A FACILE SYNTHESIS OF 6-AMINO-1-BENZYL-4-METHYL- AND 6-AMINO-1,4-DIMETHYLHEXAHYDRO-1*H*-1,4-DIAZEPINES, THE AMINE PART OF SUBSTITUTED BENZAMIDES WITH A POTENT SEROTONIN 3 RECEPTOR ANTAGONISTIC ACTIVITY

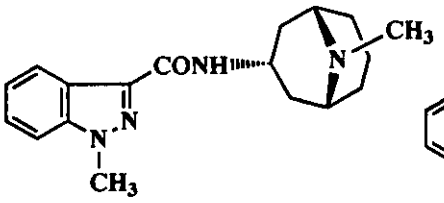
Hiroshi Harada, Yoshimi Hirokawa, Toshiya Morie, and Shiro Kato*

Exploratory Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan

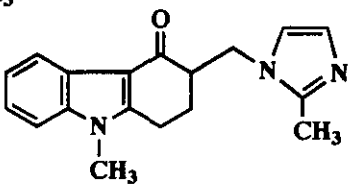
Abstract- A facile synthesis of 6-amino-1-benzyl-4-methyl- and 6-amino-1,4-dimethylhexahydro-1*H*-1,4-diazepines (**16a** and **16b**) which have served as the amine part of the new and novel benzamides (**3** and **4**) with a potent serotonin 3 receptor antagonistic activity is reported. The formation of 1,4-diazepine ring system was achieved by the reaction of tris(hydroxymethyl)nitromethane (**11**) with *N*,*N*'-disubstituted ethylenediamines (**12a** and **12b**). The dehydroxymethylation of the resultant 6-hydroxymethyl-6-nitro-1,4-diazepines (**13a** and **13b**) and successive reduction gave the target compounds (**16a** and **16b**), in approximately 15—30% overall yield.

During recent years, a number of potent and selective serotonin 3 (5-HT_3) receptor antagonists have been reported,[1] and granisetron (**1**) and ondansetron (**2**) are used clinically for the control of the emesis induced by cancer chemotherapeutic agents such as cisplatin and cyclophosphamide.[2] 5-HT_3 antagonists are being studied in man for the treatment of gastrointestinal motility disorders, migraine, schizophrenia, and anxiety.[3] On the basis of random screening, we found that the structurally novel benzamides (**3** and **4**) containing a 1,4-diazepine ring in an amine moiety showed a potent 5-HT_3 receptor antagonistic activity.[4] This paper describes a facile synthesis of 6-amino-1-benzyl-4-methyl- and 6-amino-1,4-

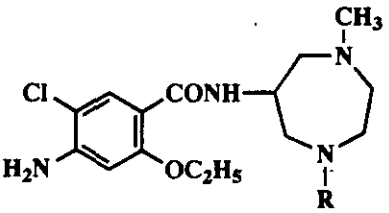
dimethylhexahydro-1*H*-1,4-diazepines (**16a** and **16b**), which are the amine part of benzamides (**3** and **4**).[5]



granisetron (**1**)



ondansetron (**2**)

