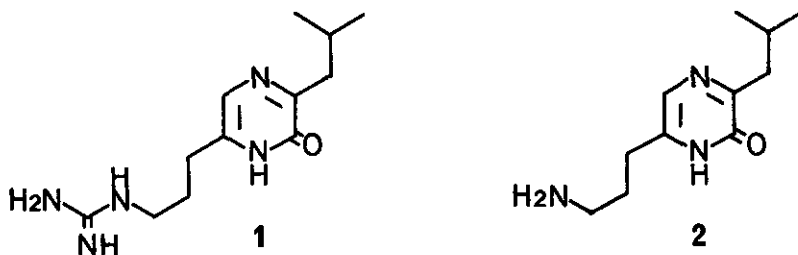


SYNTHESIS OF ARGLECIN

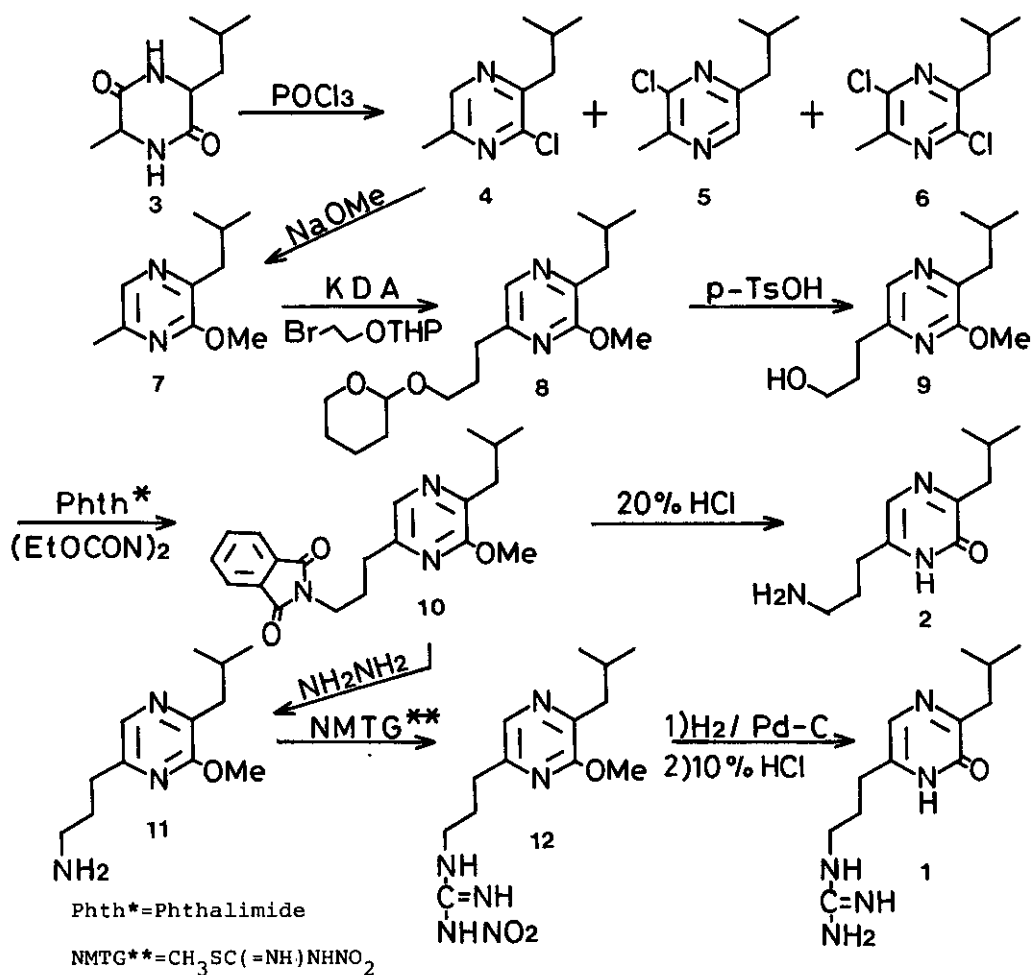
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Abstract — Arglecine (1) and its analogue, 6-(3-aminopropyl)-3-isobutyl-2(1H)-pyrazinone (2), were synthesized from DL-alanyl-leucyl anhydride in several steps.

