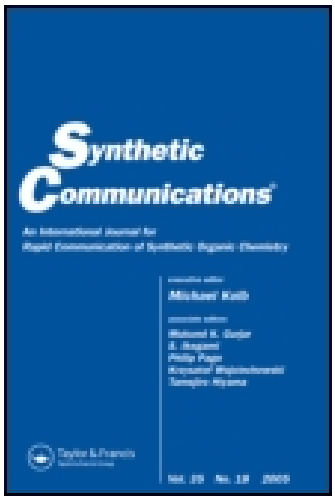

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

AN EFFICIENT SYNTHESIS OF (±)-6,7-DIMETHOXY-1-OXO-2-(3-PIPERIDYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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Published online: 09 Nov 2006.

To cite this article: Akio Kakefuda , Toshihiro Watanabe , Takumi Takahashi , Shuichi Sakamoto & Shin-Ichi Tsukamoto (2001) AN EFFICIENT SYNTHESIS OF (±)-6,7-DIMETHOXY-1-OXO-2-(3-PIPERIDYL)-1,2,3,4-TETRAHYDROISOQUINOLINE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:3, 401-408, DOI: 10.1081/SCC-100000530

To link to this article: http://dx.doi.org/10.1081/SCC-100000530

SYNTHETIC COMMUNICATIONS, 31(3), 401–408 (2001)

AN EFFICIENT SYNTHESIS OF (±)-6,7-DIMETHOXY-1-OXO-2-(3-PIPERIDYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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ABSTRACT

The synthesis of (±)-6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline (**1**) via the cyclization of dimethylacetal (**3**) under acidic condition is described.

As part of our research program, the practical preparation of 6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline **1** (Fig. 1) was required. In previous reports, 6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinolines have been prepared by the Bischler–Napieralski reaction involving the ring-closure of isocyanate with phosphorus oxychloride ($POCl_3$) (1), as well as cyclization of carbamate with polyphosphoric acid (PPA) (2). However, there are few reports

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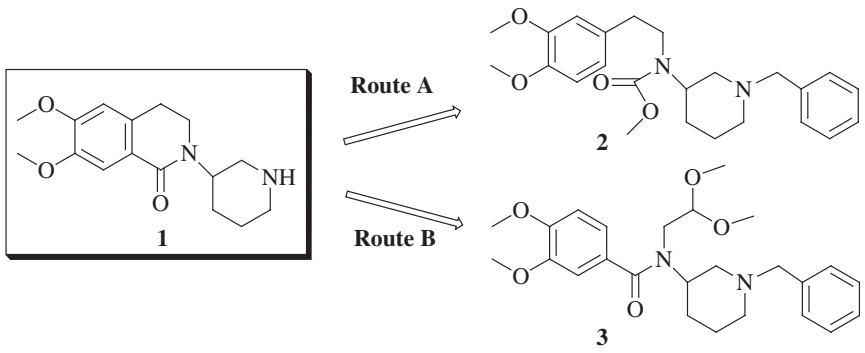
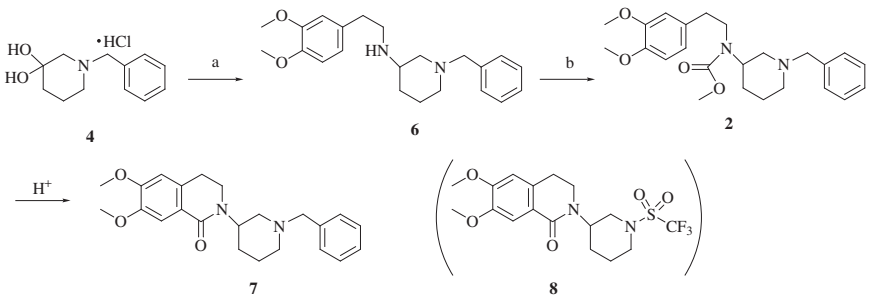


Figure 1.

on the synthesis of 2-substituted derivatives (3) and to our knowledge, for the derivatives bearing directly cyclic amine at 2-position such as **1** have never been reported. Hence, we investigated ring-closing processes of the compounds having piperidine moiety. In this communication, we describe an efficient synthesis of compound **1** via the cyclization of dimethylacetal **3**.

