EMEHETERONE: SYNTHESIS AND STRUCTURAL REVISION

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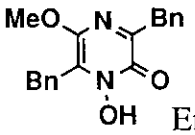
Abstract —— Emeheterone, a fungal metabolite, was synthesized from DL-phenylalanine. Based on the results of this synthesis, the structure of emeheterone was redetermined as 3,6-dibenzyl-2-hydroxy-5-methoxypyrazine 4-oxide.

In a previous paper, the oxidation of 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine by permaleic acid (PMA) was found to occur at N-1 and the synthesis of 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine 4-oxide was conducted in three steps from 2-hydroxy-3,6-diisobutyl-5-methoxypyrazine.[1] Based on the results, 3,6-dibenzyl-2-hydroxy-5-methoxypyrazine 1- (1) and 4-oxides (2) were synthesized in the present study. The ir and ^{1}H-nmr spectra and melting point of the latter compound agreed with those of emeheterone.[2] It thus became evident that the structure of emeheterone should be revised. The present study was carried out for this purpose.



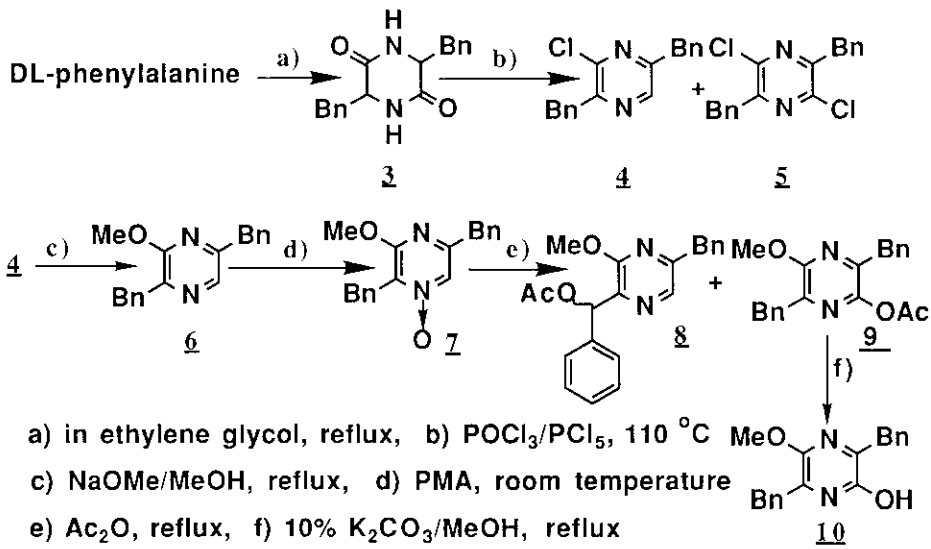
Bn = benzyl

Emeheterone (reported[2])

DL-Phenylalanine anhydride (3),[3] prepared from DL-phenylalanine by refluxing in ethylene glycol, was heated with a mixture of phosphoryl chloride and a small amount of phosphorus pentachloride at 110°C in a sealed tube to give a mixture of 3,6-dibenzyl-5-chloropyrazine (4)[4] and 3,6-dibenzyl-2,5-dichloropyrazine (5).[4] These compounds were separated from each other by silica gel column chromatography. Compound 4 was converted to the corresponding methoxypyrazine (6), which was then oxidized with permaleic acid to give 3,6-dibenzyl-5-methoxypyrazine 1-oxide (7). The signal of the pyrazine ring proton of 7 in ^{1}H-nmr spectrum appeared in a field higher than that of 6,[5] indicating that the oxidation of 6 occurred possibly at N-1.