Arglecine (1: 6-(3-guanidinopropyl)-3-isobutyl-2(1H)-pyrazinone) was isolated from the culture filtrates of *Streptomyces toxytricini* and *S. lavendulae*, and found capable of exerting an antiarrhythmic effect.^{1,2} Later, 6-(3-aminopropyl)-3-isobutyl-2(1H)-pyrazinone (2), considered possibly to be a biosynthetic precursor of 1, was also detected in the same filtrates.² The present paper describes the syntheses of these substances from DL-alanyl-leucyl anhydride (3)³.

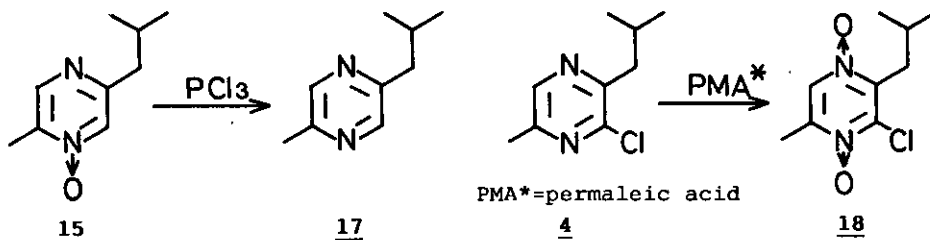
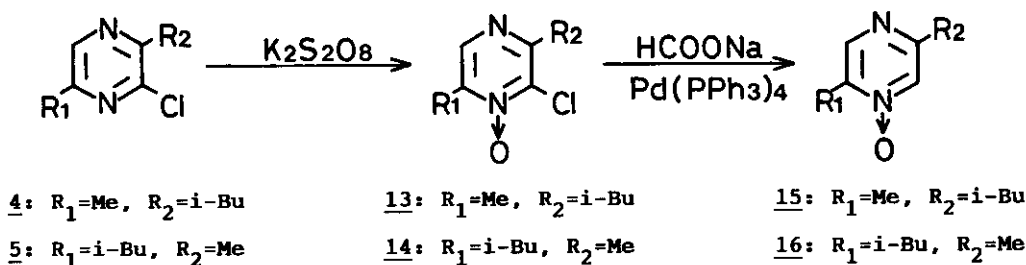


The synthetic procedures are shown in Scheme 1. Reaction of 3³ with phosphoryl chloride in the presence of phosphorus pentachloride at 140°C⁴ afforded a mixture of two monochloropyrazines (4,5) and a dichloropyrazine (6). From the mixture, 4 and 5 were extracted with conc. HCl and, further, 4 and 5 could be separated from each other by low pressure liquid chromatography. The structures of 4 and 5 were distinguished from each other by ¹H-nmr. Some of ¹H-nmr spectral data



Scheme 1. Route for the Synthesis of Arglecine and 6-(3-Aminopropyl)-3-isobutyl-2(1H)-pyrazinone

for these structures are shown in Fig. 1. The methylene proton (H_a) signal of **4** appeared downfield relative to that of **5**, and the methyl proton (H_b) signal of **4** was observed at higher position than that of **5**. Additionally, chemical shifts of α -protons on the side chains of their N-oxides (**15**, **16**), prepared according to Scheme 2, are also shown in Fig. 1. The methyl protons (H_c) of **15** were observed in a higher field and the methylene protons (H_d) of **16** were observed at lower positions than the corresponding protons of the original pyrazine (**17**). Although the methyl protons (H_c) of **16** were also observed in a higher field than the corresponding protons of **17**, the difference of the chemical shifts of H_c between **16** and **17** is smaller than that between **15** and **17**. Based on a comparison of these findings with those in the previous paper^{4,5},



