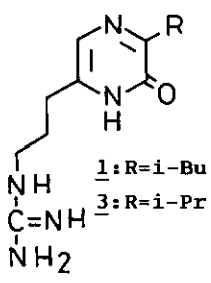
SYNTHESIS OF ARGVALIN AND ITS RELATED COMPOUND

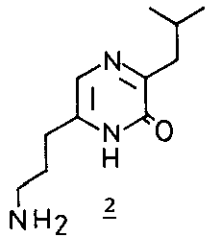
Akihiro Ohta*, Yutaka Aoyagi, Yohko Kurihara,
Akihiko Kojima, Kayo Yuasa, and Makoto Shimazaki
Tokyo College of Pharmacy
1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract —— Argvalin (3) and 6-(4-guanidinobutyl)-3-isobutyl-2(1H)-pyrazinone (4) were synthesized from DL-alanyl-valyl anhydride (6) and DL-alanyl-leucyl anhydride (5) respectively.

Recently, we have reported the synthesis of two naturally occurring pyrazines, 6-(3-guanidinopropyl)- (1: arglecin) and 6-(3-aminopropyl)-3-isobutyl-2(1H)-pyrazinones (2) which were found out from the culture filtrates of *Streptomyces toxytricini* and *S. lavendurae*.[1] Besides two substances described above, it is known that some *Streptomyces* species produce the analogous pyrazines. Namely, 6-(3-guanidinopropyl)-3-isopropyl-2(1H)-pyrazinone (3: argvalin) was isolated from the cultures of *S. filipinensis* by Umezawa et al. in 1973[2] and further 6-(4-guanidinobutyl)-3-isobutyl-2(1H)-pyrazinone (4) was discovered in the culture media of *S. toxitricini* by MacDonald et al. in 1976[3]. In this paper, the syntheses of 3 from DL-alanyl-valyl anhydride (6)[4] and 4 from DL-alanyl-leucyl anhydride (5)[5] by the same procedures as our previous report[1] are presented. The synthetic route for 3 and 4 is shown in Scheme 3.



1: R=i-Bu
3: R=i-Pr



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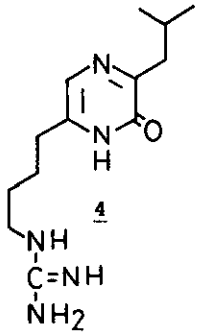
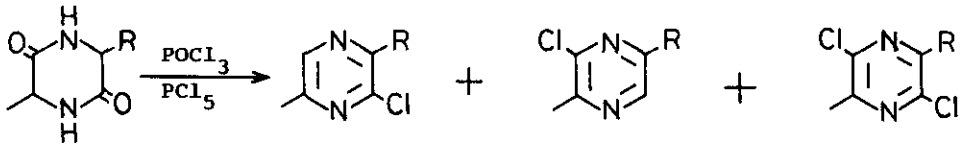


4

As shown in the previous report[1], heating of a mixture of DL-alanyl-leucyl anhydride (5)[5], phosphoryl chloride and phosphorus pentachloride at 140°C resulted in giving two monochloropyrazines (7, 9) and a dichloropyrazine (11). A distinction of the structures of 7 and 9 was accomplished on the basis of the ^{1}H-nmr spectra of these compounds and their some derivatives.



5: R=i-Bu
6: R=i-Pr

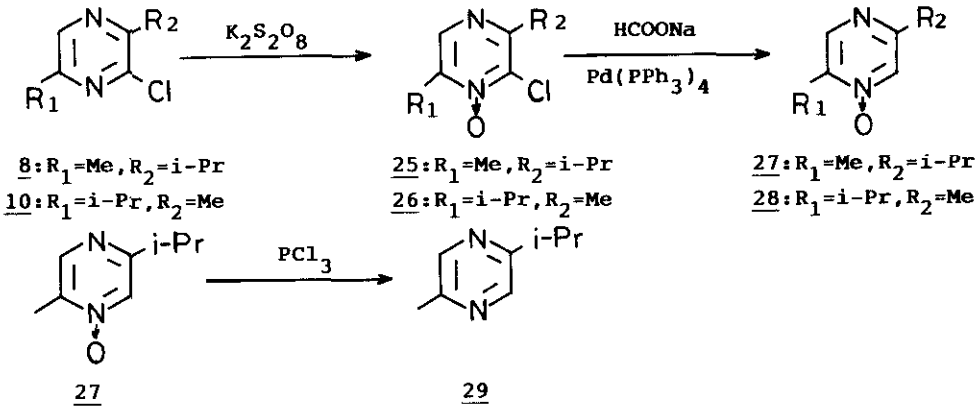
7: R=i-Bu
8: R=i-Pr

9: R=i-Bu
10: R=i-Pr

11: R=i-Bu
12: R=i-Pr

Scheme 1. Preparation of Chloropyrazines (7-12)