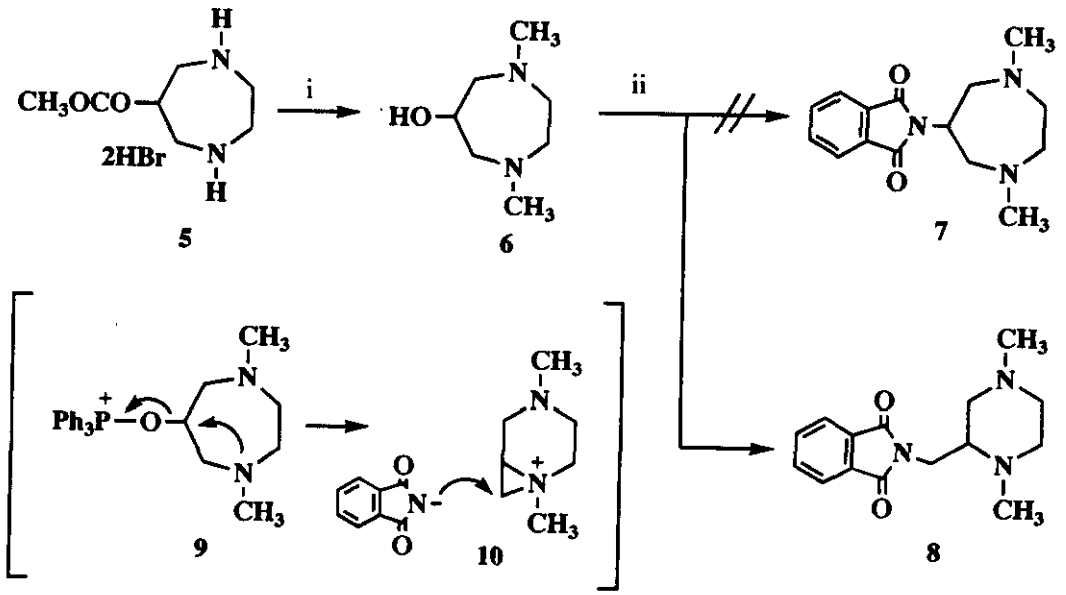


3; R = CH_2Ph

4; R = CH_3

There were very few studies on the preparation of the 1,4-diazepine derivatives having an amino group or any other suitable for its transformation into amino group at the 6 position thus far; an only report is the synthesis of 6-acetoxyhexahydro-1*H*-1,4-diazepine dihydrobromide (**5**).[6] Hence our first plan to prepare **16b** was the conversion of 1,4-dimethylhexahydro-1*H*-1,4-diazepin-6-ol (**6**), which was easily prepared from **5**, to the corresponding 6-phthalimido analogue under Mitsunobu reaction conditions.[7] The treatment of **6** with phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate

Scheme 1

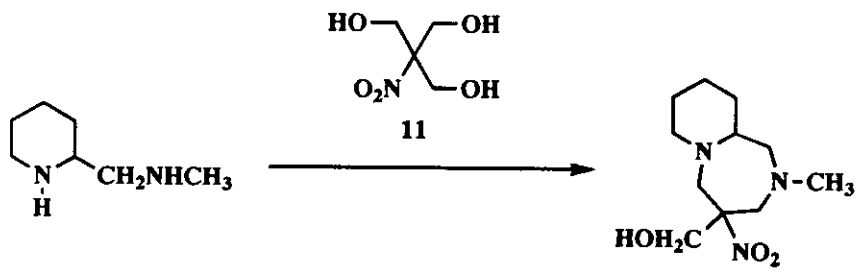


i; HCHO / HCOOH, ii; phthalimide / DEAD / Ph_3P

(DEAD) gave the ring-contracted product, 2-phthalimidomethylpiperazine (**8**), but the formation of the desired 1,4-diazepine (**7**) was not observed.[8] ^{1}H Nmr and ms spectra were clearly consistent with **8**. The formation of **8** can be considered to proceed *via* the aziridinium cation (**10**) derived from the intermediate (**9**) (Scheme 1).

The synthetic route to the 6-amino-1,4-diazepine ring involving the 6-nitro derivative is next investigated. Biere and Redmann reported that the treatment of 2-methylaminomethylpiperidine with tris(hydroxymethyl)nitromethane (**11**), which was the product of addition of formaldehyde to nitromethane, gave 4-hydroxymethyl-2-methyl-4-nitrohexahydropyrido[1,2-*a*][1,4]diazepine (Scheme