Scheme 2. Synthetic Route for Derivatives of 2-Chloro-3,6-dialkylpyrazines

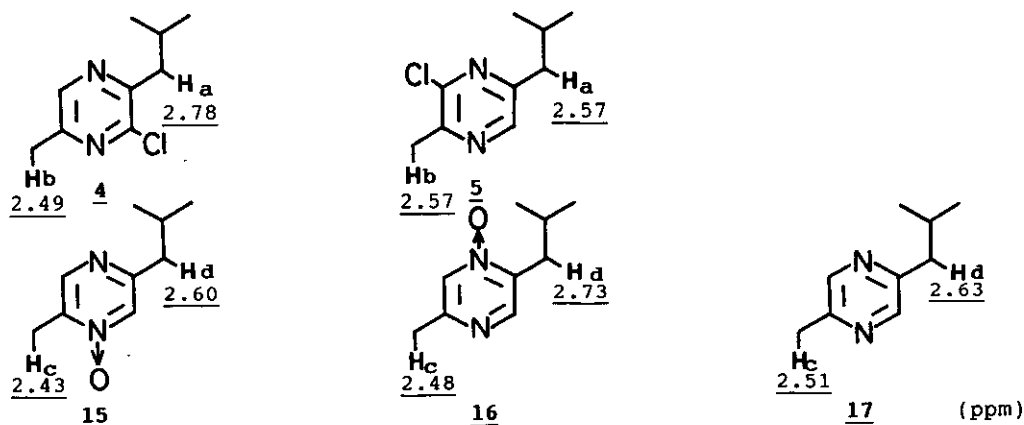
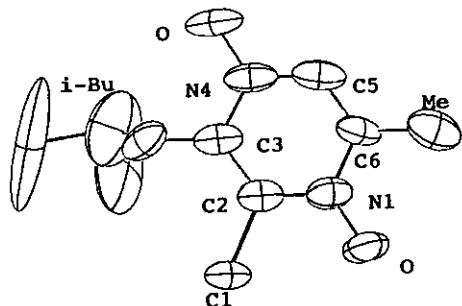


Fig.1. ¹H-Nmr Data of Derivatives prepared from 2-Chloro-3,6-dialkylpyrazines



$a=10.899 \text{ nm}$, $b=9.453 \text{ nm}$, $c=5.271 \text{ nm}$
 $\alpha=87.89$, $\beta=98.60$, $\gamma=89.61$
 $U=535.6 \text{ nm}^3$, $R=0.0948$

Fig.2. X-Ray Diffraction of 2-Chloro-3-isobutylpyrazine 1,4-Dioxide (18)

the structures of 4 and 5 are considered to have the structures shown in Fig. 1. This assignment was confirmed by X-ray analysis of the dioxide (18) as shown in Fig. 2.

First, an introduction of several alkyl groups to the methyl group on the ring of 4 was examined, but this resulted in the formation of many products that could not be separated. Then, 4 was converted to the 2-methoxy derivative (7) by reflux for 6 h with sodium methoxide in absolute methanol. The metalation of 7 was carried out with KDA (potassium diisopropylamide), and then 2-bromoethyl tetrahydropyranyl ether was added to the carbanion solution. From the products, 8 was isolated by silica gel column chromatography and deprotected by a conventional method using p-toluenesulfonic acid in methanol to obtain 9, which was converted to 10 by Mitsunobu method⁶. Compound 10 was hydrolyzed by heating with 20% HCl in a sealed tube to obtain 2 as a monohydrochloride, mp 225-227°C (decomp.) (lit.² 221-227°C). Both the ¹H- and ¹³C-nmr spectra agreed with those of the natural product². Compound 10 was treated with hydrazine monohydrate to give 11. Reaction of 11 with N-nitromethylthioguanidine produced 12, which was then hydrogenated in 10% HCl methanol solution using 10% Pd-carbon as the catalyst, followed by hydrolysis with 10% HCl to give arglecin dihydrochloride. The purification of the dihydrochloride was accomplished by using of anion (Dowex 1-X2) and cation (Amberlite CG-50) exchange resins in combination to furnish pure arglecin dihydrochloride, mp 140°C (decomp.) (lit.² 140-175°C). The ir spectrum of this dihydrochloride was identical that of the natural product presented by Tatsuta *et al.*¹. The ¹³C- and ¹H-nmr spectral data of monohydrochloride of 1 agreed with those presented by MacDonald *et al.*².

EXPERIMENTAL

None of the melting and boiling points were corrected. The following apparatus was used to obtain spectral data. NMR: Varian EM-390 (¹H) and Brucker AM-400 (¹H, ¹³C); IR spectra: Shimadzu IR-400; MS: Hitachi M-80 spectrometer. X-ray diffraction data were obtained with Rigaku AFC-5 X-ray autodiffractometer, using Mo K_α radiation.