Initially, we tried the synthesis of compound **1** from phenethylcarbamate **2** by the Bischler–Napieralski reaction (Fig. 1, Route A). Phenethylcarbamate **2** was prepared in two steps from 1-benzyl-3-piperidone hydrate **4** available from Aldrich (Scheme 1). Compound **4** was condensed with phenethylamine **5** by reductive



Condition	Yield of 7
PPA, 145°C 15 min	- (decomposed)
$POCl_3$, reflux 1h	- (no reaction)
Tf_2O, DMAP, CH_2Cl_2, r.t. 3 days	19 – 53%

Conditions; (a) 3,4-dimethoxyphenethylamine (**5**), $NaBH(OAc)_3$, AcOH, THF; (b) $ClCO_2Me$, Et_3N, THF

Scheme 1.

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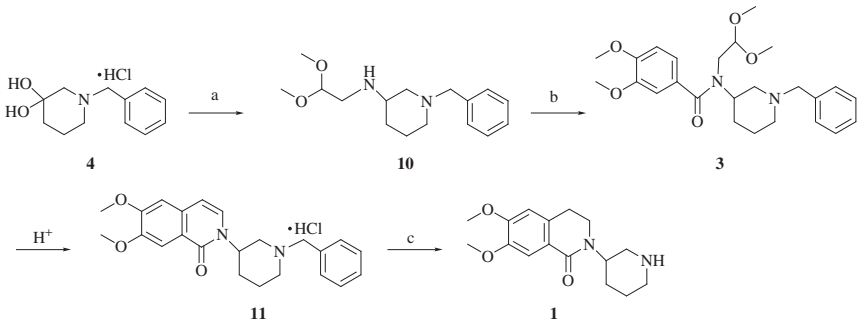
alkylation in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$ (4) to obtain amine **6**. Subsequently, amine **6** was converted to the carbamate **2** by using methyl chloroformate. The Bischler–Napieralski reaction with the carbamate **2** was attempted under the same conditions (Scheme 1). However, the cyclized compound **7** was only obtained by using trifluoromethanesulfonic anhydride (Tf_2O) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (5) in low to moderate yields. Moreover, this reaction needed both a long reaction time (3 days) and column purification to obtain pure **7** due to the formation of by-product **8**.

In the search for a more efficient method to prepare **1**, we then examined the cyclization of dimethylacetal **3** under acidic conditions (Fig. 1, Route B) (6). Compound **4** was condensed with aminoacetaldehyde dimethylacetal **9** by reductive alkylation followed by benzoylation to afford acetal **3** in 92% yield (Scheme 2). The acetal **3** was successfully cyclized to 1,2-dihydro-1-oxo-isoquinoline **11** when concentrated hydrogen chloride (conc. HCl) and acetic acid (AcOH) were employed, although **11** was obtained in moderate yield (47%) as a hydrochloride salt (Table 1, entry 1). We then attempted to improve the yield of **11** by using other acids. When trifluoroacetic acid (TFA) or methanesulfonic acid (MsOH) was used, the yield of **11** was improved (73% entry 2, 74% entry 3, respectively). Furthermore, the reaction with concentrated sulfuric acid (conc. H_2SO_4) gave **11** in better yield (78% entry 4). Studies of the amount of conc. H_2SO_4 and the reaction temperature were performed (entries 5–10). As a result, the condition using 0.2 times (mL/mmol) of conc. H_2SO_4 at 80°C was optimum (entries 8 and 10), because it allowed the reaction to be completed within an hour and the sulfate of **11** to be crystallized from the resulting reaction mixture. This condition abridged the work-up procedures of the reaction and furnished **11** in excellent reproducibility. Some kilograms of **11** were also synthesized using this condition with minimal modifications.



Conditions; (a) aminoacetaldehyde dimethylacetal (**9**), $NaBH(OAc)_3$, AcOH, THF;
(b) 3,4-dimethoxybenzoylchloride, CH_3CN; (c) H_2(3-4kg/cm^2), 20%$Pd(OH)_2$/C, AcOH, 90°C

Scheme 2.

