2.71 (m)	c)	1.72 (m, $J_{7\beta-7\alpha}=14$, $J_{7\beta-6}=10$, $J_{7\beta-7\alpha}=2$)
6 ^{b)}	3.62 (dd, $J_{2\alpha-2\beta}=11$, $J_{2\alpha-3}=6$)	2.23 (dd, $J_{2\beta-2\alpha}=11$, $J_{2\beta-3}=5$)	3.33	2.42	3.08 (m)	2.41 (m, $J_{7\alpha-7\beta}=13$, $J_{7\alpha-6}=6$, $J_{7\alpha-7\alpha}=2$)	1.78 (m, $J_{7\beta-7\alpha}=13$, $J_{7\beta-6}=10$)

a) All signals are singlets except where otherwise indicated in parentheses.

b) See Ref. 9.

c) Obscured signal.

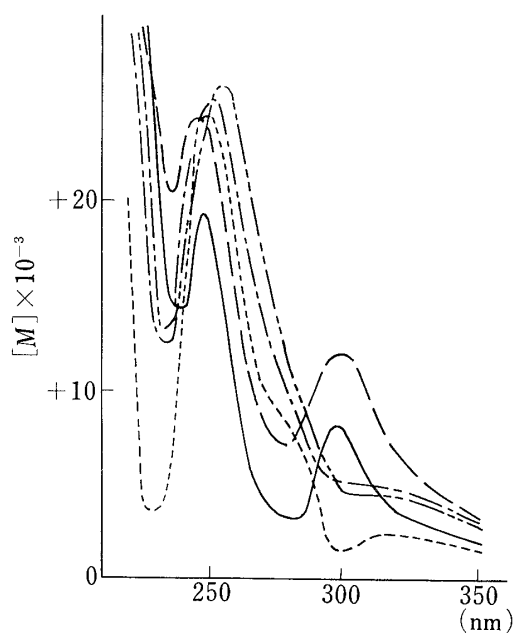


Fig. 1. ORD Spectra of 1, 2, 4, 7, and 14 in MeOH

1: ———, 2: ·····, 4: - - - - ,
7: - · - · - , 14: - - - - - .

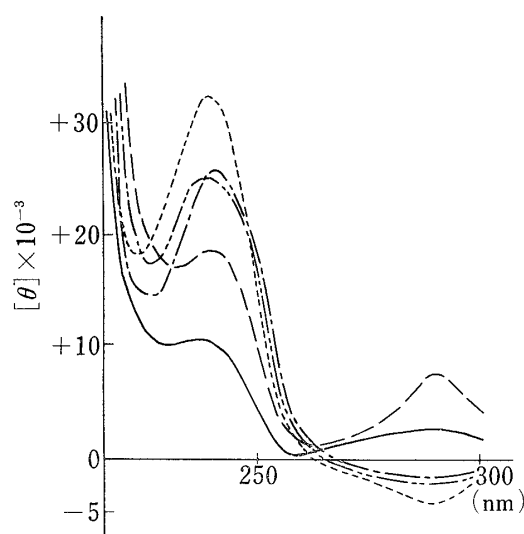


Fig. 2. CD Spectra of 1, 2, 4, 7, and 14 in MeOH

1: ———, 2: ·····, 4: - - - - ,
7: - · - · - , 14: - - - - - .

TABLE II. NMR Data for Pretazettine and Related Compounds (CDCl₃, δ)^{a)}

Compd.	C-12-H	C-9-H	C-2-H ^{b)}	C-1-H ^{c)}	OCH ₂ O	C-8 H ₂ (or H)	C-3-H	C-6a-H ^{d)}
1	6.74	6.83	5.86 (m)	5.50 (m, 11, 2, 2)	5.89	6.07	4.16 (m)	4.32 (dd)
2 ^{h)}	6.84	6.48	6.12 (m)	5.61 (m)	5.88	4.97(d) 4.62(d)	4.06 (m)	
4	6.77	6.48	5.87 (m)	5.63 (m, 11, 2, 2)	5.89	4.99	4.14 (m)	3.86 (dd)
7 ^{h)}	6.91	6.50	6.02 (m, 10, 2, 2)	5.38 (m, 10, 2, 2)	5.88	4.59 (br s)	4.03 (m)	4.00 (dd)
13	6.74	7.50	5.97 (m)	5.46 (m, 11, 2, 2)	6.03		4.16 (m)	4.47 (dd)
14	6.88	6.73	6.07 (m)	5.34 (m, 11, 2, 2)	5.89	5.83 ⁱ⁾ 5.76	4.16 (m)	4.40 (dd)
15	6.87	7.54	6.21 (m, 11, 2, 1)	5.36 (m, 11, 2, 2)	6.02		4.14 (m)	4.69 (dd)