Similarly, 2-chloro- (8) and 5-chloro-3-isopropyl-6-methylpyrazines (10) could be obtained from DL-alanyl-valyl anhydride (6)[4]. The methine proton signal (H_B) of the isopropyl group of 8 was observed in a lower field than that of 10. On the other hand, the signal of the methyl signal (H_A) of 8 appeared in a higher field than that of 10. Furthermore, 8 and 10 were converted to the corresponding 2,5-dialkylpyrazine 1-oxides (27, 28) and 2-methyl-5-isopropylpyrazine (29) according to the procedure described in Scheme 2.



8: R_1=Me, R_2=i-Pr
10: R_1=i-Pr, R_2=Me

25: R_1=Me, R_2=i-Pr
26: R_1=i-Pr, R_2=Me

27: R_1=Me, R_2=i-Pr
28: R_1=i-Pr, R_2=Me

27

29

Scheme 2. Preparation of 2,5-Dialkylpyrazine 1-Oxides (27, 28) and 2-Methyl-5-isopropylpyrazine (29)

Their ^{1}H-nmr data are shown in Fig. 1. The methyl signal (H_C) of 27 was observed in a higher field than that of 29, and the methine proton (H_D) of the isopropyl group of 28 was appeared in a lower field than that of 29. Refering to the ^{1}H-nmr data of 7, 9 and their derivatives, the structures of 8 and 10 could easily be distinguished on the basis of these ^{1}H-nmr data.

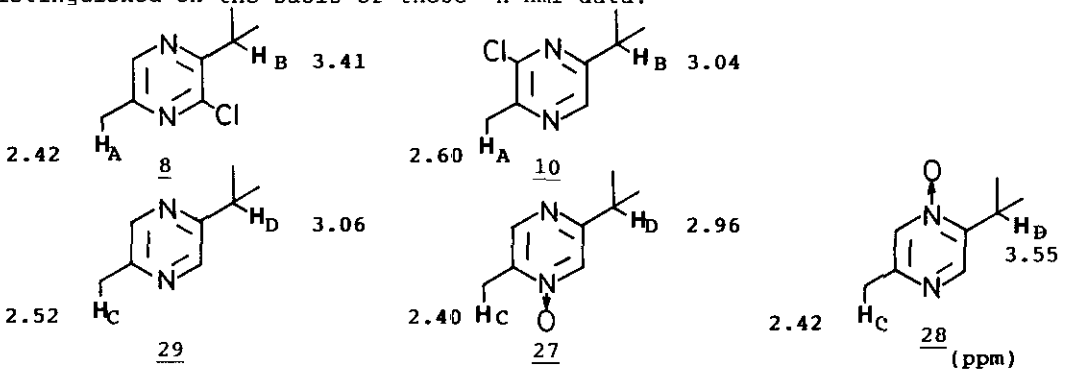
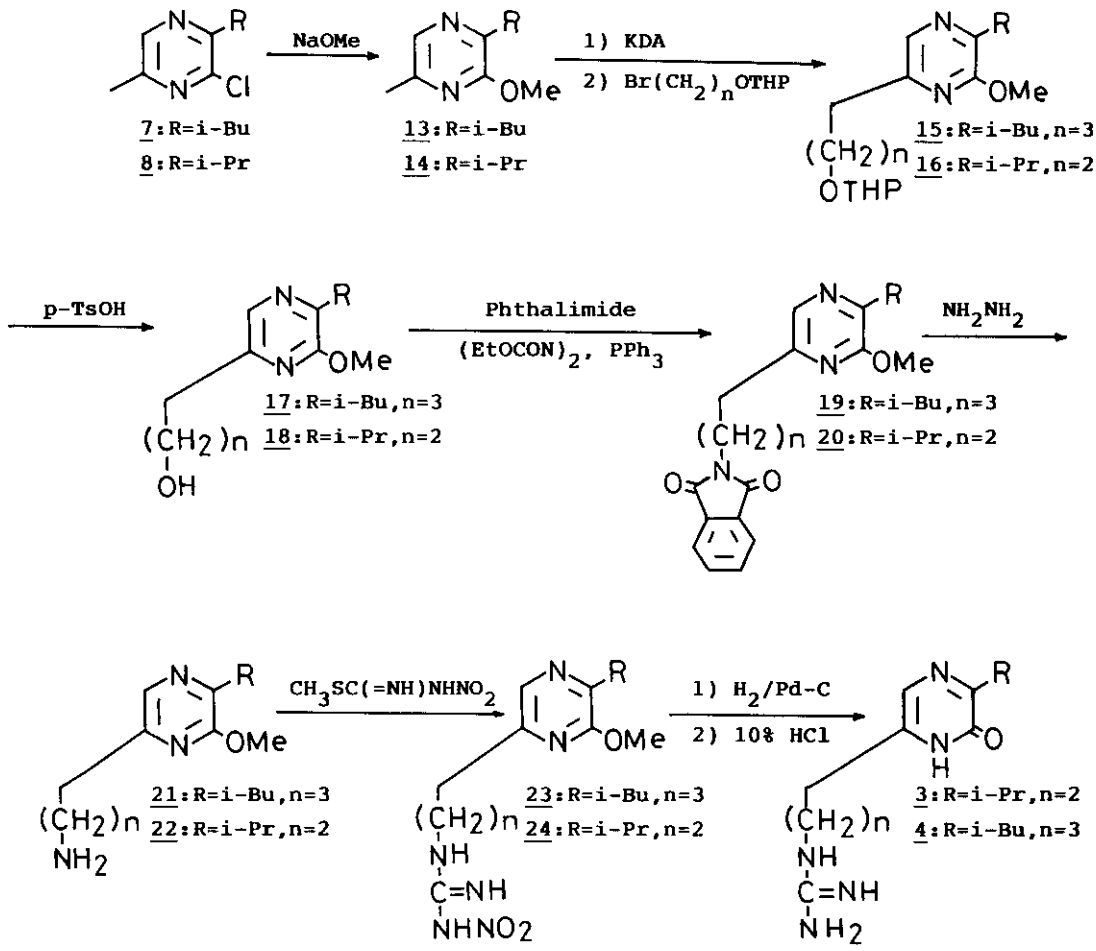