Compound 7 was heated with acetic anhydride under reflux to afford a mixture of

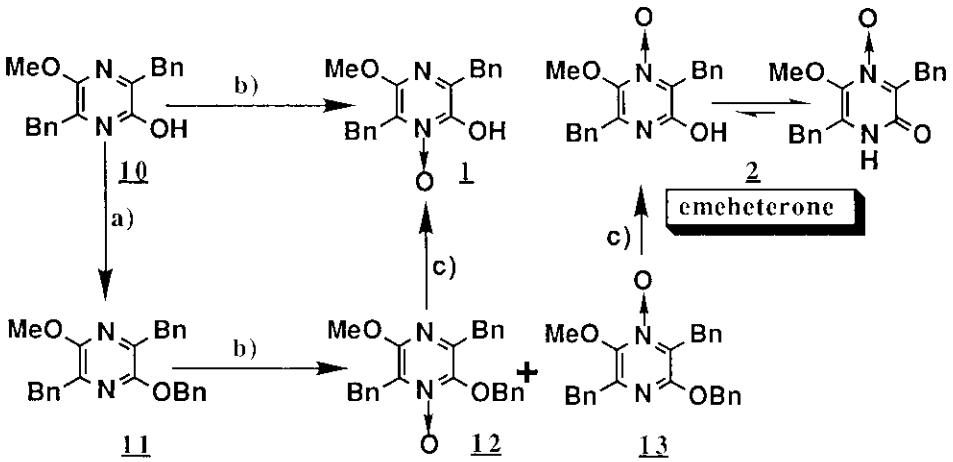
6-(α-acetoxybenzyl)-3-benzyl-5-methoxypyrazine (8) and 2-acetoxy-3,6-dibenzyl-5-methoxylpyrazine (9) (1:1.6). These were successfully separated by silica gel column chromatography. In the structure of the former (8), the position of the acetoxyl group was not confirmed. However, the rearrangement of acetoxyl group from the N-oxide group appeared likely to take place at the neighboring benzyl group. Compound 9 was hydrolyzed by heating in methanol-water containing potassium carbonate to give 3,6-dibenzyl-2-hydroxy-5-methoxypyrazine (10).



The oxidation of the 2-hydroxy-5-methoxypyrazine (10) with permaleic acid gave a monoxide. The product showed a red coloration with ferric chloride, thus indicating that oxidation may occur at N-1 to give the 2-hydroxy-5-methoxypyrazine 1-oxide (1). However, the melting point and spectral data of 1 were not identical with those of emeheterone and thus a study on synthesis of 3,6-dibenzyl- 2-hydroxy-5-methoxypyrazine 4-oxide (2) was made. Following the method reported,[1] compound 10 was benzylated to 3,6-dibenzyl-2-benzyloxy-5-methoxypyrazine (11), which was oxidized with permaleic acid to give a mixture of monoxides, 3,6-dibenzyl-2-benzyloxy-5-methoxypyrazine 1-oxide (12) and 4-oxide (13) (3:4). The products could be separated from each other by silica gel column chromatography. These

compounds could be distinguished from each other by their ^{13}C-nmr spectra.[1] In their ^{13}C-nmr spectra, C-2 of 12 and of C-5 of 13 signals could be observed in a field higher than those of 11, respectively.

The hydrogenolysis of 12 using 5% Pd-C gave 1. Under the same conditions, 2 was obtained from 13 and the product showed no coloration with ferric chloride. The spectral data and melting point of 2 were completely identical with those of emeheterone.[2] The ir spectrum of emeheterone showed a band at 1640 cm^{-1} due to an amide group, and thus emeheterone may exist primarily in the pyrazinone form.



a) BnBr, tetrametylammonium bromide, in 10% KOH/$CHCl_3$

b) PMA, c) H_2 / 5% Pd-C, in ethanol

EXPERIMENTAL

No correction was made for any of the melting or boiling points. ^{1}H-Nmr spectral data were obtained with Varian EM-390 or Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. ^{13}C-Nmr spectra were taken in $CDCl_3$ with Brucker AM-400 using TMS as the internal standard. For column chromatography, Wakogel C-200 (WAKO Pure Chemical Ind. Ltd., Tokyo) was used as the packing material. Medium-pressure column chromatography was conducted using a UVILOG ALPC-100 as the pump, UVILOG 5IIIa as the UV detector (Oyo-Bunko Kiki Co., Ltd., Tokyo) and Kiesel gel 60 (Merck AG, Darmstadt) as the packing material. The following instruments were used to obtain other spectral data. Ir spectra: Japan Spectroscopic Co. A-100; Ms: Hitachi M-80B specrometer.

Reaction of DL-Phenylalanine Anhydride (3) with a Mixture of $POCl_3$ and PCl_5

A mixture of 3 (20 g, 68 mmol), $POCl_3$ (40 ml, 430 mmol) and PCl_5 (ca. 5 g, 24 mmol) was heated at 110°C for 3 h in a sealed tube. After being cooled, the mixture was poured into ice water. The resulting mixture was made alkaline with powdered K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by column chromatography eluting with hexane to give 5 and with a mixture of hexane-Et_2O (9:1) to give 4, successively.