Preparation of 2-Chloro- (4), 5-Chloro- (5) and 2,5-Dichloro-3-isobutyl-6-methylpyrazines (6)

These compounds were prepared from DL-alanyl-leucyl anhydride³ (203.4 g, 1.11 mol) according to the previous method for the syntheses of 3,6-dialkyl-2-chloropyrazines⁴. The separation of 2-chloro- (4) and 5-chloro-3-isobutyl-6-methylpyrazines (5) was carried out using preparative liquid chromatography at a pressure of 2.0 kg/cm², with Kieselgel 60 (230-400 mesh) as the packing material and a mixture of n-hexane/THF (15:1) as the developing solvent.

4: Colorless oil; Yield: 56.1 g (27%); bp 89-90°C/9 torr; ms: m/z 184 (M⁺), 169 (M⁺-CH₃); ¹H-nmr (CDCl₃/TMS): δ 0.96 (d, J = 6.8 Hz, 6H, CH₂CH(CH₃)₂), 2.20 (m, J = 6.8 Hz, 1H, CH₂CH(CH₃)₂), 2.49 (s, 3H, CH₃), 2.78 (d, J = 6.8 Hz, 2H, CH₂CH(CH₃)₂), 8.27 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₉H₁₃N₂Cl: C, 58.53; H, 7.10; N, 15.17. Found: C, 58.42; H, 7.24; N, 15.03.

5: Colorless oil; Yield: 43.0 g (21%); bp 98-99°C/12 torr; ms: m/z 184 (M⁺), 169 (M⁺-CH₃); ¹H-nmr (CDCl₃/TMS): δ 0.87 (d, J = 6.8 Hz, 6H, CH₂CH(CH₃)₂), 2.05 (m, J = 6.8 Hz, 1H, CH₂CH(CH₃)₂), 2.57 (s, 3H, CH₃), 2.57 (d, J = 6.8 Hz, 2H, CH₂CH(CH₃)₂), 8.15 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₉H₁₃N₂Cl: C, 58.53; H, 7.10; N, 15.17. Found: C, 58.66; H, 7.37; N, 15.30.

6: Colorless oil; Yield: 10.3 g (4.3%); bp 79-81°C/17 torr; ms (chemical ionization, isobutane): m/z 219 (M⁺+1), 177 (M⁺+1-C₃H₆); ¹H-nmr (CDCl₃/TMS): δ 0.93 (d, J = 7.5 Hz, 6H, CH₂CH(CH₃)₂), 2.10 (m, J = 7.5 Hz, 1H, CH₂CH(CH₃)₂), 2.48 (s, 3H, CH₃), 2.66 (d, J = 7.5 Hz, 2H, CH₂CH(CH₃)₂) ppm; Anal. Calcd. for C₉H₁₂N₂Cl₂: C, 49.33; H, 5.52; N, 12.79. Found: C, 49.21; H, 5.49; N, 12.66.

3-Isobutyl-2-methoxy-6-methylpyrazine (7)

In a NaOMe-MeOH solution prepared from absolute MeOH (260 ml) and sodium (25.7 g, 1.12 g atom), 4 (43.1 g, 224 mmol) was heated under reflux for 6 h. After methanol was removed by distillation in vacuo, the residue was triturated with water and extracted with n-hexane. The extract was worked up in the usual manner and the product was distilled to obtain 7 (37.6 g, 93%) as a colorless oil.

7: bp 97-98°C/17 torr; ms: m/z 180 (M⁺), 165 (M⁺-CH₃), 138 (M⁺-C₃H₆); ¹H-nmr (CDCl₃/TMS): δ 0.86 (d, J = 6.8 Hz, 6H, CH₂CH(CH₃)₂), 2.13 (m, J = 6.8 Hz, 1H; CH₂CH(CH₃)₂), 2.35 (s, 3H, CH₃), 2.56 (d, J = 6.8 Hz, 2H, CH₂CH(CH₃)₂), 3.85 (s, 3H, OCH₃), 7.81 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₁₀H₁₆N₂O: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.52; H, 9.13; N, 15.27.