compd.	C-6		OCH ₃	NCH ₃	C-4a-H	C-4	
	H _α ^{e)}	H _β ^{f)}				H _α	H _β ^{g)}
1	2.97 (dd, 11, 10)	2.63 (dd, 8, 10)	3.41	2.48	2.93	2.47 (m)	1.71 (m, 14, 10, 2)
2 ^{h)}	3.29 (d, 10)	2.67 (d, 10)	3.45	2.40	2.86 (m)	2.22 (m)	1.61 (m, 13, 10, 2)
4	2.94 (dd, 11, 10)	2.62 (dd, 8, 10)	3.41	2.48	2.92 (m)	<i>j)</i>	1.77 (m, 14, 9, 2)
7 ^{h)}	3.43 (dd, 5, 11)	2.51 (dd, 3, 11)	3.43	2.39	2.64 (m)	2.24 (m)	1.70 (m, 13, 10, 3)
13	3.18 (dd, 11, 10)	2.79 (dd, 8, 10)	3.41	2.52	3.12 (m)	<i>j)</i>	1.70 (m, 13, 10, 2)
14	3.49 (dd, 5, 12)	2.56 (dd, 1, 12)	3.44	2.47	2.84 (m)	<i>j)</i>	1.68 (m, 14, 10, 3)
15	3.52 (dd, 4, 12)	2.86 (dd, 1, 12)	3.44	2.50	2.98 (m)	2.24 (m)	1.51 (m, 14, 10, 2)

- a) All signals are singlets unless otherwise indicated in parentheses.
b) The numerical values in parentheses are J_{2-1} , J_{2-3} , and J_{2-4} , respectively, as Hz value.
c) The numerical values in parentheses are J_{1-2} , J_{1-3} , and J_{1-4a} , respectively.
d) The coupling constants are given in Table III.
e) The numerical values in parentheses are $J_{6\alpha-6a}$ and $J_{6\alpha-6\beta}$, respectively.
f) The numerical values in parentheses are $J_{6\beta-6a}$ and $J_{6\beta-6\alpha}$, respectively.
g) The numerical values in parentheses are $J_{4\beta-4a}$, $J_{4\beta-3}$, and $J_{4\beta-4b}$, respectively.
h) See Ref. 9.
i) See Ref. 5b.
j) Obscured signals.

TABLE III. Coupling Constant $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in 1, 4, 7, and 13–15 (Hz)

	1	4	13	7	14	15
$J_{6a-6\alpha}$	11	11	11	5	5	4
$J_{6a-6\beta}$	8	8	8	3	1	1

chemical restraints of the β -bonded phenyl group) to a carbonyl function in a keto-alkoxide intermediate derived from an alkoxide of 2, gives 6 as a major product, while addition from the hindered side gives 3 as a minor product. This configuration of C-3 in 3 and 6 was also established by a cyclization reaction of these compounds.

A cyclization product, deoxypretazettine (4) (44.4%), $C_{18}H_{21}NO_4$, mp 112–113°, was obtained when the diol (3) was treated with 3% sulfuric acid in the same way as for deoxytazettine (7).^{8,9} The chemical shifts of 4 are given in Table II. The stereochemistry of 4 was clearly characterized by the following spectroscopic features: both its optical rotatory dispersion (ORD) and circular dichroism (CD) spectra, having positive Cotton effects centered at 290 nm, are similar to those of 1, but different from those of 2 and 7, which have negative Cotton effects (see Figs. 1 and 2). Furthermore, as shown in Table III, the coupling constants $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in 4 are larger than those in 7. These findings indicate that 4, as well as 1, has a B/D *trans* configuration and is an epimer of 7 at C-6a, while 7 has the same configuration as 2 and a B/D *cis* configuration. On the basis of these conclusions, the diols 3 and 6 can be assigned the *R*- and *S*-configuration, respectively, at C-3, since no epimerization was observed during cyclization of 3 to 4: nucleophilic attack of the secondary hydroxyl function in 3 or 6 on the benzyl cation derived from 3 or 6 by protonation at its benzyl hydroxyl group gave the cyclization product 4 or 7.