Scheme 2

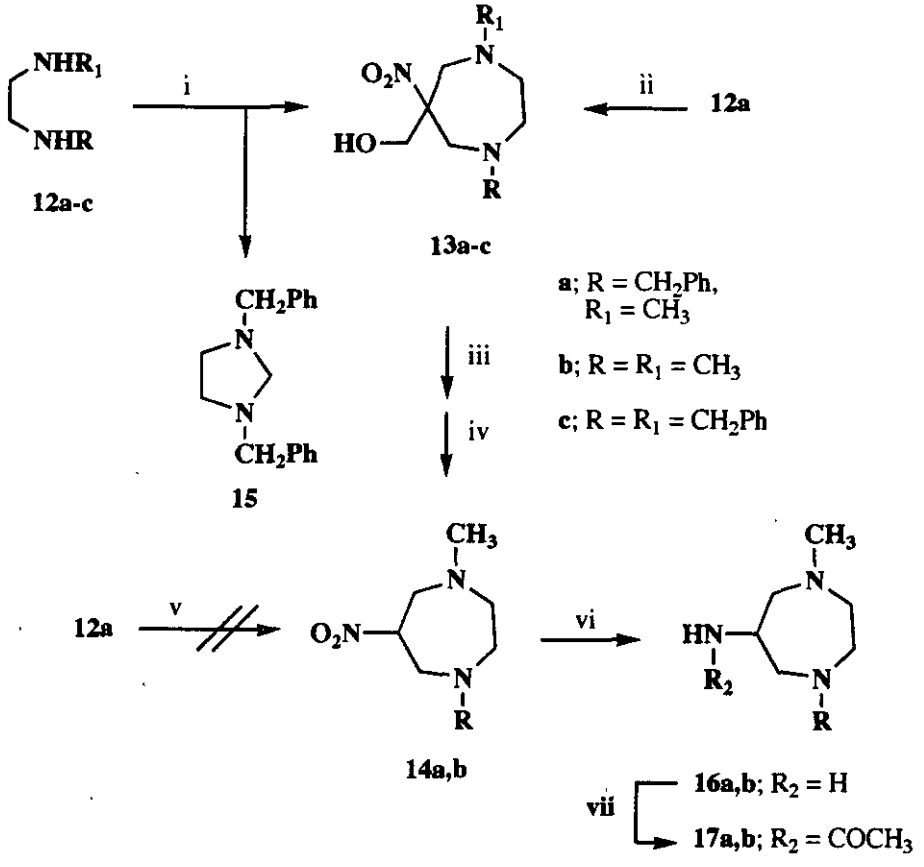


2).[9] The report on the formation of the 1,4-diazepine ring prompted us to study the reaction between *N,N'*-disubstituted ethylenediamine and **11**. Additionally, it is known that the aldolic reaction is reversible, thus under the action of strong base such as sodium methoxide the retro-aldolic reaction occurs resulting in cleavage of the C—C bond.[10] We expected that the reaction of the ethylenediamine (**12**) with **11**, followed by the retro-aldolic reaction of the 6-hydroxymethyl-6-nitro-1,4-diazepine should give the 6-nitro-1,4-diazepine. In fact, the condensation of *N*-benzyl-*N'*-methylethylenediamine (**12a**)[11] with **11** in water at 50°C smoothly proceeded to afford the 6-hydroxymethyl-6-nitro-1,4-diazepine (**13a**) as an unstable oil in 68% yield. The use of CH_3OH or 1,4-dioxane as a solvent cosiderably decreased the yield. Compound (**13a**) was likewise obtained by the reaction of **12a** with 2-nitroethanol and formaldehyde in *N,N*-dimethylformamide. The transformation of **13a** thus prepared into the 6-nitro-1,4-diazepine (**14a**) was achieved by using *tert*-C_4H_9OK as a base and successively careful acidification of the resulting potassium salt of **14a**. Compound (**14a**) was isolated as an unstable oil in 94% yield. On the other hand, the straightforward preparation of **14a** from nitromethane, **12a**, and formaldehyde was unsuccessful. Similarly, 1,4-dimethyl-6-nitrohexahydro-1*H*-1,4-diazepine (**14b**) was prepared from

N,N'-dimethylethylenediamine (**12b**) and **11** followed by treatment of *tert*-C_4H_9OK of the resultant **13b**. However the reaction of *N,N'*-dibenzylethylenediamine (**12c**) in place of **12a** and **12b** with **11** resulted in the formation of 1,3-dibenzyl-1,3-imidazolidine (**15**)[12] instead of the 1,4-diazepine (**13c**), although the reason for this observation could not be explained clearly.

The immediate hydrogenation of the 6-nitro-1,4-diazepines (**14a** and **14b**) with Raney nickel, followed by the acetylation of the resultant 6-amino-1,4-diazepines (**16a** and **16b**) with acetic anhydride gave the desired compounds (**17a** and **17b**) in 48 and 28% overall yields from **14a** and **14b**, respectively (Scheme 3). The transformation of the nitro group of **17a** and **17b** into an amino goup resulted in low yield, presumably because of the instability of the 6-nitro-1,4-diazepines (**14a** and **14b**).