Fig. 1. ^{1}H-Nmr Data of 2-Chloropyrazines (8, 10) and their Derivatives (27-29)

2-Chloropyrazines (7, 8) afforded in this way were converted to the corresponding 2-methoxypyrazines (13, 14) by heating with sodium methoxide. Compound 13 was treated with potassium diisopropylamide (KDA), followed by reaction with 3-bromopropyl tetrahydropyranyl ether to give 15. Similarly, after a treatment of 14 with KDA, 2-bromoethyl tetrahydropyranyl ether was reacted with the resulting anion to give 16. Both compounds 15 and 16 were deprotected by the reported manner[1], followed by the Mitsunobu reaction[6] to give 19 and 20. After hydrazine degradation, the produced amines (21, 22) were reacted with N-nitromethylthioguanidine to furnish 23 and 24, which were hydrogenated in the presence of Pd-C and followed by hydrolysis with 10% HCl to obtain our target compounds (3, 4). The purification of these substances was carried out by anion exchange column chromatography. The elution curve was drawn by measuring an absorbance at 310 nm and some fractions constructing the largest peak in this chart were collected. After being neutralized with 0.1 N HCl, the solution was lyophilized to give argvalin monohydrochloride, mp 174-176°C (lit.[2] 175-176°C), and dihydrochloride of 4 whose melting point was not readily observed owing to the hygroscopicity but the decomposition point was in the range from 100 to 110°C (lit.[3] 105-108°C). Furthermore, ^{1}H-nmr data of these products and ^{13}C-nmr data of 4 agreed with those reported[2,3].



Scheme 3. Synthetic Route for 3 and 4

EXPERIMENTAL

All procedures were respectively carried out under the almost same conditions as described in the previous report[1] for the synthesis of arglecin. None of melting and boiling points were corrected. The following apparatus was used to obtain spectral data. Nmr: Varian EM-390 (^{1}H) and Brucker AM-400 (^{1}H, ^{13}C); ir spectra: Shimadzu IR-400; ms: Hitachi M-80 spectrometer.