The above conclusion regarding the stereochemistry of 4 was also supported by conversion of 4 to deoxypretazettine neomethine (5) [an enantiomer of deoxytazettine neomethine (8)],^{8,9,11} *via* deoxypretazettine methine (9) [an enantiomer of deoxytazettine methine (10)].^{8,9} The

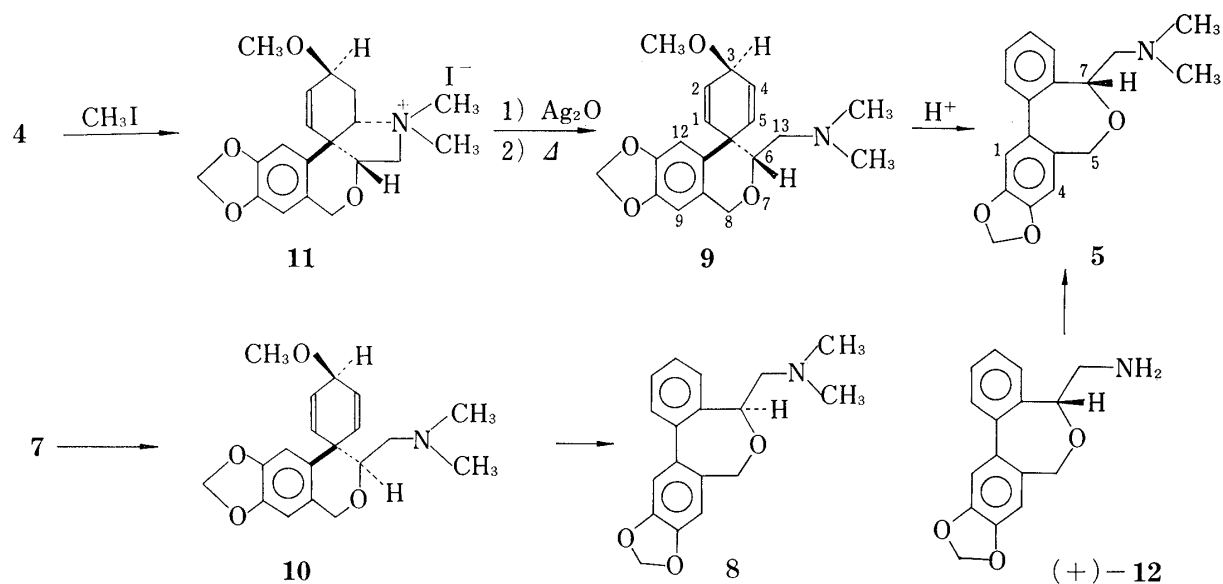
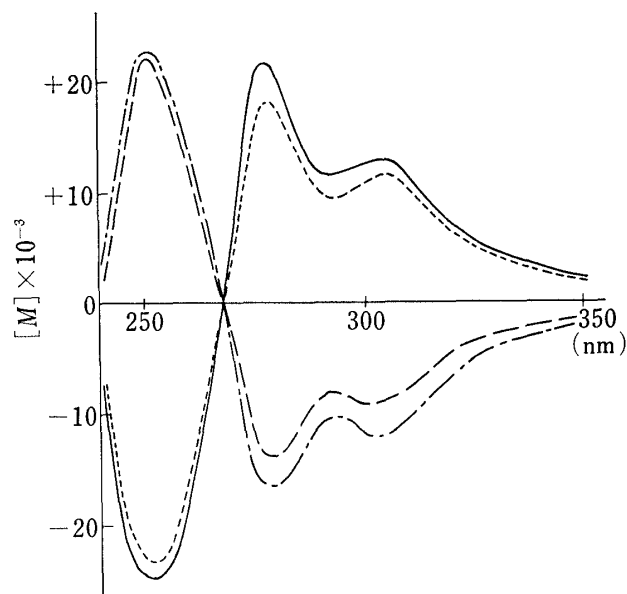
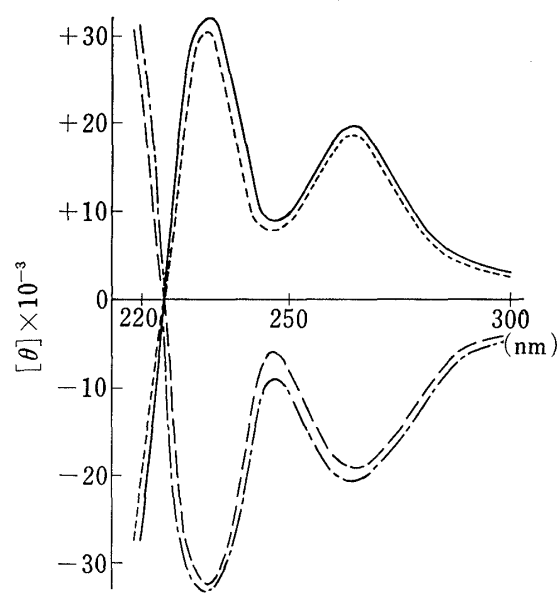