3-[6-(3-Isobutyl-2-methoxy)pyrazinyl]propyl 2-Tetrahydropyranyl Ether (8)

To a THF solution (10 ml) of KDA prepared from potassium tert-butoxide (0.48 g, 4.8 mmol) and diisopropylamine (0.65 ml, 4.8 mmol), 7 (0.8 g, 4.4 mmol) dissolved in THF (5 ml) was added at -78°C under an argon stream. The mixture was stirred for 20 min and 2-bromoethyl 2-tetrahydropyranyl ether (1 g, 4.8 mmol) was added dropwise to the solution. After stirring for 3 h at -78°C under an argon stream, 5% ammonium chloride (3 ml) was added to the reaction mixture which was extracted with n-hexane and the extract was worked up as usual. The residue was purified by liquid chromatography at a pressure of 2.0 kg/cm^2 (Kieselgel 60, 230-400 mesh, n-hexane/AcOEt) to give 8 (0.78 g, 58%) as a colorless oil. 8: bp $143\text{-}144^{\circ}\text{C}/2\text{ torr}$; ms: m/z 308 (M^+), 266 ($\text{M}^+ - \text{C}_3\text{H}_6$); $^1\text{H-nmr}$ (CDCl_3/TMS): δ 0.91 (d, $J = 6.3\text{ Hz}$, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.45-2.32 (m, 9H, THP H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTHP}$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.59 (d, $J = 6.3\text{ Hz}$, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.72 (t, $J = 6.9\text{ Hz}$, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTHP}$), 3.26-3.95 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTHP}$, THP H), 3.88 (s, 3H, OCH_3), 4.54 (m, 1H, THP H), 7.86 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_3$: C, 66.20; H, 9.15; N, 9.08. Found: C, 66.23; H, 9.26; N, 9.03.

6-(3-Hydroxypropyl)-3-isobutyl-2-methoxypyrazine (9)

A mixture of 8 (2.02 g, 6.6 mmol) and p-toluenesulfonic acid (2.00 g, 11.6 mmol) was dispersed in methanol (20 ml) by ultrasonic waves for 2 h. The solvent was removed by distillation *in vacuo* and the residue was extracted with Et_2O . After being washed successively with water, 10% potassium bicarbonate and water, the extract was worked up with usual way to give an oily substance which was subsequently purified by distillation to give 9 (1.45 g, 100%) as a colorless oil.

9: bp $122\text{-}125^{\circ}\text{C}/2\text{ torr}$; ms: m/z 225 ($\text{M}^+ + 1$), 183 ($\text{M}^+ + 1 - \text{C}_3\text{H}_6$); $^1\text{H-nmr}$ (CDCl_3/TMS): δ 0.93 (d, $J = 6.6\text{ Hz}$, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.82-2.32 (m, 3H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 2.65 (d, $J = 6.6\text{ Hz}$, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.80 (m, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 3.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 3.94 (s, 3H, OCH_3), 7.92 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 64.39; H, 9.11; N, 12.38.

6-(3-Phthalimidopropyl)-3-isobutyl-2-methoxypyrazine (10)

To a THF solution of 9 (0.58 g, 2.6 mmol), phthalimide (0.43 g, 2.9 mmol) and diethyl azodicarboxylate (0.48 ml, 2.9 mmol), triphenylphosphine (0.76 g, 2.9 mmol), dissolved in THF (3.0 ml), was added dropwise under an argon stream.

The mixture was stirred overnight and the solvent was removed by distillation. The residue was triturated with benzene, followed by filtration of the mixture. The filtrate was washed with 5% potassium hydroxide and water and worked up as usual to give a crystalline solid, which was submitted to liquid chromatography at 2.0 kg/cm² of pressure (Kieselgel 60, 230-400 mesh, n-hexane/AcOEt) to give 10 (0.86 g, 93%). The product was recrystallized from n-hexane to obtain colorless prisms.

10: mp 86-87°C (n-hexane); ms: m/z 353 (M⁺), 311 (M⁺-C₃H₆); ¹H-nmr (CDCl₃/TMS): δ 0.89 (d, J = 6.0 Hz, 6H, CH₂CH(CH₃)₂), 1.92-2.39 (m, 3H, CH₂CH(CH₃)₂, CH₂CH₂CH₂phthalimide), 2.57 (d, J = 6.0 Hz, 2H, CH₂CH(CH₃)₂), 2.75 (t, J = 6.0 Hz, 2H, CH₂CH₂CH₂phthalimide), 3.79 (t, J = 6.0 Hz, 2H, CH₂CH₂CH₂phthalimide), 3.92 (s, 3H, OCH₃), 7.56-7.84 (m, 4H, benzene H), 7.86 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₂₀H₂₃N₃O₃: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.19; H, 6.57; N, 11.94.