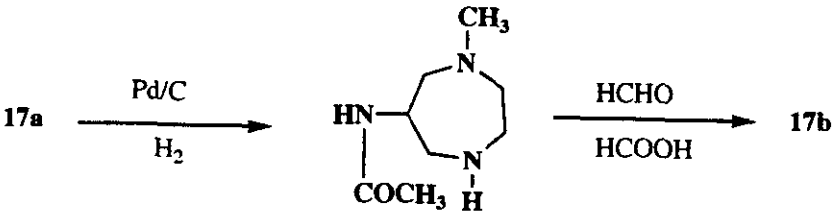
Scheme 3



i; **11** / H_2O, ii; 2-nitroethanol / HCHO, iii; tert-C_4H_9OK / CH_3OH, iv; NH_2OH HCl, v; nitromethane / HCHO, vi; Raney Ni / H_2, vii; $(CH_3CO)_2O$

The 1,4-dimethyl-1,4-diazepine (**17b**) was alternatively prepared by hydrogenolysis of **17a** and subsequent treatment of the 1,4-diazepine (**18**) with formic acid-formaldehyde (Scheme 4). Acid hydrolysis of the 6-acetylamino-1,4-diazepines (**17a** and **17b**) produced the desired amines (**16a** and **16b**).

Scheme 4



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*In conclusion, a facile synthesis of the 6-amino-1,4-diazepines (**16a** and **16b**) has been developed in approximately 15—30% overall yield.*

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 260-10 spectrophotometer. Secondary ion mass spectra were obtained on a Hitachi M-80B spectrometers. ^{1}H Nmr spectra were recorded with a Varian XL-300 (300 MHz) and a Gemini-200 (200 MHz) spectrometers in $CDCl_3$. *Chemical shifts are expressed as* δ (ppm) values with Me_4Si as an internal standard, and coupling constants (*J*) are given in Hz. Organic extracts were dried over anhydrous Na_2SO_4 or anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. *Merck silica gel 60 (70—230 mesh) was used for column chromatography.*

1,4-Dimethylhexahydro-1*H*-1,4-diazepin-6-ol (6). A solution of **5**[6] (20.0 g, 57 mmol), 35% formaldehyde (16.1 g, 0.19 mol), and formic acid (20 ml) was heated to reflux for 7 h. The reaction mixture was concentrated to dryness, and the oily residue was diluted with a small amount of water. The aqueous solution was basified with solid K_2CO_3 and then extracted with $CHCl_3$. The solvent was evaporated to leave an oil, which was distilled to give 7.0 g (78%) of **6** as a pale yellow oil, bp 75—78°C

/ 1 mmHg; *Anal.* Calcd for $C_7H_{16}N_2O$: C, 58.30; H, 11.18; N, 19.43. Found: C, 58.06; H, 11.20; N, 19.29. ^{1}H nmr (300 MHz) δ: 2.41 (s, 6H, CH_3 × 2), 2.38—2.50 (m, 2H), 2.66—2.84 (m, 6H), 3.77 (m, 1H, 6-CH); ir (neat) ν cm^{-1}, 3420, 2930, 2840, 2800. 1450; ms *m/z*: 145 (MH^+).

***N*-[(1,4-Dimethyl-2-piperazinyl)methyl]phthalimide (8).** To a mixture of **6** (3.0 g, 21 mmol), triphenylphosphine (5.5 g, 21 mmol), phthalimide (3.1 g, 21 mmol), and anhydrous tetrahydrofuran (THF, 30 ml) was added dropwise a solution of diethyl azodicarboxylate (DEAD, 3.6 g, 21 mmol) in anhydrous THF (10 ml) at 5°C. The mixture was stirred at room temperature for 20 h. After the solvent was evaporated, the residue was dissolved in $CH_3CO_2C_2H_5$ (AcOEt) and 10% HCl. The aqueous layer was separated, basified with 10% aqueous K_2CO_3, and then extracted with $CHCl_3$. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with AcOEt to AcOEt:CH_3OH = 9:1 to give a solid. The solid was recrystallized from AcOEt:*n*-hexane = 1:1 to afford 1.4 g (24%) of **8**, mp 101—103°C; *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.86; H, 7.04; N, 15.18. ^{1}H Nmr (200 MHz) δ: 2.01 (m, 1H), 2.13—2.55 (m, 3H), 2.23 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.55—2.73 (m, 2H), 2.78 (m, 1H), 3.71 (dd, 1H, J = 8.0, 14.0, $(CO)_2NC\underline{H}_2$), 3.93 (d, 1H, J = 3.5, 14.0, $(CO)_2NC\underline{H}_2$), 7.65—7.79, 7.79—7.91 (m, 4H); ir (KBr) ν cm^{-1}, 2920, 2780, 1755, 1705, 1390, 1375; ms *m/z*: 274 (MH^+), 113 (M^+—$CH_2N(CO)_2C_6H_4$).

