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Five variants (methods A—E) of a synthetic route to 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**3b**) using *N*-benzyl-*N'*-methylethylenediamine (**8a**) are described. The reaction of **8a** with 1-benzenesulfonyl-2-bromomethylaziridine (**7**), 2-phenyl-4-(*p*-toluenesulfonyloxymethyl)oxazoline (**13**), and β, β-dibromoisobutyric acid (**15**) resulted in the direct cyclization to give the precursor of **3b**, 6-substituted 1,4-diazepine derivatives **9**, **14**, and **16**, respectively (methods A—C). These compounds were transformed into the desired **3b**. The preparation of 1,4-diazepine ring from methyl 2-*tert*-butoxycarbonylaminopropenate (**18**) was alternatively achieved by the intramolecular amidation of the intermediate **19a** (method D) or reductive cyclization of the aminoaldehyde **23a** (method E). Method E was found to efficiently produce the 6-amino-1,4-diazepine **3b**.

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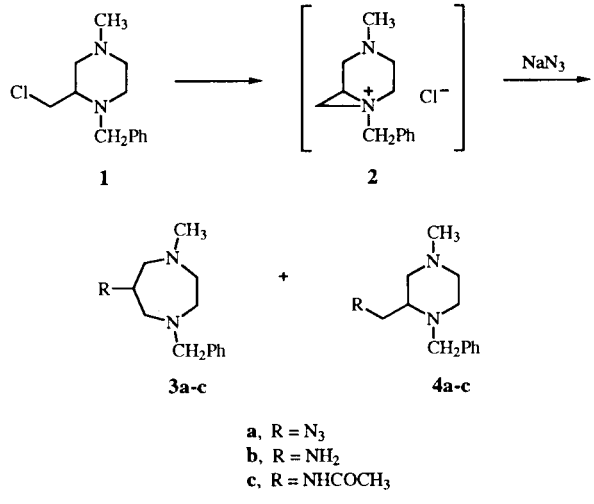
We have previously reported that the nucleophilic reaction of 1-benzyl-2-chloromethyl-4-methylpiperazine (**1**) with sodium azide gave a mixture of the ring-expanded azido derivative **3a** and the normally substituted product **4a** *via* the postulated aziridinium cation intermediate **2**. The products were isolated as the *N*-acetyl derivatives **3c** and **4c** in 15% and 68% yields, respectively [1] (Scheme 1). 6-Amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**3b**) is an important fragment for the preparation of the new benzamide **5** and carboxamide **6** with a potent serotonin 3 receptor antagonistic activity [2] (Figure 1). However, the application of this ring expansion of **1** in a large-scale production seems not to be practical because of the low yield of the product **3c** and the use of sodium azide. The present work was undertaken in order to establish practical and convenient synthetic method for **3b**. Here we describe five synthetic routes (methods A—E) to 6-aminohexahydro-1*H*-1,4-diazepine ring using *N*-benzyl-*N'*-methylethylenediamine (**8a**).

Scheme 1



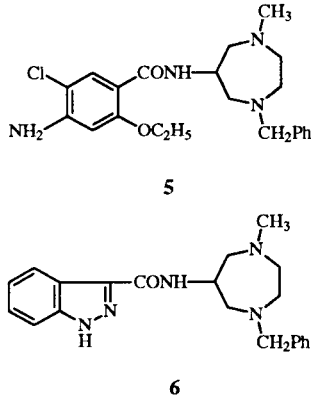
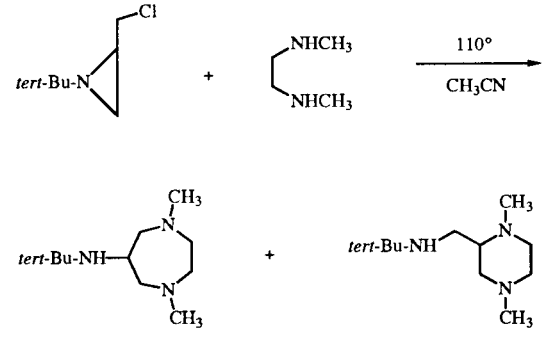