2-Chloro-3-isopropyl-6-methylpyrazine (**8**)

Colorless oil; Yield: 34%; bp 94-95°C/14 torr; ms: m/z 170 (M^+), 155 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.21 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.42 (s, 3H, CH_3), 3.41 (m, 1H, $C\underline{H}(CH_3)_2$), 8.23 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_8H_{11}N_2Cl$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.05; H, 6.47; N, 16.31.

5-Chloro-3-isopropyl-6-methylpyrazine (**10**)

Colorless oil; Yield: 10%; bp 94-95°C/10 torr; ms: m/z 170 (M^+), 155 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.30 (d, J = 6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.60 (s, 3H, CH_3), 3.04 (m, 1H, $C\underline{H}(CH_3)_2$), 8.26 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_8H_{11}N_2Cl$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.13; H, 6.49; N, 16.15.

2,5-Dichloro-3-isopropyl-6-methylpyrazine (**12**)

Colorless oil; Yield: 2%; bp 67-68°C/4 torr; ms: m/z 204 (M^+), 189 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.27 (d, J = 7.2 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.60 (s, 3H, CH_3), 3.40 (m, 1H, $C\underline{H}(CH_3)_2$) ppm; Anal. Calcd for $C_8H_{10}N_2Cl_2$: C, 46.85; H, 4.91; N, 13.66. Found: C, 46.69; H, 4.90; N, 13.41.

2-Methoxy-3-isopropyl-6-methylpyrazine (**14**)

Colorless oil; Yield: 83%; bp 72-73°C/5 torr; ms: m/z 166 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.25 (d, J = 6.3 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.41 (s, 3H, CH_3), 3.43 (m, 1H, $C\underline{H}(CH_3)_2$), 3.97 (s, 3H, OCH_3), 7.97 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.87; H, 8.48; N, 16.78.

4-(3-Isobutyl-2-methoxy-6-pyrazinyl)butyl Tetrahydropyranyl Ether (**15**)

Colorless oil; Yield: 71%; bp 180°C/3 torr; ms: m/z 322 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 0.92 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.33-2.33 (m, 11H, THP H, $CH_2C\underline{H}_2C\underline{H}_2CH_2OTHP$ and $CH_2C\underline{H}(CH_3)_2$), 2.57-2.80 (m, 4H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_2CH_2CH_2OTHP$), 3.27-4.03 (m, 7H, OCH_3, $CH_2CH_2CH_2C\underline{H}_2OTHP$ and THP H), 4.57 (m, 1H, THP H), 7.88 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69. Found: C, 66.77; H, 9.37; N, 8.44.

3-(3-Isopropyl-2-methoxy-6-pyrazinyl)propyl Tetrahydropyranyl Ether (**16**)

Colorless oil; Yield: 83%; bp 81-82°C/7 torr; ms: m/z 294 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 1.24 (d, J = 6.9 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.37-2.21 (m, 8H, THP H and $CH_2C\underline{H}_2CH_2OTHP$), 2.78 (t, J = 7.7 Hz, 2H, $C\underline{H}_2CH_2CH_2OTHP$), 3.03-3.65 (m, 3H, $C\underline{H}(CH_3)_2$ and THP H), 3.70-3.95 (m, 5H, OCH_3 and $CH_2CH_2C\underline{H}_2OTHP$), 4.60 (m, 1H, THP H), 7.96 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{16}H_{26}N_2O_3$: C, 65.28; H, 8.90; N, 9.52. Found: C, 64.98; H, 8.88; N, 9.27.

6-(4-Hydroxybutyl)-3-isobutyl-2-methoxypyrazine (**17**)

Colorless oil; Yield: 90%; bp 160°C/2 torr; ms: m/z 238 (M^+), 196 ($M^+-C_3H_6$); ^{1}H-nmr ($CDCl_3$/ TMS): 0.92 (d, J = 6.9 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.50-2.37 (m, 5H, $CH_2C\underline{H}(CH_3)_2$ and $CH_2C\underline{H}_2C\underline{H}_2CH_2OH$), 2.49 (bs, 1H, OH), 2.57-2.81 (m, 4H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_2CH_2CH_2OH$), 3.65 (t, J = 6.6 Hz, 2H, $CH_2CH_2CH_2C\underline{H}_2OH$), 3.91 (s, 3H, OCH_3), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.44; H, 9.30; N, 11.59.

