2,2-Dibenzylbenzo[*b*]thiophen-3(2H)-one (9)——A solution of **6** (3 g) in ether (50 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (4.5 g) in ether (90 ml), and the reaction mixture was stirred at 25° for 5 hr. The excess hydride was hydrolyzed with 10% HCl and the organic layer was separated. The aqueous layer was extracted with ether. The combined extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give an oily product (2.7 g), which was dissolved in acetic anhydride (20 ml) and dimethylsulfoxide (30 ml). The mixture was stirred at room temperature overnight, poured into ice-water, stirred for 2 hr, and then extracted with *n*-hexane. The extract was washed with H_2O several times, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on silica gel with benzene–*n*-hexane (1: 2) to give **9** (1.2 g, 44%), mp 129—131° (from MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (CO). NMR ($CDCl_3$) δ: 3.10, 3.24 (2H each, ABq, J=14 Hz), 6.9—7.9 (14H, m). UV (EtOH) nm (log ε): 239 (4.19), 260 (3.52), 370 (3.09). *Anal.* Calcd for $C_{22}H_{18}OS$: C, 79.96; H, 5.49. Found: C, 79.66; H, 5.49.

2-Benzyl-3-benzyloxybenzo[*b*]thiophene (10)——A mixture of **7** (100 mg, 0.3 mmol) and $LiAlH_4$ (32 mg) in ether (30 ml) was stirred at room temperature for 0.5 hr. The excess hydride was decomposed by addition of a saturated solution of Rochelle salt. The ether layer was separated, washed wtih H_2O, dried ($MgSO_4$), and concentrated. The residue was passed through a short column with benzene to give **10** (64 mg) as colorless crystals, mp 96.5—98.5°. NMR ($CDCl_3$) δ: 4.03 (2H, s), 5.06 (2H, s), 6.8—7.9 (14H, m). UV (EtOH) nm (log ε): 234 (4.50), 241 sh (4.35), 265 (3.85), 291 (3.55), 301 (3.44). *Anal.* Calcd for $C_{22}H_{18}OS$: C, 79.96; H, 5.49. Found: C, 79.68; H, 5.39.

Thermolysis of 2b——A mixture of **2b** (156 mg, 1 mmol) and silver oxide (62 mg) in MeOH (16 ml) was refluxed with stirring for 4 hr. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel with benzene to give **12** (55 mg, 42%), mp 55—56° (lit.[5] mp 59°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. NMR ($CDCl_3$) δ: 6.28 (1H, d, J=7.5 Hz), 7.15—8.2 (4H, m), 7.78 (1H, d, J=7.5 Hz).

Photolysis of 2c——A solution of **2c** (300 mg, 1.6 mmol) in absolute MeOH (30 ml) was irradiated for 3 hr and concentrated. The residue was purified by column chromatography on silica gel with benzene–EtOAc (4: 1) to give **13** (25 mg, 8%) as an oil.[5] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (CO). NMR ($CDCl_3$) δ: 2.77 (3H, s), 3.76 (3H, s), 3.4—4.3 (3H, m), 6.4—7.5 (4H, m).

Photolysis of 2d——A solution of **2d** (300 mg, 1.7 mmol) in MeOH (30 ml) was irradiated for 5 hr, then concentrated. The residue was purified by column chromatography on silica gel with benzene–EtOAc (2: 1) to give **14** (134 mg, 44%) as an oil.[5] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (CO). NMR ($CDCl_3$) δ: 2.15—2.6 (2H, m), 2.85—3.2 (2H, m), 3.70 (3H, s), 3.9—4.2 (1H, m), 6.95—7.5 (4H, m).

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Isolation of O-Demethyllycoramine from Bulbs of *Lycoris radiata* Herb.

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The bulbs of *Lycoris radiata* Herb. (Amaryllidaceae) were found to contain a new phenolic base, O-demethyllycoramine (O-demethyldihydrogalanthamine) (**3**), as well as previously isolated alkaloids, such as pretazettine (**1**), lycorine (**4**), lycoramine (**5**), lycorenine (**6**), demethylhomolycorine (**7**), hippeastrine (**8**), and homolycorine (**9**). The structure of **3** was confirmed by demethylation of lycoramine (**5**) with pyridine hydrochloride.