6-(3-Aminopropyl)-3-isobutyl-2-methoxypyrazine (11)

A mixture of 10 (5.57 g, 15.8 mmol) and hydrazine monohydrate (0.8 ml) was refluxed for 4 h in ethanol (30 ml). The solvent was removed by distillation in vacuo and the residue was dissolved in 1.7% potassium hydroxide. The solution was extracted with Et₂O and the extract was worked up with usual way. The resulting oil was distilled under a reduced pressure to give 11 (2.92 g, 83%) as a colorless oil.

11: bp 109-110°C/2 torr; ms: m/z 223 (M⁺); ¹H-nmr (CDCl₃/TMS): δ 0.92 (d, J = 6.3 Hz, 6H, CH₂CH(CH₃)₂), 1.57 (bs, 2H, CH₂CH₂CH₂NH₂), 1.68-2.44 (m, 3H, CH₂CH(CH₃)₂, CH₂CH₂CH₂NH₂), 2.58-2.89 (m, 4H, CH₂CH(CH₃)₂, CH₂CH₂CH₂NH₂), 3.91 (s, 3H, OCH₃), 7.86 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₁₂H₂₁N₃O: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.51; H, 9.57; N, 18.56.

3-Isobutyl-2-methoxy-6-(3-N-nitroguanidinopropyl)pyrazine (12)

A mixture of 11 (1.14 g, 5.1 mmol) and N-nitromethylthioguanidine (0.76 g, 5.6 mmol) was heated at 40°C for 5 min in absolute EtOH (20 ml) and allowed to stand for one day at room temperature. The solvent was removed by distillation in vacuo and the residue was purified by column chromatography (Wakogel C-200, 100-200 mesh, CHCl₃/AcOEt) to give 12 (1.35 g, 85%). The product was recrystallized from AcOEt/iso-Pr₂O to obtain colorless needles.

12: mp 131-132°C (AcOEt/iso-Pr₂O); ms: m/z 310 (M⁺); ¹H-nmr (CDCl₃/TMS): δ 0.91 (d, J = 6.3 Hz, 6H, CH₂CH(CH₃)₂), 1.71 (bs, 1H, NHC(=NH)NHNO₂), 1.85-2.38 (m, 3H, CH₂CH(CH₃)₂, CH₂CH₂CH₂NH), 2.64 (d, J = 6.3 Hz, 2H, CH₂CH(CH₃)₂), 2.76 (t, J = 6.3 Hz, 2H, CH₂CH₂CH₂NH), 3.41 (m, 2H, CH₂CH₂CH₂NH), 3.94 (s, 3H, OCH₃), 7.35-7.58 (m, 1H, NHC(=NH)NHNO₂), 8.45-8.82 (m, 1H, NHC(=NH)NHNO₂), 7.92 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₁₃H₂₂N₆O₃: C, 50.31; H, 7.15; N, 27.08. Found: C, 50.38; H, 7.32; N, 27.09.

Arglecin Mono- and Dihydrochlorides

In an apparatus for catalytic hydrogenations, 12 (0.62 g, 2.0 mmol) dissolved in 10% HCl-MeOH solution (25 ml) was shaken with hydrogen in the presence of 10% Pd-carbon (167 mg). Following the absorption of hydrogen, the catalyst was removed by filtration and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 10% HCl (20 ml) and the solution was refluxed for 2 h. The reaction mixture was neutralized with the anion exchange resin (Dowex 1-X2) conditioned to the OH form by 1N NaOH, and then the cation exchange resin (Amberlite CG-50, 20 ml) conditioned to the H form by 3N HCl was added to the solution. The suspension was stirred for 15 h and the resin was collected by filtration and washed with water. Adsorbates to the resin were eluted with 3N HCl and, after neutralizing with Dowex 1-X2, the eluate was concentrated in vacuo and applied onto a column packed with Dowex 1-X2 (20 ml). This chromatography was conducted using water as the solvent under a pressure of 4.0 kg/cm². The elution curve was drawn by measuring the UV-absorption of the eluate at 310 nm and the fractions corresponding to the largest peak were collected. After being adjusted to pH 3.0 with 0.1N HCl, the eluates were concentrated to a small amount and subsequently lyophilized to give arglecin dihydrochloride (100.3 mg, 15%) as a colorless solid, mp 140°C (decomp.) (lit.² 140-175°C). But on adjusting the pH to 5.3, arglecin monohydrochloride was obtained as a colorless oil.