Chart 3

- 11) Warnhoff reported that the configuration at C-6a in 7 would be unaffected during the degradation of 7 to 8 and especially during the conversion of 10 to 8 [E.W. Warnhoff, "Molecular Rearrangement," Vol. 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N.Y., 1964, p. 851].

Fig. 3. ORD Spectra of **5** and **8** in MeOH

5 from **9**: ———, **5** from (+)-**12**: - - - - -,
8 from **10**: - · - · - ·, **8** from (-)-**12**: · · · · ·.

Fig. 4. CD Spectra of **5** and **8** in MeOH

5 from **9**: ———, **5** from (+)-**12**: - - - - -,
8 from **10**: - · - · - ·, **8** from (-)-**12**: · · · · ·.

methine (**9**), prepared by Hofmann degradation of the methiodide (**11**) of **4**, showed $[\alpha]_D^{25} +65.7^\circ$ ($c=1.41$, ethanol), while **10** showed $[\alpha]_D^{25} -64.2^\circ$ (ethanol).⁸⁾ The NMR spectrum of **9** was found to be identical with that of **10**. Rearrangement of **9** with hydrochloric acid gave an amorphous neomethine (**5**), $C_{18}H_{19}NO_3$, $[\alpha]_D^{25} +39.1^\circ$ ($c=0.64$, ethanol). This neomethine was characterized by means of its NMR spectrum (see "Experimental"), which is identical with that of **8**.

On the other hand, the structure of this compound from the natural source was confirmed by synthesis of **5** from (+)-7-aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c,e*]oxepin [(+)-**12**], which was obtained by resolution of the corresponding racemic compound [(±)-**12**]⁹⁾ with di-*p*-toluoyl-*L*-tartaric acid. Eschweiler-Clarke methylation of (+)-**12** gave 7-dimethylaminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c,e*]oxepin, $[\alpha]_D^{25} +37.1^\circ$ ($c=0.7$, ethanol), which was found to be identical with the neomethine (**5**) obtained from **4** by comparison of their NMR, ORD, and CD spectra (see Figs. 3 and 4). The specific rotations, ORD, and CD spectra of **5** and **8** are equal in magnitude though opposite in sign or direction, as shown in Figs. 3 and 4. Therefore, the neomethine (**5**) is an optical antipode of **8** and has the *R*-configuration at C-7, since the *R*-configuration at C-6a in **4** would be unaffected during the degradation of **4** to **9**.¹¹⁾ This conclusion also supports the finding that **3** has the *R*-configuration at C-3. On the basis of these results, we attempted to convert the diol **3** to pretazettine (**1**).

Oxidation of **3** in chloroform with manganese dioxide at room temperature gave three products, pretazettine (**1**)³⁻⁵⁾ (amorphous) (29.5%), 3-epimacronine (**13**)^{5c)} (21.6%), mp 125—127°, and tazettine (**2**)⁷⁾ (9.4%), mp 202—203°. These products were characterized by means of their NMR spectra, as listed in Table II. The base **1** was crystallized as its hydrochloride, mp 223—224° (dec.), $C_{18}H_{21}NO_5 \cdot HCl$, and picrate, mp 202—203°, which were identical with those of authentic samples of **1** by direct comparison. The base **13** is a further oxidation product of **1**, while **2** appears to be an extraction artifact of **1**.

Similar oxidation of the diol **6** gave 6a-epipretazettine (**14**)^{5b)} (amorphous) (35.2%) and a new product 6a-epi-3-epimacronine (**15**) (20.4%), mp 105—108°, $C_{18}H_{19}NO_5$. The structures of the two products were determined by NMR spectroscopy (see Table II). On the basis of the coupling constants $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in these oxidation products, it is concluded that **1** and **13** have the same *R*-configuration at C-6a as that of **3** at C-3, while **14** and **15** have the *S*-con-

figuration at C-6a (see Table III).