Keywords——O-demethyllycoramine; pretazettine; lycoramine; lycorenine; demethylhomolycorine; hippeastrine; homolycorine; Amaryllidaceae; pyridine hydrochloride

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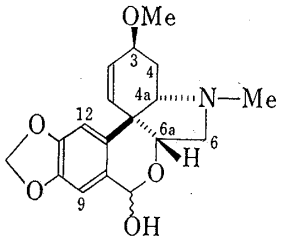
1) Location: *a) 1-78, Sho-machi, Tokushima 770, Japan; b) Ikawadani, Tarumi-ku, Kobe 673, Japan.*

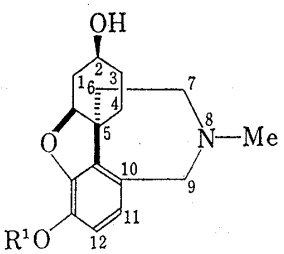
Previously we reported[2] the isolation of pretazettine (**1**),[3] which showed antileukemic activity[4] and sanguinine (O-demethylgalanthamine) (**2**) from *Lycoris radiata* Herb. and *Lycoris sanguinea* Maxim. var *Kiushiana* Makino (both Amaryllidaceae), respectively.

This paper describes the isolation of a new phenolic base, O-demethyllycoramine (O-demethyldihydrogalanthamine) (**3**), as well as pretazettine (**1**), lycorine (**4**), lycoramine (**5**),[5] lycorenine (**6**),[6] demethylhomolycorine (**7**),[7] hippeastrine (**8**),[8] and homolycorine (**9**),[7,9] from bulbs of *L. radiata* Herb.

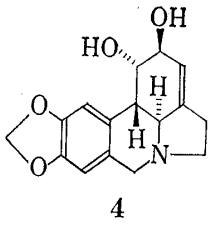
Crude basic material was extracted from fresh bulbs of *L. radiata* Herb. by the method of Wildman and Bailey.[3c] Lycorine (**4**) was isolated from a chloroform solution of the crude material, utilizing its low solubility in this solvent, and was identified by direct comparison with an authentic sample of **4**. The chloroform solution was subjected to preparative thin-layer chromatography (PLC) using silica gel-chloroform–methanol to give four fractions, *Rf* 0.00—0.06, *Rf* 0.12—0.23, *Rf* 0.23—0.47, and *Rf* 0.57—0.74. The first fraction gave O-demethyllycoramine (**3**) and pretazettine (**1**), and the second, lycoramine (**5**) and lycorenine (**6**). Demethylhomolycorine (**7**) and hippeastrine (**8**) were obtained from the third fraction,



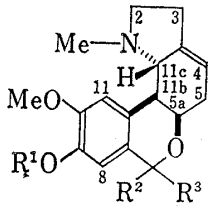
1



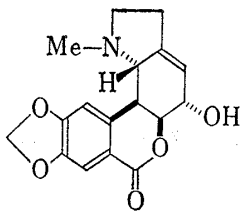
2 : R^1=H
double bond at C_3
3 : R^1=H
5 : R^1=Me



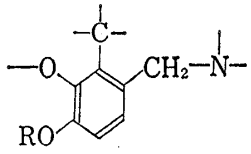
4



6 : R^1=Me, R^2=OH, R^3=H
7 : R^1=H, R^2, R^3=O
9 : R^1=Me, R^2, R^3=O
10 : R^1=Me, R^2=OEt, R^3=H



8



A

Chart 1

2) S. Kobayashi, S. Takeda, H. Ishikawa, H. Matsumoto, M. Kihara, T. Shingu, A. Numata, and S. Uyeo, *Chem. Pharm. Bull.*, **24**, 1537 (1976).
3) *a*) W.C. Wildman and D.T. Bailey, *J. Am. Chem. Soc.*, **89**, 5541 (1967); *b*) *Idem*, *ibid.*, **91**, 150 (1969); *c*) *Idem*, *J. Org. Chem.*, 33, 3749 (1968).
4) *a*) E. Furusawa, N. Suzuki, S. Tani, S. Furusawa, G.Y. Ishioka, and J. Motobu, *Proc. Soc. Exp. Biol. Med.*, **143**, 33 (1973); *b*) E. Furusawa, N. Suzuki, S. Furusawa, and J.Y.B. Lee, *ibid.*, **149**, 771 (1975).
5) *a*) S. Uyeo and J. Koizumi, *Chem. Pharm. Bull.*, **1**, 202 (1953); *b*) H. Kondo, K. Tomimura, and S. Ishiwata, *Yakugaku Zasshi*, **52**, 433 (1932); *c*) D.J. Williams and D. Rogers, *Proc. Chem. Soc.*, London, **1964**, 357.
6) M. Fales, L.D. Giuffrida, and W.C. Wildman, *J. Am. Chem. Soc.*, **78**, 4145 (1956).
7) S. Uyeo and N. Yanaihara, *J. Chem. Soc.*, **1959**, 172.
8) H.G. Boit, *Chem. Ber.*, **89**, 1129 (1956).
9) H. Kondo and T. Tomimura, *Yakugaku Zasshi*, **49**, 438 (1929).