Figure 1

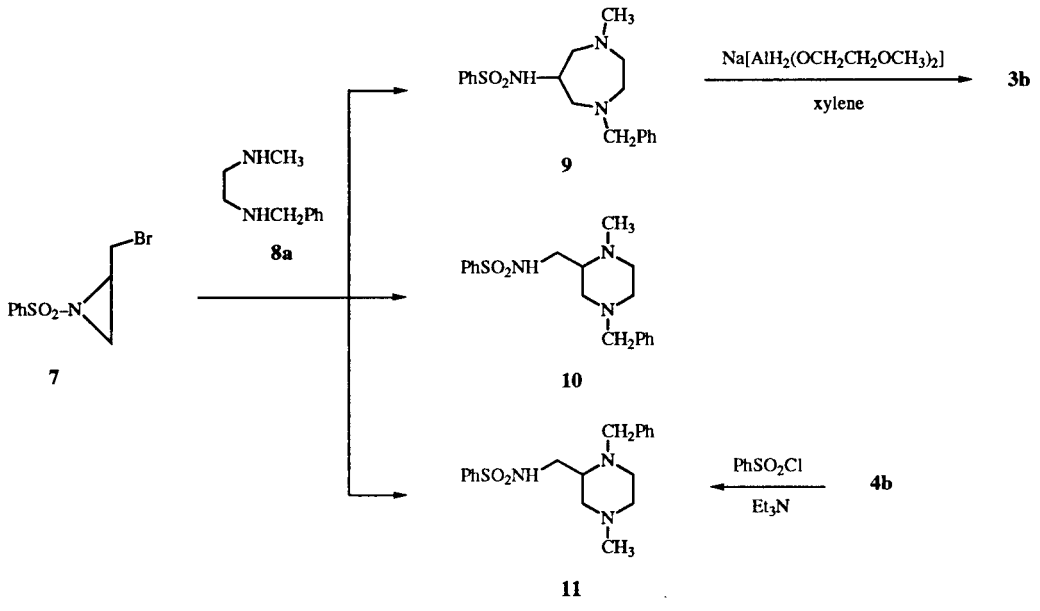
Chemistry

Gaertner reported that 6-*tert*-butylamino-1,4-dimethylhexahydro-1*H*-1,4-diazepine was obtained by treatment of 1-*tert*-butyl-2-chloromethylaziridine with *N,N'*-dimethylethylenediamine in acetonitlile (110°, 1—3 days) along with the six-membered product, 2-(*tert*-butylaminomethyl)-1,4-dimethylpiperazine, in 9% and 54% yields, respectively [3] (Scheme 2). In a first synthetic method for 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-