NMR Spectra of Pretazettine (1) and Related Compounds

R-Type compounds (such as **1** and **4**) having the *R*-configuration at C-6a, were distinguished from *S*-type compounds (such as **7** and **14**) having the *S*-configuration at C-6a, by NMR spectroscopic evidence. First, a clear difference in the coupling constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ between these two types of compound was observed, as mentioned above. Secondly, the signals (δ 2.94—2.97) of C-6-H α in the *R*-type compounds (**1** and **4**) appeared at higher field than those (δ 3.43—3.49) of the *S*-type compounds (**14** and **7**), indicating that α -protons at C-6 in the former are more shielded by the double bond at C-1 than those in the latter. For the same reason, the diols **3** and **6** were concluded to be *R*- and *S*-type compounds, respectively, since the signal of C-2-H α (which corresponds to C-6-H α in four-ring-system compounds) of **3** and **6** appeared at δ 2.96 and 3.62, respectively. Thirdly, irradiation of the signals of C-6a-H in the *S*-type compounds (**7**, **14**, and **15**) gave NOE increments (7, 8, and 5%, respectively) in the signals of C-1-H, but this was not the case in the *R*-type compounds. In contrast, since the spatial relation of C-1-H to the 7-oxygen is 1,3-diaxial-like in the *R*-type compounds, the signals of C-1-H in **1** and **4** appeared at lower field than those of the *S*-type compounds (**14** and **7**, respectively) (see Table II). The chemical shifts of C-2-H and C-12-H in the *R*-type compounds (**1**, **4**, and **13**) appeared at higher field than the corresponding signals of the *S*-type compounds (**14**, **7**, and **15**, respectively).

Irradiation of the signals of C-4-H β in **4** and **13** (*R*-type compounds) and in **7** and **15** (*S*-type compounds) gave NOE increments (10, 10, 11, and 8%, respectively) in the signals of C-12-H. This indicates that the spatial relation of ring A to ring C is very similar in the two types of compounds, and that ring C in these compounds has a half-chair conformation, as in **1** and **2**.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi model EPI-G2 for IR spectra, a Shimadzu model UV-200 for UV spectra, a Yanagimoto model OR-50 for optical rotations, a JASCO model ORD/UV-5 for ORD spectra, a JASCO model J-40C for CD spectra, and a JEOL model JNM-PS-100 or a Hitachi model R-22 for NMR spectra, using TMS as an internal standard. The plates used for preparative thin-layer chromatography (PLC) were coated with aluminum oxide (Merck, GF₂₅₄) and silica gel (Kieselgel, PF₂₅₄ Merck).

Lithium Aluminum Hydride Reduction of Tazettine (2)—A mixture of **2** (1.985 g), dry THF (65 ml), and LAH (750 mg) was stirred at room temperature for 10 hr. After addition of CHCl₃ (30 ml) and H₂O (3 ml), the mixture was extracted with CHCl₃. The extract was dried over Na₂SO₄ and concentrated to give an oil (2.2 g), which was triturated with acetone to afford **6** (1.137 g) as white needles, mp 114—118° (lit.⁹ mp 117—119°). This compound was identical with a sample of **6**⁹ by direct comparison. The mother liquor separated from **6** was subjected to PLC using Al₂O₃—[benzene—acetone (4:1)]. Elution of materials of *Rf* 0.05—0.19 with CHCl₃—MeOH—acetone (1:1:1) gave an oil (391 mg), which was triturated with acetone—ether to afford **3** (270 mg, 13.5%) as white prisms, mp 139—141°. *Anal.* Calcd for C₁₈H₂₃NO₅: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.81; H, 6.98; N, 4.20. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 288 (3.55), 242 (3.77). Elution of materials of *Rf* 0.35—0.57 with the same solvents gave additional **6** (116 mg, total 1.253 g, 62.7%).