and homolycorine (**9**) and O-ethyllycorenine (**10**) (a secondary product formed from 6) from the fourth.

A new phenolic base, O-demethyllycoramine (**3**), mp 204—207°, $C_{16}H_{17}NO_3$ (deduced by high resolution mass spectrometry), gave a blue-green color with ferric chloride reagent. The infrared (IR) spectrum of **3** showed hydroxyl absorptions at 3400 and 3150 cm^{-1}, but no carbonyl absorption. The ultraviolet (UV) spectrum, having $\lambda_{max}^{methanol}$ 283 nm (log. ε 3.38) and $\lambda_{shoulder}^{methanol}$ 228 nm (log. ε 3.90), and the optical rotatory dispersion (ORD) curve were quite similar to those of lycoramine (**5**). In the nuclear magnetic resonance (NMR) spectrum (pyridine-d_5) of **3**, two pairs of doublets at δ 3.67 and 4.09 (each 1H, J=15 Hz) and at δ 6.69 and 7.05 (each 1H, J=8 Hz) revealed the presence of a benzylic methylene group attached to a nitrogen atom and two aromatic *ortho* protons, respectively. These findings indicate that the aromatic ring of **3** resembles the benzenoid ring of **5** and that **3** has the partial formula **A** (see Chart 1). In view of the remarkable similarity between the values for **3** and **5**, the new phenolic base appears to be O-demethyllycoramine (**3**).

To confirm this assignment, lycoramine (**5**) was treated with dry pyridine hydrochloride[10] at 190° to give O-demethyllycoramine (**3**), which was found to be identical with a sample of **3** from the natural source by direct comparison of their IR, NMR, and ORD spectra and by the mixed melting point test.

Pretazettine (amorphous) (**1**) was characterized as its hydrochloride, mp 219—221° (dec.), which was found to be identical with an authentic sample[2] of **1** by direct comparison.

Lycoramine (**5**),[5] mp 120—122°, lycorenine (**6**),[6] mp 199—200°, demethylhomolycorine (**7**),[7] mp 208—210°, and homolycorine (**9**),[7,9] mp 167—169°, were all identified by direct comparison with authentic samples.

Hippeastrine (**8**),[8,11] mp 210—212°, was identified by elemental analysis and spectral data.

O-Ethyllycorenine (**10**)[12] (mp 96—98°), an artifact formed from lycorenine (**6**), was characterized by comparison of its physical and spectral data with those of an authentic sample obtained from **6** by the method of Uyeo and Yamato.[12]

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi EPI-G2 for IR spectra, a Shimadzu UV-200 for UV spectra, a Hitachi RMU-6C or a JEOL JMS D-300 for MS, a Yanagimoto OR-50 for optical rotations, a JASCO ORD/UV-5 for ORD spectra, and a JEOL JNM-PS-100 or a Hitachi R-22 for NMR spectra, using TMS as an internal standard. The plates used for PLC were coated with silica gel (Kieselgel, PF_{254} Merck) and aluminum oxide (GF_{254} Merck).

Isolation of Alkaloids from *L. radiata* Herb.——According to the procedure previously reported,[2] crude alkaloids (7.708 g, 0.1675%) were obtained from fresh rhizomes (4.6 kg) of this plant, collected in our Faculty plot.[1a] The crude alkaloids were separated into $CHCl_3$-insoluble (890 mg, 0.019%) and $CHCl_3$-soluble (6.819 g) materials by mixing with $CHCl_3$ (80 ml).