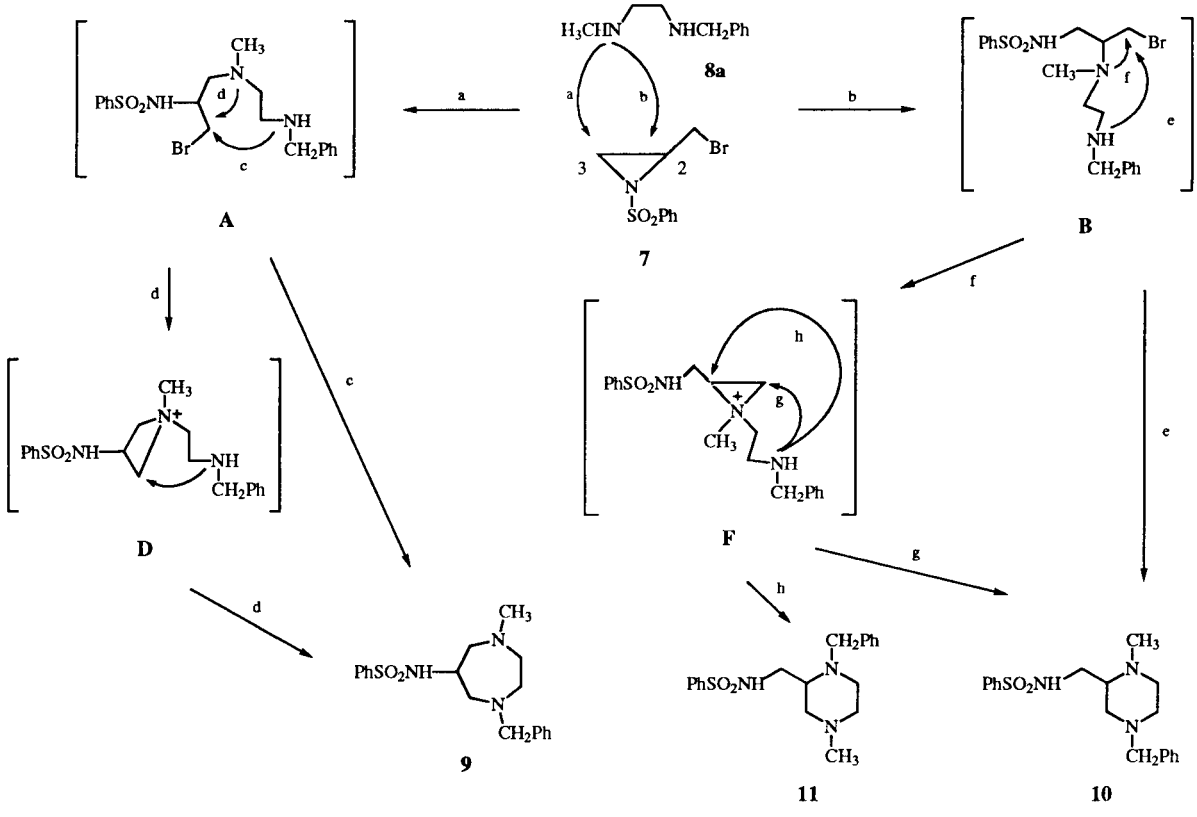
Scheme 2



Scheme 3 (Method A)



Scheme 4



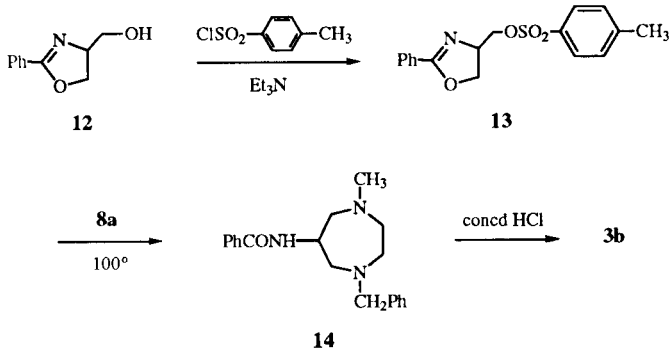
diazepine (**3b**), we applied his procedure; the reaction of 1-benzenesulfonyl-2-bromomethylaziridine (**7**) [4] as an activated aziridine, instead of 1-*tert*-butyl-2-chloromethylaziridine, with *N*-benzyl-*N'*-methylethylenediamine (**8a**) [5] was investigated. Refluxing **7** with **8a** in ethyl acetate for 4 hours afforded the expected seven-membered product **9** and 3- and 2-(benzenesulfonylaminomethyl)-1-benzyl-4-methylpiperazines (**10** and **11**) in 21%, 5%, and 50% yields, respectively. These compounds were characterized by ms and ^{1}H-nmr spectra [1]. Additionally, the piperazine

11 was identical with the benzenesulfonyl derivative of **4b** reported previously [1]. Attempted *N*-deprotection of **9** to **3b** by hydrobromic or hydroiodic acid was unsuccessful. On the other hand, the benzenesulfonyl group of **9** was successfully removed by treatment of sodium bis(2-methoxyethoxy)aluminum hydride in xylene to give the target **3b** (Scheme 3, method A).

On the basis of the results described above, the possible pathway of the reaction is shown in Scheme 4. In the reaction of **7** with the methylamino moiety of the ethylenediamine **8a**, because the process involving the substitution of the bromine is presumed to take place considerably more slowly, an aziridine ring-opening reaction dominantly occurs; the cleavage of C_3-N (path *a*) and C_2-N (path *b*) bonds of the aziridine ring of **7** gives the intermediates **A** and **B**, respectively. The seven-membered product, the 1,4-diazepine **9**, may be formed from the intermediate **A** directly (path *c*) and/or *via* the azetidinium cation **D** (path *d*). On the other hand, the intramolecular cyclization (path *e*) of the intermediate **B** and/or the cleavage (path *g*) of the aziridine ring in **F** which is formed from **B** by path *f* results in the formation of the 3-(benzenesulfonylaminomethyl)piperazine **10**. The regioisomeric piperazine **11** may be given involving path *h* in the aziridinium cation **F**.