6-(3-Hydroxypropyl)-3-isopropyl-2-methoxypyrazine (**18**)

Colorless oil; Yield: 95%; bp 125-126°C/1 torr; ms: m/z 210 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 1.23 (d, J = 6.9 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.97 (m, 2H, $CH_2C\underline{H}_2CH_2OH$), 2.37-2.57 (bs, 1H, OH), 2.79 (t, J = 6.6 Hz, 2H, $C\underline{H}_2CH_2CH_2OH$), 3.30 (m, 1H, $C\underline{H}(CH_3)_2$), 3.67 (t, J = 6.6 Hz, 2H, $CH_2CH_2C\underline{H}_2OH$), 4.66 (s, 3H, OCH_3), 7.90 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.92; H, 8.62; N, 13.31.

6-(4-Phthalimidobutyl)-3-isobutyl-2-methoxypyrazine (**19**)

Colorless needles (hexane); Yield: 85%; mp 100°C; ms: m/z 367 (M^+), 325 ($M^+-C_3H_6$); ^{1}H-nmr ($CDCl_3$/TMS): 0.91 (d, J = 6.3 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.67-2.39 (m, 5H, $CH_2C\underline{H}(CH_3)_2$ and $CH_2C\underline{H}_2C\underline{H}_2CH_2N$), 2.55-2.83 (m, 4H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_2CH_2CH_2N$), 3.64-3.80 (m, 2H, $CH_2CH_2CH_2C\underline{H}_2N$), 3.87 (s, 3H, OCH_3), 7.58-7.93 (m, 5H, phthalimide H and pyrazine H) ppm; Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.88; H, 6.93; N, 11.36.

6-(3-Phthalimidopropyl)-3-isopropyl-2-methoxypyrazine (**20**)

Colorless prisms (hexane); Yield 85%; mp 112-114°C; ms: m/z 339 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 1.18 (d, J = 6.9 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.96-2.45 (m, 2H, $CH_2C\underline{H}_2CH_2N$), 2.70 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CH_2CH_2N$), 2.97-3.47 (m, 1H, $C\underline{H}(CH_3)_2$), 3.79 (t, J = 7.2 Hz, 2H, $CH_2CH_2C\underline{H}_2N$), 3.93 (s, 3H, OCH_3), 7.59-7.86 (m, 4H, phthalimide H), 7.88 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.46; H, 6.24; N, 12.46.

6-(4-Aminobutyl)-3-isobutyl-2-methoxypyrazine (**21**)

Colorless oil; Yield: 92%; bp 125°C/2 torr; ms: m/z 237 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 0.91 (d, J = 6.3 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.28-2.38 (m, 7H, $CH_2C\underline{H}(CH_3)_2$ and $CH_2C\underline{H}_2C\underline{H}_2CH_2N\underline{H}_2$), 2.54-2.83 (m, 6H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_2CH_2C\underline{H}_2NH_2$), 3.91 (s, 3H, OCH_3), 7.88 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{13}H_{23}N_3O$: C, 65.79; H, 9.77; N, 17.71. Found: C, 66.01; H, 9.92; N, 17.88.

6-(3-Aminopropyl)-3-isopropyl-2-methoxypyrazine (**22**)

Colorless oil; Yield: 92%; bp 105-107°C/1 torr; ms: m/z 209 (M^+), 179 (M^+-CH_2NH_2); ^{1}H-nmr ($CDCl_3$/TMS): 1.24 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.54 (s, 2H, NH_2), 1.85 (m, 2H, $CH_2C\underline{H}_2CH_2NH_2$), 2.65 (d, J = 7.5 Hz, 2H, $C\underline{H}_2CH_2CH_2NH_2$), 2.76 (t, J = 7.5 Hz, 2H, $CH_2CH_2C\underline{H}_2NH_2$), 3.10-3.46 (m, 1H, $C\underline{H}(CH_3)_2$), 3.93 (s, 3H, OCH_3), 7.88 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{11}H_{19}N_3O$: C, 63.12; H, 9.15; N, 20.08. Found: C, 62.93; H, 9.16; N, 19.99.