Arglecin Monohydrochloride: ¹³C-Nmr (D₂O/TSP): δ 22.4 (2C), 27.3, 27.5 (2C), 40.9, 41.5, 123.0, 139.5, 157.4, 157.5, 158.7 ppm. (lit.²: δ 22.6 (2C), 27.7 (3C), 41.3, 41.7, 123.0, 139.7, 157.4, 157.6, 158.7 ppm); ¹H-nmr (D₂O/H₂O): δ 0.71 (d, 6H, CH₂CH(CH₃)₂), 1.76-1.88 (m, 3H, CH₂CH(CH₃)₂, CH₂CH₂CH₂NH), 2.37 (d, 2H, CH₂CH(CH₃)₂), 2.50 (t, 2H, CH₂CH₂CH₂NH), 3.10 (t, 2H, CH₂CH₂CH₂NH), 7.11 (s, 1H, pyrazine H) ppm. (lit.²: δ 0.85 (d), 1.81-2.15 (m), 2.51 (d), 2.65 (t), 3.25 (t), 7.23 (s) ppm).

6-(3-Aminopropyl)-2-hydroxy-3-isobutylpyrazine (2) Monohydrochloride

In a sealed tube, **10** (0.40 g, 1.1 mmol) was heated with conc. HCl (5 ml) at 160°C for 10 h. After cooling, the precipitates were removed by filtration and the filtrate was evaporated under a reduced pressure to obtain a brownish solid, which was recrystallized from AcOEt/MeOH to give 6-(3-aminopropyl)-2-hydroxy-3-isobutylpyrazine monohydrochloride (0.25 g, 81%). This compound was sublimed at 170°C/0.04 torr to give the monohydrochloride as colorless prisms, mp 225-227°C (decomp.) (lit.² 221-227°C).

2-Monohydrochloride: ¹³C-Nmr (D₂O/TSP): δ 24.5 (2C), 28.4, 29.4, 29.6, 41.4, 43.7, 125.1, 141.0, 159.9, 160.9 ppm. (lit.²: 22.7 (2C), 26.6, 27.5, 27.7, 39.7, 41.7, 123.0, 139.0, 157.7, 158.7 ppm); ¹H-Nmr (D₂O/TSP): δ 0.93 (d, 6H, CH₂CH(CH₃)₂), 1.80-2.30 (m, 3H, CH₂CH(CH₃)₂, CH₂CH₂CH₂NH₂), 2.59 (d, 2H, CH₂CH(CH₃)₂), 2.73 (t, 2H, CH₂CH₂CH₂NH₂), 3.11 (t, 2H, CH₂CH₂CH₂NH₂), 7.31 (s, 1H, pyrazine H) ppm. (lit.²: 0.85 (d), 1.86-2.18 (m), 2.53 (d), 2.68 (t), 3.08 (t), 7.26 (s) ppm); Anal. Calcd. for C₁₁H₁₉N₃O·HCl: C, 53.76; H, 8.20; N, 17.10. Found: C, 53.77; H, 8.21; N, 17.15.

Oxidation of 2-Chloro-3,6-dialkylpyrazines (4,5) with Potassium Persulfate

The reaction of **4** (0.87 g, 4.7 mmol) and **5** (1.61 g, 8.9 mmol) was respectively carried out according to the previous method⁷.

13: Colorless oil; Yield: 0.74 g (78%); bp 120°C/6 torr; ms: m/z 200 (M⁺), 185 (M⁺-CH₃), 158 (M⁺-C₃H₆); ¹H-nmr (CDCl₃/TMS): δ 0.87 (d, J = 6.8 Hz, 6H, CH₂CH(CH₃)₂), 2.15 (m, 1H, CH₂CH(CH₃)₂), 2.37 (s, 3H, CH₃), 2.70 (d, J = 6.8 Hz, 2H, CH₂CH(CH₃)₂), 8.14 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₉H₁₃N₂OCl: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.99; H, 6.56; N, 13.97.