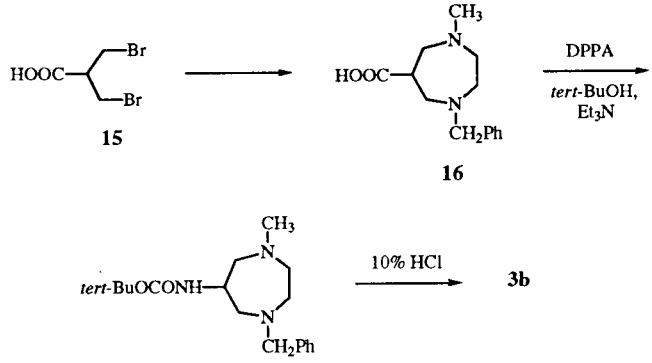
In order to improve the yield of the 1,4-diazepine derivative and avoid the formation of the isomeric piperazine derivatives, we next examined the reaction of **8a** with 2-phenyl-4-(*p*-toluenesulfonyloxymethyl)oxazoline (**13**). Compound **13** was prepared from 2-phenyloxazoline-4-methanol (**12**) [6] and *p*-toluenesulfonyl chloride. The reaction of **13** with **8a** did not proceed in refluxing toluene. However, we found that **13** reacted with **8a** at 100° without solvent, furnishing only the 6-benzoylamino-1,4-diazepine **14** in 31% yield. Acid hydrolysis of the benzoyl group of **14** produced the desired amine **3b** (Scheme 5, method B).

Scheme 5 (Method B)



For the third method, we carried out the transformation of the 1,4-diazepine-6-carboxylic acid **16** into 6-amino-1,4-diazepine **3b** using the Curtius rearrangement. The key intermediate 1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine-6-carboxylic acid (**16**) could be prepared from β,β-dibromoisobutyric acid (**15**) [7] and the ethylenediamine **8a** in a good yield. The treatment of **16** with diphenylphosphoryl azide (DPPA) in *tert*-butyl alcohol afforded the 6-(*tert*-butoxycarbonylamino)-1,4-diazepine **17** in a poor yield (8%). The *tert*-butoxycarbonyl (Boc) group of **17** was hydrolyzed by 10% hydrochloric acid to give the amine **3b** (Scheme 6, method C).

Scheme 6 (Method C)