3,6-Dibenzyl-5-chloropyrazine (4); colorless prisms (hexane); mp 37-37.5°C (lit.,[4] mp 35.5-37°C); yield: 6.2 g (31%).

3,6-Dibenzyl-2,5-dichloropyrazine (5); colorless prisms (iso-PrOH); mp 117.5-118°C (lit.,[4] mp 107-109°C); yield: 9.2 g (41%).

Synthesis of 3,6-Dibenzyl-5-methoxypyrazine (6)

A chloropyrazine (4) (70 g, 0.238 mol) was added to a MeOH solution of NaOMe, prepared from Na (27 g, 1.2 g atom) and MeOH (600 ml), and the reaction mixture was refluxed for 6 h. Following removal of the solvent by distillation in vacuo, the residue was triturated with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aq. NaCl and dried over Na_2SO_4. The solvent was evaporated and the resulting oil was purified by distillation. Colorless oil; bp 150°C/0.01 torr; yield: 65.6 g (95%); ms: m/z 290 (M^+); ^{1}H-nmr (90 MHz): δ 3.82 (s, 3H, OCH_3), 3.88 (s, 2H, CH_2Ph), 3.99 (s, 2H, CH_2Ph), 7.06-7.22 (m, 10H, benzene H), 7.82 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.60; H, 6.40; N, 9.64.

Synthesis of 3,6-Dibenzyl-5-methoxypyrazine 1-Oxide (7)

A mixture of 6 (50 g, 170 mmol), 60% H_2O_2 (30 g, 520 mmol) and maleic anhydride (55 g, 560 mmol) in $CHCl_3$ (1.1 l) was allowed to stand for 12 h at room temperature and then washed with H_2O, 5% $KHCO_3$ and saturated aq. NaCl, successively. The organic layer was worked up as usual to give 7, which was purified by recrystallization. Colorless needles (MeOH); mp 102.5-103.5°C; yield: 49.4 g (95%); ms: m/z 306 (M^+), 289 (M^+-OH); ^{1}H-nmr (90 MHz): δ 3.88 (s, 2H, CH_2Ph), 3.99 (s, 3H, OCH_3), 4.19 (s, 2H, CH_2Ph), 7.13-7.43 (m, 10H, benzene H), 7.57 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.52; H, 6.03; N, 9.08.

Reaction of 3,6-Dibenzyl-5-methoxypyrazine 1-Oxide (7) with Ac_2O

A solution of 7 (50 g, 163 mmol) in Ac_2O (400 ml) was refluxed for 1.5 h. The reaction mixture was concentrated to dryness and the oily residue was poured into ice water. The mixture was made alkaline with powdered K_2CO_3 and extracted with $CHCl_3$. After the usual work-up of the $CHCl_3$ extract, the product was purified by silica gel chromatography using hexane containing an increasing amount of Et_2O, to elute 9 and 8, successively. Compound 9 was used for the synthesis of 10 without further purification.

6-(α-Acetoxybenzyl)-3-benzyl-5-methoxypyrazine (8); Colorless oil; bp 180°C/1 torr; yield: 31.2 g (55%); ms: m/z 348 (M^+); ir (neat): 1740 (νCO) cm^{-1}; ^{1}H-nmr (90 MHz): δ 2.13 (s, 3H, $COCH_3$), 3.93 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2Ph), 7.00 (s, 1H, CH(OAc)Ph, 7.20-7.53 (m, 10H, benzene H), 7.97 (s, 1H, pyrazine H) ppm; Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.79; N, 8.04. Found: C, 72.46; H, 5.82; N, 8.07.

2-Acetoxy-3,6-dibenzyl-5-methoxypyrazine (9); Pale yellow-green oil; yield: 19.8 g (35%); ms: m/z 348 (M^+); ir (neat): 1770 (νCO) cm^{-1}; ^{1}H-nmr (90 MHz): δ 2.14 (s, 3H, $COCH_3$), 3.80 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2Ph), 3.98 (s, 2H, CH_2Ph), 7.07-7.23 (m, 10H, benzene H) ppm.