1-Benzyl-6-hydroxymethyl-4-methyl-6-nitrohexahydro-1*H*-1,4-diazepine (13a). From Tris-(hydroxymethyl)nitromethane (11). To a mixture of **11** (118.9 g, 0.79 mol), $NaHCO_3$ (40.0 g, 0.48 mol), and water (1000 ml) was added dropwise **12a** (123.0 g, 0.75 mol). The mixture was heated at *ca.* 50°C for 2 h and then cooled to room temperature. The resultant oil was dissolved in CH_2Cl_2. The organic layer was separated, washed with brine, and dried. The solvent was evaporated at *ca.* 35°C to leave an oil, which was chromatographed on silica gel with AcOEt to give 141.4 g (68%) of **13a** as a pale yellow unstable oil.[13] ^{1}H Nmr (300 MHz) δ: 2.41 (s, 3H, CH_3), 2.50—2.81 (m, 4H, 2-CH_2, 3-CH_2), 2.91 (d, J = 14.0, 1H, 5- or 7-C$\underline{H}_2$), 3.11 (d, J = 14.0, 1H, 5- or 7-C$\underline{H}_2$), 3.44 (d, J = 14.0, 1H, 5- or 7-C$\underline{H}_2$), 3.47 (d, J = 14.0, 1H, 5- or 7-C$\underline{H}_2$), 3.63 (d, J = 13.5, 1H, C$\underline{H}_2$Ph), 3.73 (d, J = 13.5, 1H, C$\underline{H}_2$Ph), 3.80 (s, 2H, C$\underline{H}_2$OH), 7.22—7.40 (m, 5H, arom H); ir (neat) ν cm^{-1}, 2930, 2810, 1530, 1450, 1345, 1050.

From 2-Nitroethanol and Formaldehyde. To a mixture of **12a** (24.3 g, 0.15 mol), 2-nitroethanol (13.5 g, 0.15 mol), and *N*,*N*-dimethylformamide (25 ml) was added dropwise a solution of 37% formaldehyde

(24.1 g, 0.30 mol) in DMF (5 ml) over a period of 45 min at 5°C. After the reaction mixture was stirred at room temperature for 5 h, the mixture was poured into ice-water and extracted with $(C_2H_5)_2O$. The solvent was evaporated to give a oily residue, which was chromatographed on silica gel with AcOEt to afford 19.1 g (46%) of **13a** as a pale yellow oil. This oil was identified with the sample obtained above, on the basis of tlc, ir, and ^{1}H nmr comparisons.

1,4-Dimethyl-6-hydroxymethyl-6-nitrohexahydro-1*H*-1,4-diazepine (13b). In a similar manner to that described above, compound (**13b**) was prepared from **12b** and **11** in 52% yield as an oil. ^{1}H Nmr (300 MHz) δ: 2.43 (s, 6H, CH_3 × 2), 2.50—2.73 (m, 4H, 2-CH_2, 3-CH_2), 2.98 (d, J = 14.0, 2H, 5-C$\underline{H}_2$, 7-C$\underline{H}_2$), 3.42 (d, J = 14.0, 2H, 5-C$\underline{H}_2$, 7-C$\underline{H}_2$), 3.96 (s, 2H, C$\underline{H}_2$OH); ir (neat) ν cm^{-1}, 2945, 2805, 1535, 1455, 1285, 1345, 1085, 1055.