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Table 1. Cyclization of **3** Under Acidic Conditions

Entry	Scale (mmol)	Condition	Time (h)	Isolated Yield of **11** (%)
1	5.0	conc. HCl 5 mL, AcOH 5 mL, 60°C	4	47[a]
2	5.0	TFA 10 mL, 50°C	24	73[b]
3	5.0	MsOH 2 Eq, AcOH 5 mL, 60°C	20	74[b]
4	5.0	conc. H_2SO_4 5 mL, AcOH 5 mL, 60°C	8	78[b]
5	5.0	conc. H_2SO_4 5 mL, AcOH 5 mL, 80°C	3	82[b]
6	5.0	conc. H_2SO_4 5 mL, AcOH 5 mL, 100°C	1	65[b]
7	5.0	conc. H_2SO_4 2.5 mL, AcOH 5 mL, 80°C	2	83[b]
8	5.0	conc. H_2SO_4 1 mL, AcOH 5 mL, 80°C	1	85[c]
9	5.0	conc. H_2SO_4 0.5 mL, AcOH 5 mL, 80°C	2	—[d]
10	189	conc. H_2SO_4 37.8 mL, AcOH 189 mL, 80°C	1	82[c]

[a] After column purification, the hydrochloride was obtained.
[b] The hydrochloride was obtained without column purification.
[c] The sulfate was obtained from the resulting reaction mixture, then was converted to the hydrochloride.
[d] The reaction was complicated.

Finally, the resulting **11** was hydrogenated over palladium hydroxide in AcOH to give 1-oxo-1,2,3,4-tetrahydroisoquinoline **1** in 82% yield. In conclusion, we demonstrated an efficient synthesis of (±)-6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline. This method can offer a useful pathway for the synthesis of various 2-substituted-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinolines.

EXPERIMENTAL

Melting points were measured with a Yanaco MP-500D melting point apparatus without correction. ^{1}H NMR spectra were obtained on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-LX2000 mass spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer.

Methyl (±)-*N*-(1-Benzyl-3-piperidyl)-*N′*-(3,4-dimethoxyphenethyl) Carbamate (2). To a suspension of 1-benzyl-3-piperidone monohydrochloride monohydrate **4** (10.0 g, 44.3 mmol) and 3,4-dimethoxyphenethylamine **5** (8.03 g, 44.3 mmol) in tetrahydrofuran (THF, 100 mL) were added AcOH (2.54 mL, 44.3 mmol) and $NaBH(OAc)_3$ (10.3 g, 48.7 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was made alkaline with 5 *N*

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NaOHaq. at 0°C, then extracted with $CHCl_3$ (50 mL × 2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1-benzyl-3-[(3,4-dimethoxyphenethyl)amino]piperidine **6** (14.2 g, 90%) as a yellow oil. To a solution of **6** (14.2 g, 40.1 mmol) and Et_3N (6.70 mol, 48.1 mmol) in THF (100 mL) was added dropwise a solution of methyl chloroformate (3.40 mL, 44.1 mmol) in THF (10 mL) at 0°C, and the mixture was stirred at 0°C for 1 h. The resulting mixture was concentrated in vacuo and the residue was dissolved in H_2O (150 mL), then extracted with AcOEt (50 mL × 2). The combined extract was washed with 1 *N* NaOHaq. (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give **2** (16.2 g, 98%) as a yellow oil. This material may be used in the next cyclization step or converted to its oxalate salt. The oxalate salt was obtained from MeOH–AcOEt as a colorless powder: m.p. 145–146°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68–1.78 (4H, m, 4-H_2 and 5-H_2 of piperidine), 2.41 (2H, br s, 1-H_2 or 6-H_2 of piperidine), 2.66 (2H, br s , 3,4-$(OMe)_2PhCH_2$), 2.95–2.97 (2H, m, 1-H_2 or 6-H_2 of piperidine), 3.27–3.29 (2H, m, MeO_2 $CNCH_2$), 3.60 (3H, s, OMe), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.95 (3H, br s, CH_2Ph and 3-H of piperidine), 6.70 (1H, d, $J = 7.2$ Hz, 5- or 6-H of 3,4-$(OMe)_2$Ph), 6.78 (1H, s, 2-H of 3,4-$(MeO)_2$Ph), 6.86 (1H, d, $J = 7.2$ Hz, 5- or 6-H of 3,4-$(MeO)_2$Ph), 7.40 (5H, brs, CH_2Ph); MS (FAB) *m/z* 413 (MH^+); Anal. calcd. for $C_{24}H_{32}N_2O_4 \cdot C_2H_2O_4$: C 62.14, H 6.82, N 5.57. Found: C 62.01, H 6.81, N 5.47.