The $CHCl_3$-insoluble material (70 mg) was recrystallized from EtOH to give lycorine (**4**) (30 mg), mp 257—264° (dec.). The $CHCl_3$-soluble material (6.819 g) was subjected to PLC using SiO_2-[$CHCl_3$–MeOH (10: 1)] to give four fractions: I, *Rf* 0.00—0.06 (474 mg); II, *Rf* 0.12—0.23 (932 mg); III, *Rf* 0.23—0.47 (1.87 g); IV, *Rf* 0.59—0.74 (573 mg). Each fraction was eluted with $CHCl_3$–MeOH (1: 1). Fraction I was further subjected to PLC using SiO_2-[$CHCl_3$–MeOH–diethylamine (92: 3: 5)] to give two fractions: I-A, *Rf* 0.17—0.25 (20 mg); I-B, *Rf* 0.41—0.56 (170 mg). Fraction I-A gave crude O-demethyllycoramine (**3**). Fraction I-B gave amorphous pretazettine (**1**). Fraction II was purified by PLC using SiO_2-[$CHCl_3$–MeOH–diethylamine (92: 3: 5)] to give a material (400 mg, *Rf* 0.38—0.48) which was subjected to PLC using Al_2O_3-[benzene–acetone (1: 2)] to afford two crude bases, lycoramine (**5**) (213 mg) (*Rf* 0.39—0.62) and lycorenine (**6**) (34 mg) (*Rf* 0.62—0.68). Fraction III gave crude demethylhomolycorine (**7**) (129 mg) (*Rf* 0.11—0.24), hippeastrine (**8**) (55 mg) (*Rf* 0.24—0.31), and lycorenine (**6**) (470 mg) (*Rf* 0.56—0.72) when subjected to PLC

10) V. Prey, *Chem. Ber.*, **75**, 445 (1942).
11) M.R. Yagudaev, A. Kh. Abduazimov, and S. Yu. Yunnsov, *Khim. Prir. Soedin.*, **6**, 94 (1970) [*C.A.*, **73** 45641*h* (1970)].
12) S. Uyeo and Y. Yamato, *Yakugaku Zasshi*, **85**, 615 (1965).

using SiO_2-[$CHCl_3$–diethylamine (10: 1)]. On PLC using SiO_2-[CH_2Cl_2–MeOH (10: 1)], fraction IV gave three crude bases, O-ethyllycorenine (**10**) (130 mg) (*Rf* 0.1—0.2), additional **6** (24 mg) (*Rf* 0.38—0.56), and homolycorine (**9**) (120 mg) (*Rf* 0.56—0.73).

O-Demethyllycoramine (3)——Crude **3** was recrystallized from benzene–EtOH (2: 1) as colorless prisms (5 mg, 0.0001%), mp 204—207°. ORD (c=0.0145, EtOH) $[M]^{23}$ (nm): −653° (315), −3007° (294) (trough), −542° (275) (peak), −6919° (244) (trough), −6341° (240). NMR (pyridine-d_5) δ: 7.05 and 6.69 (each 1H, d=8 Hz, AB type of C-12-H and C-11-H), 4.32 (1H, t, C-16-H), 4.24 (1H, m, C-2-H), 4.09 and 3.67 (each 1H, d, J=15 Hz, AB type of C-9 H_2), 2.36 (3H, s, NCH_3); ($CDCl_3$): 6.60 and 6.32 (each 1H, d, J=8 Hz, AB type of C-12-H and C-11-H), 4.36 (1H, m, C-16-H), 4.10 (1H, m, C-2-H), 4.07 and 3.62 (each 1H, d, J=15 Hz, AB type of C-9 H_2), 2.37 (3H, s, NCH_3). Mass Spectrum m/e: Calcd for $C_{16}H_{21}NO_3$: 275.1519. Found: 257.1482.

Conversion of Lycoramine (**5**) **to O-Demethyllycoramine** (3)——A mixture of **5** (200 mg) and dry pyridine hydrochloride[10] (320 mg) was stirred at 190° for 1 hr. The reaction mixture was subjected to PLC using SiO_2-[$CHCl_3$–MeOH–diethylamine (92: 3: 5)] to give crude **3** (46 mg) (*Rf* 0.28—0.39). Recrystallization of the crude base from benzene–EtOH gave **3** (21 mg, 11.3%) as colorless prisms, mp 209—211°. $[\alpha]_D^{23}$ −111.9° (c=0.59, EtOH). ORD (c=0.0147, EtOH). $[M]^{22}$ (nm): −748° (315), −3190° (294) (trough), −636° (275) (peak), −7106° (244), −6545° (240). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.61; H, 7.70; N, 4.81. This base was found to be identical with a sample of **3** from the natural source by direct comparison of their IR, NMR, and ORD spectra and by the mixed melting point test.