6-(4-Nitroguanidinobutyl)-3-isobutyl-2-methoxypyrazine (**23**)

Colorless needles (AcOEt); Yield: 87%; mp 135-137°C; ms: m/z 324 (M^+); ^{1}H-nmr ($CDCl_3$/TMS): 0.92 (d, J = 6.6 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.59-2.36 (m, 5H, $CH_2C\underline{H}(CH_3)_2$ and $CH_2C\underline{H}_2C\underline{H}_2CH_2NH$), 2.59-2.85 (m, 4H, $C\underline{H}_2CH(CH_3)_2$ and $C\underline{H}_2CH_2CH_2CH_2NH$), 3.16-3.47 (m, 2H, $CH_2CH_2CH_2C\underline{H}_2NH$), 3.90 (s, 3H, OCH_3), 7.83 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{14}H_{24}N_6O_3$: C, 51.83; H, 7.46; N, 25.91. Found: C, 51.81; H, 7.49; N, 25.90.

6-(3-Nitroguanidinopropyl)-3-isopropyl-2-methoxypyrazine (**24**)

Colorless needles (AcOEt/iso-Pr_2O); Yield: 100%; mp 120-121°C; ms (ci, isobutane): m/z 297 (M^++1); ^{1}H-nmr ($CDCl_3$/ TMS): 1.23 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.03-2.10 (m, 2H, $CH_2C\underline{H}_2CH_2NH$), 2.76 (t, J = 6.8 Hz, 2H, $C\underline{H}_2CH_2CH_2NH$), 3.28-3.35 (m, 1H, $C\underline{H}(CH_3)_2$), 3.41-3.46 (m, 2H, $CH_2CH_2C\underline{H}_2NH$), 3.95 (s, 3H, OCH_3), 7.91 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{12}H_{20}N_6O_3$: C, 48.64; H, 6.80; N, 28.36. Found: C, 48.84; H, 6.94; N, 28.53.

2-Chloro-3-isopropyl-6-methylpyrazine 1-Oxide (**25**)

Colorless needles (n-hexane); Yield: 87%; mp 82-83°C; ms: m/z 186 (M^+), 171 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): 1.29 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.47 (s, 3H, CH_3), 3.47 (m, 1H, $C\underline{H}(CH_3)_2$), 8.27 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_8H_{11}N_2OCl$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.38; H, 5.94; N, 14.92.

2-Chloro-3-methyl-6-isopropylpyrazine 1-Oxide (**26**)

Colorless plates (n-hexane); Yield: 82%; mp 94-95°C; ms: m/z 186 (M^+), 169 (M^+-OH); ^{1}H-nmr ($CDCl_3$/TMS): 1.32 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.62 (s, 3H, CH_3), 3.58 (m, 1H, $C\underline{H}(CH_3)_2$), 8.18 (s, 1H, pyrazine H). ppm; Anal. Calcd for $C_8H_{11}N_2OCl$: C, 51.48; H, 5.94; N, 15.01. Found: C, 51.69; H, 6.00; N, 14.91.

2-Methyl-5-isopropylpyrazine 1-Oxide (**27**)

Colorless oil; Yield: 87%; bp 95-96°C/4 torr; ms: m/z 152 (M^+), 137 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): 1.28 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.40 (s, 3H, CH_3), 2.96 (m, 1H, $C\underline{H}(CH_3)_2$), 8.05 (s, 1H, pyrazine 6-H), 8.36 (s, 1H, pyrazine 3-H) ppm; Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.83; H, 7.93; N, 18.29.

2-Isopropyl-5-methylpyrazine 1-Oxide (**28**)

Colorless needles (hexane); Yield: 15%; mp 72-73°C; ms: m/z 152 (M^+), 135 (M^+-OH); ^{1}H-nmr ($CDCl_3$/TMS): 1.28 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.42 (s, 3H, CH_3), 3.55 (m, 1H, $C\underline{H}(CH_3)_2$), 7.96 (s, 1H, pyrazine 6-H), 8.27 (s, 1H, pyrazine 3-H) ppm; Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.06; H, 7.88; N, 18,39.

2-Methyl-5-isopropylpyrazine (**29**)

Colorless oil; Yield: 55%; bp 54-55°C/18 torr; ms: m/z 136 (M^+), 121 (M^+-CH_3); ^{1}H-nmr ($CDCl_3$/TMS): 1.29 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 2.52 (s, 3H, CH_3), 3.06 (m, 1H, $C\underline{H}(CH_3)_2$), 8.35 (s, 2H, pyrazine H) ppm; Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.13; H, 8.92; N, 20.42.

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