14: Colorless oil; Yield: 1.58 g (88%); bp 115-118°C/3 torr; ms: m/z 200 (M⁺), 185 (M⁺-CH₃); ¹H-nmr (CDCl₃/TMS): δ 0.92 (d, J = 6.6 Hz, 6H, CH₂CH(CH₃)₂), 2.17 (m, J = 6.6 Hz, 1H, CH₂CH(CH₃)₂), 2.57 (s, 3H, CH₃), 2.67 (d, J = 6.6 Hz, 2H, CH₂CH(CH₃)₂), 8.07 (s, 1H, pyrazine H) ppm; Anal. Calcd. for C₉H₁₃N₂OCl: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.91; H, 6.58; N, 13.97.

Dechlorination of 2-Chloro-3,6-dialkylpyrazine 1-Oxides (13,14)

The reaction of **13** (0.53 g, 2.6 mmol) and **14** (1.12 g, 6.1 mmol) was respectively carried out according to the previous method⁸.

15: Colorless oil; Yield: 0.33 g (76%); bp 120°C/3 torr; ms: m/z 166 (M⁺), 151 (M⁺-CH₃), 124 (M⁺-C₃H₆); ¹H-nmr (CDCl₃/TMS): δ 0.94 (d, J = 6.3 Hz, 6H,

$\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.11 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.43 (s, 3H, CH_3), 2.60 (d, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 8.05 (s, 1H, pyrazine 2-H), 8.41 (s, 1H, pyrazine 5-H) ppm; Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.60; H, 8.75; N, 16.74.

16: Colorless oil; Yield: 0.49 g (48%); bp 94-95°C/1 torr; ms: m/z 166 (M^+), 149 (M^+-OH), 124 ($\text{M}^+-\text{C}_3\text{H}_6$); ^1H -nmr (CDCl_3/TMS): δ 0.95 (d, J = 6.3 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.24 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.48 (s, 3H, CH_3), 2.73 (d, J = 6.3 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 8.05 (s, 1H, pyrazine 2-H), 8.31 (s, 1H, pyrazine 5-H) ppm; Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.82; H, 8.56; N, 16.71.

Deoxygenation of 15 Using Phosphorus Trichloride

A mixture of **15** (0.21 g, 1.3 mmol) and phosphorus trichloride (3 ml) was heated at 100°C for 30 min in a sealed tube. The reaction mixture was poured into ice water and made alkaline with K_2CO_3 . The solution was extracted with n-pentane and the extract was worked up as usual to give an oil. This product was purified by low pressure liquid chromatography (Kieselgel 60, 230-400 mesh), using n-hexane/AcOEt as the solvent under a pressure of 2.0 kg/cm² to obtain 3-isobutyl-6-methylpyrazine (**17**: 0.11 g, 56%) as a colorless oil.

17: bp 47-48°C/10 torr; ms: m/z 150 (M^+), 135 (M^+-CH_3), 108 ($\text{M}^+-\text{C}_3\text{H}_6$); ^1H -nmr (CDCl_3/TMS): δ 1.07 (d, J = 6.3 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.08 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.51 (s, 3H, CH_3), 2.63 (d, J = 6.3 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 8.30 (s, 1H, pyrazine H), 8.38 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{N}_2$: C, 71.96; H, 9.39; N, 18.65. Found: C, 71.73; H, 9.39; N, 18.59.

Permaleic Acid Oxidation of 4

The reaction of **4** (1.4 g, 7.7 mmol) was carried out according to the previous method⁴.

18: Colorless needles; Yield: 0.77 g (46%); mp 129-130°C (n-hexane); ms: m/z 216 (M^+), 199 (M^+-OH), 182 (M^+-2OH); ^1H -nmr (CDCl_3/TMS): δ 0.99 (d, J = 6.3 Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.30 (m, 1H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.45 (s, 3H, CH_3), 2.95 (d, J = 6.3 Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 8.30 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: C, 49.89; H, 6.05; N, 12.93. Found: C, 50.03; H, 6.05; N, 12.94.

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