Deoxypretazettine (4)—A solution of **3** (19 mg) in 3% H₂SO₄ (3 ml) was heated at 100° for 1.5 hr. The reaction mixture was washed with ether, made basic with Na₂CO₃, dried, and concentrated *in vacuo* to give an oil (16 mg). The oil was subjected to PLC using Al₂O₃—[benzene—acetone (4:1)]. Elution of materials of *Rf* 0.69—0.83 with CHCl₃—MeOH—acetone (1:1:1) gave **4** (8 mg, 44.4%), mp 112—113° (from ether). $[\alpha]_D^{25} +307.0^\circ$ ($c=0.6$, EtOH). *Anal.* Calcd for C₁₈H₂₁NO₄: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.76; H, 6.75; N, 4.41. IR ν_{\max}^{KBr} cm⁻¹: 1620 (C=C). UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 290 (3.63), 241 (3.74). ORD ($c=0.0105$, MeOH) $[\text{M}]^{20}$ (nm): +12000° (298) (peak), +7180° (279) (trough), +24600° (242) (peak), +20400° (236) (trough), +29400° (225). CD ($c=0.0097$, MeOH) $[\theta]^{23}$ (nm): +4550 (300), +7790 (290), +974 (263), +18810 (238), +16860 (231), +34650 (220).

Deoxypretazettine Methiodide (11)—A solution of **4** (27 mg) and methyl iodide (1 g) in MeOH (2 ml) was refluxed for 3 hr. Work-up in the usual way gave **11** (30 mg, 76.9%) as white needles, mp 237—238° (dec.) (from acetone). *Anal.* Calcd for C₁₉H₂₄INO₄: C, 49.90; H, 5.29; N, 3.06. Found: C, 49.50; H, 5.18; N, 2.91.

Deoxypretazettine Methine (9)—A mixture of **11** (35 mg) in H₂O (3 ml) and Ag₂O (from 85 mg of AgNO₃ and excess 5% NaOH) was stirred at room temperature for 1 hr. The filtrate was evaporated to dryness

under reduced pressure and the residue was heated in a vacuum at 100° for 30 min. Work-up in the usual way gave **9** (22 mg, 88.0%) as an oil. NMR (CDCl₃) δ : 6.69 (1H, s, C-12-H), 6.44 (1H, s, C-9-H), 6.16—5.68 (4H, m, C-1, 2, 4, and 5-H), 5.87 (2H, s, OCH₂O), 4.81 (2H, s, C-8H₂), 4.38 (1H, br s, C-3-H), 3.65 (1H, dd, $J_{6-13l}=8$, $J_{6-13h}=2$ Hz, C-6-H), 3.44 (3H, s, OCH₃), 2.42 [1H, dd, $J_{13l-13h}=13$, $J_{13l-6}=8$ Hz, C-13-H (lower)], 2.28 [6H, s, N(CH₃)₂], 2.20 (1H, dd, $J_{13h-13l}=13$, $J_{13h-6}=2$ Hz, C-13-H (higher)]. These NMR spectral data are consistent with those of deoxytazettine methine (**10**).⁹

Resolution of (\pm)-7-Aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c,e*]oxepin [(\pm)-12**] with Di-*p*-toluoyl-L-tartaric Acid**—A solution of (\pm)-**12** (162 mg) and di-*p*-toluoyl-L-tartaric acid (257 mg) in MeOH (1 ml) was left to stand at room temperature overnight to give the tartrate (58 mg) as white needles, mp 194—195° (dec.) (from MeOH). This salt was dissolved in H₂O (10 ml), made basic with 10% NaOH, and extracted with CHCl₃. Work-up in the usual way gave an oil (28 mg), which was triturated with ether to afford (+)-**12**, mp 121—123° (from ether). $[\alpha]_D^{25} +39.0^\circ$ ($c=1.0$, EtOH). NMR (CDCl₃) δ : 6.99 (1H, s, C-1-H), 6.86 (1H, s, C-4-H), 5.99 (2H, s, OCH₂O), 4.40 and 4.08 (each 1H, d, $J=12$ Hz, AB-type of C-5H₂), 4.22 (1H, m, C-7-H), 3.06 (2H, m, C-13H₂), 2.02 (2H, br s, NH₂). This spectrum was identical with that of (–)-**12**.⁹