Synthesis of 3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine (10)

A solution of 9 (17.0 g, 48.9 mmol), 10% K_2CO_3 (100 ml) and MeOH (100 ml) was refluxed gently for 0.5 h. MeOH was then removed by distillation in vacuo. The resulting solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated aq. NaCl and worked up as usual to give a solid, which was purified by recrystallization. Pale yellow needles (MeOH); mp 168-168.5°C; yield: 14.8 g (99%); ms: m/z 306 (M^+), 291 (M^+-CH_3); ^{1}H-nmr (400 MHz): δ 3.91 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2Ph), 4.06 (s, 2H, CH_2Ph), 7.17-7.38 (m, 10H, benzene H), 12.58 (br s, 1H, OH or NH) ppm; ^{13}C-nmr: δ 36.13 (t, CH_2Ph), 38.27 (t, CH_2Ph), 54.05 (q, OCH_3), 126.24 (d), 126.47 (d), 128.29 (d), 128.47 (d), 129.13 (d), 129.26 (d), 134.67 (s), 138.15 (s), 138.65 (s), 140.47 (s), 150.30 (s, C-5), 153.18 (s, C-2) ppm; Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.57; H, 5.89; N, 9.11.

Oxidation of 3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine (10)

A solution of 90% H_2O_2 (227 mg, 6.0 mmol) and maleic anhydride (588 mg, 6.0 mmol) in $CHCl_3$ (20 ml) was refluxed for 5 min. After cooling, 10 (612 mg, 2.0 mmol) was added to the solution. The reaction mixture was stirred for 1 day at room temperature, then washed with H_2O and worked up as usual. The product was purified by recrystallization.

3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine 1-Oxide (1): Colorless plates (MeOH); mp 100-101°C; yield: 464 mg (72%); ms: m/z 322 (M^+), 305 (M^+-OH); ^{1}H-nmr (400 MHz): δ 3.97 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2Ph), 4.24 (s, 2H, CH_2Ph), 7.21-7.41 (m, 10H, benzene H), 8.57 (br s, 1H, OH or NOH) ppm; ^{13}C-nmr: δ 30.11 (t, CH_2Ph), 38.25 (t, CH_2Ph), 54.31 (q, OCH_3), 126.64 (d), 126.90 (d), 127.97 (s), 128.44 (d), 128.52 (d), 129.13 (d), 129.22 (d), 136.39 (s), 136.67 (s), 137.69 (s), 147.01 (s, C-2), 150.42 (s, C-5) ppm; Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.84 H, 5.63; N, 8.72.

Benzylation of 3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine (10)

On a solution of 10 (7.0 g, 22.9 mmol), BnBr (5.4 ml, 45.8 mmol), 10% KOH (100 ml) and a catalytic amount of Me_4NBr in $CHCl_3$ (100 ml) an ultrasonic operation was carried out at 30°C. After 1.5 days, the $CHCl_3$ layer was taken, washed with H_2O, and saturated aq. NaCl, successively. It was then worked up as usual. The product was purified by column chromatography, eluting with hexane containig an increasing amount of Et_2O to give 11 as a solid, which was purified by recrystallization. Colorless needles (hexane); mp 56-57°C; yield: 7.25 g (80%); ms: m/z 396 (M^+); ^{1}H-nmr (400 MHz): δ 3.88 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2Ph), 4.03 (s, 2H, CH_2Ph), 5.30 (s, 2H, OCH_2Ph), 7.16-7.30 (m, 15H, benzene H) ppm; ^{13}C-nmr: δ 37.72 (t, CH_2Ph), 37.96 (t, CH_2Ph), 53.74 (q, OCH_3), 67.86 (t, OCH_2Ph), 126.11 (d), 127.55 (d), 127.95 (d), 128.21 (d), 128.27 (d), 129.23 (d), 137.67 (s), 137.76 (s), 138.89 (s), 138.99 (s), 151.82 (s, C-2), 152.69 (s, C-5) ppm; Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.73; H, 6.16; N, 7.03

Oxidation of 3,6-Dibenzyl-2-benzyloxy-5-methoxypyrazine (11)

A solution of 90% H_2O_2 (340 mg, 6.0 mmol) and maleic anhydride (647 mg, 6.0 mmol) in $CHCl_3$ (30 ml) was refluxed for 5 min. After cooling, 11 (824 mg, 2.0 mmol) was added to the solution. The mixture was stirred for 1 day at room temperature

and worked up as before to give oily products, which were purified by medium-pressure column chromatography using hexane containing an increasing amount of Et_2O, to give 12 and 13.