Pretazettine (**1**) **Hydrochloride**[2]——This hydrochloride (76 mg) was prepared from amorphous **1** (100 mg) and recrystallized from EtOH as colorless prisms, mp 219—221° (dec.) [lit.[2] mp 223—224° (dec.)]. *Anal.* Calcd for $C_{18}H_{21}NO_5 \cdot HCl$: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.80; H, 6.11; N, 3.76. This hydrochloride was shown to be identical with that of an authentic sample of **1** on direct comparison of the IR spectra and the TLC behavior, and in the mixed melting point test.

Lycoramine (**5**)[2,5]——Crude **5** (213 mg) was recrystallized from ether as colorless cubes (160 mg, 0.00348 %), mp 120—122° (lit.[5a] mp 120—121.5°). $[\alpha]_D^{22}$ −96.0° (c=0.71, EtOH) [lit.[5b] $[\alpha]_D^{27}$ −98.15° (EtOH)]. ORD (c=0.0145, EtOH) $[M]^{23}$ (nm): −778° (330), −3753° (290) (trough), −839° (270) (peak), 6305° (240). NMR (pyridine-d_5) δ: 6.69 and 6.62 (each 1H, d, J=8 Hz, AB type of C-12-H and C-11-H), 4.32 (1H, t, C-16-H), 4.22 (1H, m, C-2-H), 4.04 and 3.65 (each 1H, d, J=15 Hz, AB type of C-9 H_2), 3.69 (3H, s, OCH_3), 2.33 (3H, s, NCH_3). *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.43; H, 8.15; N, 4.88.

Lycorenine (**6**)[6,13]——Crude **6** (574 mg) was recrystallized from acetone as colorless prisms (522 mg, 0.0114%), mp 199—203°. $[\alpha]_D^{22}$ +172.4° (c=0.7, EtOH).

Demethylhomolycorine (**7**)[7]——Crude **7** (129 mg) was recrystallized from ethyl acetate as colorless needles (123 mg, 0.0027%), mp 207—208°. $[\alpha]_D^{22}$ +98.0° (c=0.68, $CHCl_3$). NMR ($CDCl_3$) δ: 7.56 (1H, s, C-8-H), 6.99 (1H, s, C-11-H), 5.49 (1H, br s, C-4-H), 4.76 (1H, m, C-5a-H), 3.90 (3H, s, OCH_3), 3.16 (1H, m, C-11b-H), 2.00 (3H, s, NCH_3).

Hippeastrine (**8**)[8,11]——Crude **8** (55 mg) was recrystallized from ethyl acetate as colorless needles (28 mg, 0.0006%), mp 210—212°. $[\alpha]_D^{22}$ +162.0° (c=0.53, $CHCl_3$).

Homolycorine (**9**)[7,9,13]——Crude **9** (120 mg) was recrystallized from ethyl acetate as colorless cubes (81 mg, 0.00175%), mp 167—169°. $[\alpha]_D^{23}$ +80.0° (c=0.67, EtOH).

O-Ethyllycorenine (**10**)[12]——Crude **10** (30 mg) was recrystallized from pet. ether as colorless needles (19.8 mg, 0.00043%), mp 96—98°. $[\alpha]_D^{23}$ +166.2° (c=0.37, EtOH). NMR ($CDCl_3$) δ: 6.87 and 6.78 (each 1H, s, C-11-H and C-8-H), 5.64 (1H, s, C-7-H), 5.48 (1H, m, C-4-H), 4.30 (1H, m, C-5a-H), 3.85 and 3.83 (each 3H, s, 2×OCH_3), 3.78 (2H, q, J=7 Hz, OCH_2CH_3), 3.12 (1H, m, C-11b-H), 2.08 (3H, s, NCH_3), 1.29 (3H, t, J=7 Hz, OCH_2CH_3).

The same base (**10**) (15 mg) was also obtained by treatment of **6** (20 mg) in benzene with dry HCl, followed by treatment with EtOH.

Acknowledgement The authors wish to express their thanks to President S. Uyeo, Shizuoka College of Pharmacy, for his encouragement.

13) W.A. Hawksworth, P.W. Jeffs, B.K. Tidd, and T.P. Toube, *J. Chem. Soc.*, **1965**, 1991.