Deoxypretazettine Neomethine (5)—(i) From **9**: A solution of **9** (21 mg) in 5% HCl (3 ml) was stirred at room temperature for 1 hr. The reaction mixture was extracted with ether, dried, and concentrated to give 6-phenylpiperonyl alcohol (3 mg), mp 97—98°, (lit.⁸) mp 102—104°. Anal. Calcd for C₁₄H₁₂O₃: C, 73.67; H, 5.30. Found: C, 73.65; H, 5.22. NMR (CDCl₃) δ : 7.36 (5H, m, aromatic H), 7.03 (1H, s, C-2-H or C-5-H), 6.76 (1H, s, C-5-H or C-2-H), 5.99 (2H, s, OCH₂O), 4.49 (2H, s, ArCH₂OH). The acidic aqueous solution separated from the ethereal extract was made basic with Na₂CO₃ and extracted with ether. The extract gave **5** (10 mg, 52.6%) as an oil. NMR (CDCl₃) δ : 7.42 (4H, s, aromatic H), 7.00 (1H, s, C-1-H), 6.87 (1H, s, C-4-H), 6.00 (2H, s, OCH₂O), 4.38 (1H, dd, $J_{7-12h}=5$, $J_{7-12l}=8$ Hz, C-7-H), 4.36 and 4.04 (each 1H, d, $J=12$ Hz, AB-type of C-5H₂), 2.92 [1H, dd, $J_{12l-12h}=12$, $J_{12l-7}=8$ Hz, C-12-H (lower)], 2.58 [1H, dd, $J_{12l-12h}=12$, $J_{12h-7}=5$ Hz, C-12-H (higher)], 2.23 [6H, s, N(CH₃)₂]. This NMR spectrum was identical with that of **8**.⁹ ORD ($c=0.0045$, MeOH) $[\text{M}]^{27}$ (nm): +3300° (350), +11900° (306) (peak), +11200° (290) (trough), +22400° (278) (peak), 0° (268), –22400° (253) (trough), –1980° (240). CD ($c=0.0102$, MeOH) $[\theta]^{25}$ (nm): +4390 (290), +19870 (265), +8750 (246), +32670 (232), 0 (222), –39140 (215).

The oil (**5**) was crystallized as its hydrochloride, mp 218—219° (from acetone). Anal. Calcd for C₁₈H₁₉NO₃·HCl·1/2H₂O: C, 63.06; H, 6.18; N, 4.09. Found: C, 62.86; H, 6.33; N, 3.97.

(ii) From (+)-**12**: A mixture of (+)-**12** (21 mg), HCOOH (0.5 ml) and formalin (0.3 ml) was heated in a sealed tube at 100° for 14.5 hr. Work-up in the usual way gave **5** (14 mg, 60.5%) as an oil. $[\alpha]_D^{21} +37.1^\circ$ ($c=0.7$, EtOH). ORD ($c=0.0023$, MeOH) $[\text{M}]^{20}$ (nm): +4510° (350), +12860° (306) (peak), +9650° (292) (trough), +17880° (278) (peak), 0° (268), –23140° (252) (trough), –7720° (242). CD ($c=0.0086$, MeOH) $[\theta]^{20}$ (nm): +4820 (290), +19370 (265), +7590 (246), +30390 (232), 0 (222), –33830 (215). The oil (**5**) was converted to its hydrochloride, mp 221—222°. The free neomethine and its hydrochloride obtained by method (i) were identical with those prepared from (+)-**12** by method (ii) as judged by direct comparison.

Oxidation of 3-Epitazettadiol (3) with MnO₂—A mixture of **3** (75 mg) in CHCl₃ (7 ml) and MnO₂¹² (375 mg) was stirred at room temperature for 80 min. Work-up in the usual way gave an oil (81 mg), which was subjected to PLC using SiO₂–[CHCl₃–MeOH–diethylamine (92:3:5)] to afford three fractions: I, *R_f* 0.36—0.48; II, *R_f* 0.56—0.61; III, *R_f* 0.72—0.81. Each fraction was eluted with CHCl₃–MeOH–acetone (1:1:1). Fraction I gave **1** (22 mg, 29.5%). UV $\lambda_{\text{max}}^{\text{MeOH}}$ nm (log. ϵ): 291 (3.64), 241 (3.67). ORD ($c=0.0092$, MeOH) $[\text{M}]^{27}$ (nm): +4700° (310), +7940° (294) (peak), +3250° (280) (trough), +19500° (246) (peak), +14400° (238) (trough), +36700° (224). CD ($c=0.0100$, MeOH) $[\theta]^{23}$ (nm): +830 (300), +2640 (290), +160 (256), +10920 (237), +1010 (230), +17890 (220).

The amorphous **1** (8 mg) was crystallized as its hydrochloride, mp 223—224° (from EtOH) (lit.⁴) mp 223—224°. Anal. Calcd for C₁₈H₂₁NO₅·HCl: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.49; H, 6.10; N, 3.30. Treatment of the hydrochloride of **1** with picric acid gave its picrate, mp 202—203° (dec.) [lit.⁴] mp 204—205° (dec.).