(±)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (7) and (±)-6,7-dimethoxy-1-oxo-2-[1-(trifluoromethanesulfonyl)-3-piperidyl]-1,2,3,4-tetrahydroisoquinoline (8). To a solution of **2** (6.31 g, 15.3 mmol) and DMAP (4.67 g, 38.2 mmol) in CH_2Cl_2 (120 mL) was added dropwise a solution of Tf_2O (10.3 mL, 61.2 mmol) in CH_2Cl_2 (10 mL) at 0°C, and the mixture was stirred at room temperature for 3 days. The reaction mixture was partitioned between $CHCl_3$ (50 mL × 2) and H_2O (150 mL) and the combined $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a mixture of **7** and **8**. The mixture can be separated by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1 for **7**, 99/1 for **8**) to give **7** (3.11 g, 53%) as a yellow oil and **8** as a yellow form.

Compound **7** may be converted to its hydrochloride salt. The hydrochloride salt of **7** was obtained from EtOH–AcOEt as a colorless powder: m.p. 232–238°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74–1.93 (4H, m, 4-H_2 and 5-H_2 of piperidine), 2.87 (2H, br s, 4-H_2 of isoquinoline), 2.88 (1H, br s, 1-H or 6-H of piperidine), 3.19–3.24 (2H, m, 1-H and 6-H of piperidine), 3.31 (1H, br s, 1-H or 6-H of piperidine), 3.44 (2H, br s, 3-H_2 of isoquinoline), 3.75 (3H, s, OMe), 3.81 (3H, s, OMe), 4.32 (2H, t, $J = 4.8$ Hz, CH_2Ph), 4.85–4.87 (1H, m, 3-H of piperidine), 6.89 (1H, s, 5-H of isoquinoline), 7.34 (1H, s, 8-H of isoquinoline), 7.46–7.48 (3H, m, CH_2Ph), 7.59–7.61 (2H, m, CH_2Ph), 10.64 (1H, brs, HCl); MS (FAB) *m/z* 381 (MH^+); Anal. calcd. for $C_{23}H_{28}N_2O_3 \cdot HCl \cdot 0.3H_2O$: C 65.41, H 7.06, N 6.63, Cl 8.39. Found: C 65.38, H 7.12, N 6.65, Cl 8.17.

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Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.96 (4H, m, 4-H_2 and 5-H_2 of piperidine), 2.89–2.93 (2H, m, 4-H_2 of isoquinoline), 2.98–3.02 (1H, m, 1-H or 6-H of piperidine), 3.25–3.33 (1H, m, 1-H or 6-H of piperidine), 3.38–3.57 (2H, m, 3-H_2 of isoquinoline), 3.92 (6H, s, $(OMe)_2$), 3.94–4.01 (2H, m, 1-H and 6-H of piperidine), 4.47 (1H, br s, 3-H of piperidine), 6.63 (1H, s, 5-H of isoquinoline), 7.58 (1H, s, 8-H of isoquinoline); MS (FAB) *m/z* 423 (MH^+).

(±)-*N*-(1-Benzyl-3-piperidyl)-*N*-(2,2-dimethoxyethyl)-3,4-dimethoxybenzamide (3). To a suspension of 1-benzyl-3-piperidonemonohydrochloride monohydrate **4** (46.4 g, 205 mmol) in THF (380 mL) were added aminoacetaldehyde dimethylacetal (21.6 g, 205 mmol), AcOH (11.8 mL, 205 mmol), and $NaBH(OAc)_3$ (47.9 g, 226 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was made alkaline with 5 *N* NaOHaq. at 0°C, then extracted with AcOEt (200 mL × 2). The combined extract was washed with saturated NaClaq. (200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 1-benzyl-3-[(2,2-dimethoxyethyl)amino]piperidine **10** (52.7 g, 92%) as a yellow oil. To a solution of **10** (52.7 g, 189 mmol) in CH_3CN (400 mL) was added dropwise a solution of 3,4-dimethoxybenzoylchloride (39.9 g, 199 mmol) in CH_3CN (100 mL) at 0°C, and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was made alkaline with 5 *N* NaOHaq. at 0°C, then extracted with AcOEt (250 mL × 2). The combined extract was washed with 0.5 *N* NaOHaq. (200 mL × 2), saturated NaClaq. (200 mL), and dried over anhydrous Na_2SO_4, then concentrated in vacuo to give **3** (97.4 g, 99%) as a brown oil. This material may be used in the next cyclization step: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51–1.89 (4H, m, 4-H_2 and 5-H_2 of piperidine), 2.10 (2H, br s, 1-H and 6-H of piperidine), 2.74–2.84 (2H, m, 1-H and 6-H of piperidine), 3.34–3.68 (10H, m, $(OMe)_2$ and $CONCH_2$ and CH_2Ph), 3.80 (3H, s, OMe), 3.91 (1H, brs, $CH(OMe)_2$), 3.92 (3H, s, OMe), 4.65 (1H, br s, 3-H of piperidine), 6.81–6.88 (3H, m, 3,4-$(MeO)_2$Ph), 7.24–7.33 (5H, m, CH_2Ph); MS (FAB) *m/z* 443 (MH^+); HRMS calcd. for $C_{25}H_{34}N_2O_5$:443.2521. Found: 443.2545.