3,6-Dibenzyl-2-benzyloxy-5-methoxypyrazine 1-Oxide (12); Colorless needles (hexane); mp 103-104°C; yield: 741 mg (30%); ms: m/z 412 (M^+), 395 (M^+-OH); ^{1}H-nmr (400 MHz): δ 3.84 (s, 2H, CH_2Ph), 3.92 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2Ph), 5.24 (s, 2H, OCH_2Ph), 7.16-7.41 (m, 15H, benzene H) ppm; ^{13}C-nmr: δ 29.74 (t, CH_2Ph), 38.10 (t, CH_2Ph), 54.29 (q, OCH_3), 73.71 (t, OCH_2Ph), 126.51 (d), 126.63 (d), 128.35 (d), 128.40 (d), 128.53 (d), 128.66 (d), 129.12 (d), 129.14 (d), 133.48 (s), 135.80 (s), 136.87 (s), 138.03 (s), 143.38 (s), 147.89 (s, C-2), 155.81 (s, C-5), ppm; Anal. Calcd for $C_{26}H_{24}N_2O_3$: C, 75.70; H, 5.87; N, 6.79. Found: C, 75.77; H, 5.87; N, 6.82.

3,6-Dibenzyl-2-benzyloxy-5-methoxypyrazine 4-Oxide (13); Colorless oil; bp 200°C/0.001 torr; yield: 989 mg (40%); ms: m/z 412 (M^+), 395 (M^+-OH); ^{1}H-nmr (400 MHz): δ 3.85 (s, 3H, OCH_3), 3.99 (s, 2H, CH_2Ph), 4.21 (s, 2H, CH_2Ph), 5.38 (s, 2H, OCH_2Ph), 7.18-7.35 (m, 15H, benzene H) ppm; ^{13}C-nmr: δ 29.76 (t, CH_2Ph), 38.36 (t, CH_2Ph), 59.88 (q, OCH_3), 68.61 (t, OCH_2Ph), 126.64 (d), 128.05 (d), 128.17 (d), 128.37 (d), 128.47 (d), 128.50 (d), 129.14 (d), 129.31 (d), 133.75 (s), 136.60 (s), 136.81 (s), 138.04 (s), 142.87 (s), 149.49 (s, C-5), 155.13 (s, C-2) ppm; High Resol. ms, Calcd for $C_{26}H_{23}N_2O_2$ (M^+ - OH): 395.1758. Found: 395.1766.

General Procedure for Hydrogenolysis of 3,6-Dibenzyl-2-benzyloxy-5-methoxypyrazine 1- (12) and 4-Oxide (13)

A solution of 12 or 13 (412 mg, 1 mmol) in EtOH (5 ml) was shaken in the presence of 5% Pd-C (412 mg) in H_2 stream. When the absorption speed of H_2 slowed down (30 min), the reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by recrystallization.

3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine 1-Oxide (1); Yield: 225 mg (70%).

3,6-Dibenzyl-2-hydroxy-5-methoxypyrazine 4-Oxide (2); Colorless needles (benzene); mp 214-215°C (lit.,[2] mp 215-217°C); yield: 290 mg (90%); ms: m/z 322 (M^+), 305 (M^+-OH); ir (KBr): 1640 (νCO) cm^{-1}; ^{1}H-nmr (400 MHz): δ 3.91 (s, 3H, OCH_3), 3.93 (2H, s, CH_2Ph), 4.20 (2H, s, CH_2Ph), 7.21-7.45 (m, 10H, benzene H), 12.80 (br s, 1H, OH or NH) ppm; ^{13}C-nmr: δ 30.31 (t, CH_2Ph); 33.96 (t, CH_2Ph), 61.62 (q, OCH_3), 126.78 (d), 127.53 (d), 128.34 (d), 128.43 (d), 129.00 (d), 129.06 (d),

129.50 (d), 129.57 (s), 135.78 (s), 136.45 (s), 140.49 (s), 144.17 (s, C-5), 158.35 (s, C-2) ppm; Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.86; H, 5.57; N, 8.66.

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