The base (**1**) thus obtained from **3** by MnO₂ oxidation was identical with an authentic sample of **1** from the natural source as judged by direct comparison of the spectral data for the free bases and salts and by the mixed melting point test.

Fraction II gave **2** (7 mg, 9.4%), mp 202—203°, which was identical with an authentic sample of **2** by direct comparison. ORD ($c=0.0109$, MeOH) $[\text{M}]^{20}$ (nm): +1820° (350), +2430° (310) (peak), +1820° (298) (trough), +24800° (248) (peak), +3640° (229) (trough), +15800° (222). CD ($c=0.0987$, MeOH) $[\theta]^{23}$ (nm): –1680 (300), –3700 (298), +32270 (239), +18120 (223), +28840 (218).

Fraction III gave **13** (16 mg, 21.6%), mp 125—127° (from acetone) (lit.^{5c}) mp 130—131°. $[\alpha]_D^{17} +267.0^\circ$ ($c=0.54$, CHCl₃) [lit.^{5c}] $[\alpha]_D^{24} +276^\circ$ ($c=0.95$, CHCl₃). Anal. Calcd for C₁₈H₁₉NO₅: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.58; H, 5.57; N, 4.19. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1730, 1710 (CO), 1610 (C=C).

Oxidation of Tazattadiol (6) with MnO₂—A mixture of **6** (100 mg) in CHCl₃ (10 ml) and MnO₂¹² (500 mg)

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was stirred at room temperature for 1 hr. Work-up in the usual way gave an oil (105 mg), which, when subjected to PLC using Al_2O_3 -[benzene-acetone (4:1)], gave three fractions: I, *Rf* 0.08—0.22; II, *Rf* 0.33—0.52; III, *Rf* 0.66—0.82. Each fraction was eluted with CHCl_3 -MeOH-acetone (1:1:1). Fraction I gave **6** (12 mg), mp 112—117°. Fraction II gave amorphous **14** (35 mg, 35.2%). $[\alpha]_D^{18} +195.0^\circ$ ($c=0.48$, MeOH) [lit.^{5b}] $[\alpha]_D^{24} +188^\circ$ (MeOH). MS *m/e*: Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_5$: 331.1418. Found: 331.1378. ORD ($c=0.0108$, MeOH) $[\text{M}]^{26}$ (nm): +3060° (350), +4570° (302), +27500° (253) (peak), +12800° (236) (trough), +27500° (226). CD ($c=0.0100$, MeOH) $[\theta]^{23}$ (nm): -660 (300), -1820 (286), 0 (266), +24920 (239), +17560 (227), +31450 (220).

Fraction III gave **15** (20 mg, 20.4%), mp 105—108° (from ether). $[\alpha]_D^{17} +142.0^\circ$ ($c=0.52$, CHCl_3). *Anal.* Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.76; H, 5.88; N, 4.06. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1720 (CO), 1620 (C=C).

Deoxytazettine (7)⁹⁾—ORD ($c=0.0101$, MeOH) $[\text{M}]^{20}$ (nm): +3120° (350), +4980° (295), +25600° (251) (peak), +12500° (234) (through), +26800° (224). CD ($c=0.0096$, MeOH) $[\theta]^{23}$ (nm): -6530 (300), -9830 (287), 0 (267), +21250 (241), +11450 (226), +30000 (218).

Deoxytazettine Neomethine (8)⁹⁾—(i) The sample from the natural source: ORD ($c=0.0049$, MeOH) $[\text{M}]^{27}$ (nm): -1220° (350), -8520° (304) (trough), -7070° (290) (peak), -13570° (278) (trough), 0° (268), +21920° (253) (peak), +610° (242). CD ($c=0.0081$, MeOH) $[\theta]^{23}$ (nm): -4250 (300), -18630 (264), -5960 (246), -33090 (232), 0 (221), +33940 (215).

(ii) The synthetic sample: ORD ($c=0.0030$, MeOH) $[\text{M}]^{27}$ (nm): -1980° (350), -11970° (304) (trough), -9980° (292) (peak), -16960° (278) (trough), 0° (268), +21950° (252) (peak), +780° (242). CD ($c=0.0103$, MeOH) $[\theta]^{23}$ (nm): -4320 (300), -20860 (264), -8650 (246), -33000 (232), 0 (222), +28810 (215).

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