(±)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2-dihydroisoquinoline (11). To a solution of **3** (97.4 g, 196 mmol) in AcOH (196 mL) was added conc. H_2SO_4 (39.2 mL), and the mixture was stirred at 80°C for 1 h. The mixture was cooled to room temperature to allow crystallization from the resulting solution. To the mixture was added acetone (300 mL) and the mixture was further stirred at 4°C for 4 h, then the resulting crystals were collected and washed with acetone to give the sulfate salt of **11** as a slightly brown powder. The sulfate salt of **11** was dissolved in H_2O (200 mL) and made alkaline with 5 *N* NaOHaq. at 0°C, then extracted with $CHCl_3$ (200 mL × 2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give **11** as a brown foam.

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Compound **11** was converted to its hydrochloride salt. The hydrochloride salt of **11** was obtained from EtOH–AcOEt as a slightly brown powder (64.5 g, 82%): m.p. 256–259°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86–1.88 (4H, m, 4-H_2 and 5-H_2 of piperidine), 2.03–2.08 (3H, m, 1-H and 6-H of piperidine), 2.97 (1H, br s, 1-H or 6-H of piperidine), 3.85 (3H, s, OMe), 3.88 (3H, s, OMe), 4.30–4.39 (2H, m, CH_2Ph), 5.30 (1H, brs, 3-H of piperidine), 6.63 (1H, d, $J = 7.2$ Hz, 3-H of isoquinoline), 7.16 (1H, s, 5-H of isoquinoline), 7.37 (1H, d, $J = 7.2$ Hz, 4-H of isoquinoline), 7.45–7.46 (3H, m, CH_2Ph), 7.61 (1H, s, 8-H of isoquinoline), 7.76–7.78 (2H, m, CH_2Ph), 11.07 (1H, brs, HCl); MS (FAB) m/z 379 (MH^+); Anal. calcd. for $C_{23}H_{26}N_2O_3 \cdot HCl$: C 66.58, H 6.56, N 6.75, Cl 8.54. Found: C 66.70, H 6.58, N 6.70, Cl 8.48.

(±)-6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline (1). To a solution of the hydrochloride salt of **11** (21.2 g, 51.0 mmol) in AcOH (106 mL) was added palladium hydroxide on carbon (20 wt% 10.6 g), and the mixture was stirred under hydrogen pressure (3–4 kg/cm^2) at 90°C for 2 days. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O (100 mL) and made alkaline with 5 *N* NaOHaq. at 0°C, then extracted with $CHCl_3$ (100 mL × 2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residual solid was recrystallized from AcOEt to give **1** (12.4 g, 84%) as a colorless powder: m.p. 139–140°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.73 (2H, m, 4-H_2 of piperidine), 1.80–1.90 (2H, m, 5-H_2 of piperidine), 2.46–2.53 (1H, m, 1-H or 6-H of piperidine), 2.66–2.72 (1H, m, 1-H or 6-H of piperidine), 2.84–2.87 (2H, m, 4-H_2 of isoquinoline), 3.02–3.09 (2H, m, 1-H and 6-H of piperidine), 3.41–3.53 (2H, m, 3-H_2 of isoquinoline), 3.73 (3H, s, OMe), 3.74 (3H, s, OMe), 4.59–4.66 (1H, m, 3-H of piperidine), 6.63 (1H, s, 5-H of isoquinoline), 7.60 (1H, s, 8-H of isoquinoline); MS (FAB) *m/z* 291 (MH^+); Anal. calcd. for $C_{16}H_{22}N_2O_3$: C 66.18, H 7.64, N 9.65. Found: C 65.98, H 7.62, N 9.61.

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Received in Japan March 6, 2000