1-Benzyl-4-methyl-6-nitrohexahydro-1*H*-1,4-diazepine (14a). Potassium *tert*-butoxide (25.9 g, 0.23 mol) was added portionwise to a solution of **13a** (53.6 g, 0.19 mol) in CH_3OH (200 ml) at 25°C. The mixture was heated at *ca.* 40°C for 0.5 h and then cooled to room temperature. After the solvent was evaporated, the residue was dissolved in a solution of $NH_2OH \cdot HCl$ (16.0 g, 0.23 mol) in water (300 ml) at 10°C and extracted with CH_2Cl_2. The extract was washed with brine, and the solvent was evaporated at *ca.* 25°C. The oily residue was immediately chromatographed on silica gel with AcOEt to give 45.0 g (94%) of **14a** as a pale yellow unstable oil.[13] ^{1}H Nmr (300 MHz) δ: 2.44 (s, 3H, CH_3), 2.50—2.81 (m, 4H, 2-CH_2, 3-CH_2), 3.12 (dd, J = 6.0, 14.0, 1H, 5-C$\underline{H}_2$ or 7-C$\underline{H}_2$), 3.23 (dd, J = 6.0, 14.0, 1H, 5-C$\underline{H}_2$ or 7-C$\underline{H}_2$), 3.35 (dd, J = 6.0, 14.0, 1H, 5-C$\underline{H}_2$ or 7-C$\underline{H}_2$), 3.39 (dd, J = 6.0, 14.0, 1H, 5-C$\underline{H}_2$ or 7-C$\underline{H}_2$), 3.69 (d, J = 13.5, 1H, C$\underline{H}_2$Ph), 3.76 (d, J = 13.5, 1H, C$\underline{H}_2$Ph), 4.60 (quint, J = 6.0, 1H, 6-CH), 7.22—7.40 (m, 5H, arom H); ir (neat) ν cm^{-1}, 2925, 2795, 1530, 1440, 1345, 1005.

6-Acetylamino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (17a). A mixture of **14a** (38.0 g, 0.15 mol), wet Raney nickel (4 g), and 95% aqueous C_2H_5OH (700 ml) was hydrogenated at room temperature and atmospheric pressure, until no more hydrogen was consumed. The catalyst was filtered off, and the filtrate was concentrated to dryness to leave an oily residue including 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**16a**). The residue was dissolved in $CHCl_3$ (200 ml) and then acetic anhydride (30.0 g, 0.29 mol) was added to the solution. The mixture was stirred at room temperature for

2 h and washed successively with 10% aqueous NaOH, water, and brine. After the solvent was evaporated, the crude product was purified by silica gel column chromatography with $CHCl_3$:CH_3OH = 9:1 to give 19.2 g (48%) of **17a**. This compound was identified with the sample obtained in the alternative synthesis,[14] on the basis of tlc, ir, and ^1H nmr comparisons.

6-Acetylamino-1,4-dimethylhexahydro-1*H*-1,4-diazepine (17b). From Compound (13b). Compound (**13b**) was prepared *via* **14b** according to the same method as employed for the preparation of **17a** from **13a** to give **17b** in 28% yield. ^1H Nmr (300 MHz) δ 2.02 (s, 3H, $COCH_3$), 2.37 (s, 6H, $CH_3 \times 2$), 2.30—2.51 (m, 4H), 2.59 (dd, J = 4.0, 13.0, 2H, 5-C$\underline{H}_2$, 7-C$\underline{H}_2$), 2.77 (dd, J = 4.0, 13.0, 2H, 5-C$\underline{H}_2$, 7-C$\underline{H}_2$), 4.06 (m, 1H, 6-CH), 6.75 (br s, 1H, NHCO); ir (neat) ν cm^{-1}, 2930, 2800, 1535, 1450, 1365; ms *m/z*: 186 (MH^+).

From Compound (17a). A solution of **17a** (19.0 g, 73 mmol) in C_2H_5OH (300 ml)—CH_3CO_2H (30 ml) mixture was hydrogenated over 10% palladium on carbon (3.0 g) at 60°C. After the theoretical amount of hydrogen was absorbed, the catalyst was filtered off. The filtrate was concentrated to dryness, and the residue was dissolved in formic acid (25 ml) and 35% formaldehyde (19.0 g, 0.22 mol). The mixture was heated to reflux for 7 h and concentrated to dryness. The oily residue was dissolved in a small amount of water, basified with solid K_2CO_3, and extracted with $CHCl_3$. The solvent was evaporated to leave an oily residue, which was chromatographed on silica gel with $CHCl_3$:CH_3OH = 9:1 to give 6.5 g (48%) of **17b** as an oil. The ^1H nmr spectrum was identical with that of the sample described above.

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