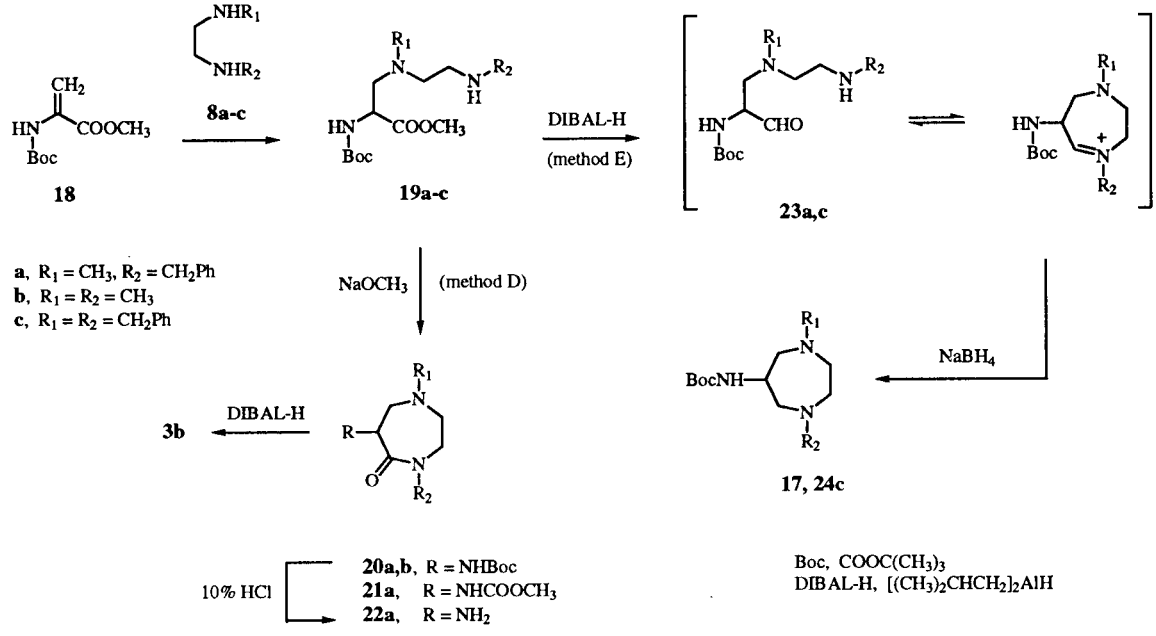


DPPA; $(PhO)_2P(O)N_3$

Our final plan to prepare **3b** is a stepwise synthesis from methyl 2-*tert*-butoxycarbonylaminopropenate (**18**) [8] as depicted in Scheme 7. The reaction of **18** with **8a** without solvent furnished methyl N^3-(2-benzylaminoethyl)-N^2-*tert*-butoxycarbonyl-N^3-methyl-2,3-diaminopropionate (**19a**) in a good yield. Compound **19a** was then cyclized by treatment with sodium methoxide to give 1-benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepin-7-one (**20a**) in 50% yield along with an ester interchanged product **21a** in 22% yield. The use of potassium *tert*-butoxide or trimethyl aluminum in place of sodium methoxide resulted in a poor yield. On the other hand, the treatment of **18** with *N,N'*-dimethylethylenediamine (**8b**) instead of **8a** directly furnished the 1,4-diazepin-7-one **20b** in 19% yield without isolation of **19b**. After the deprotection of the Boc group of **20a** by 10% hydrochloric acid, the resultant 6-amino-1,4-diazepin-7-one **22a** was reduced by diisobutylaluminum hydride (DIBAL-H) to give the desired product **3b** (method D).

In an alternative synthesis of **3b**, the treatment of **19a** with DIBAL-H at -70°, followed by reductive cyclization of the resulting aminoaldehyde **23a** afforded the 6-*tert*-butoxycarbonylamino-1,4-diazepine **17** in 81% yield (method E); the cyclization was considered to proceed *via* the immonium salt of **23a**. The reaction course of **18** with the starting *N,N'*-dibenzylethylenediamine (**8c**) was essen-

Scheme 7



tially the same as those in the above method E: **18** to **19c** (room temperature 15 hours, 40%), **19c** to **23c** (-70°, 1 hour), **23c** to **24c** (-20°, 15 hours, 53% from **19c**).

In conclusion, we have found five methods A—E for the preparation of 6-amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**3b**) using *N*-benzyl-*N'*-methylethylenediamine (**8a**). Among them, method E involving the reductive cyclization of aminoaldehyde **23a** appears to be superior to the other four due to simple operation and the good overall yield of **3b** (58% from **18** through **19a**, **23a**, and **17**).

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ir spectra were recorded on a Hitachi 260-10 spectrometer. Electron ionization and secondary ion mass spectra were obtained on a JEOL JMS D-300 and a Hitachi M-80B spectrometers, respectively. The ^{1}H-nmr spectra were recorded with a Varian Gemini-200 spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). The extract was dried over anhydrous sodium sulfate or magnesium sulfate. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70—230 mesh) was used for column chromatography.

Method A. 6-Benzenesulfonylamino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**9**), 3-(Benzenesulfonylaminomethyl)-1-benzyl-4-methylpiperazine (**10**), and 2-(Benzenesulfonylaminomethyl)-1-benzyl-4-methylpiperazine (**11**).

A solution of 1-benzenesulfonyl-2-bromomethylaziridine [4] (**7**, 35.3 g, 0.13 mole), *N*-benzyl-*N'*-methylethylenediamine [5] (**8a**, 21.0 g, 0.13 mole), and triethylamine (25.8 g, 0.26 mole) in ethyl acetate (400 ml) was heated to reflux for 4 hours and then cooled to room temperature. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with *n*-hexane:acetone:ethyl acetate = 2:1:1 to give 9.8 g (21%) of **9** as an oil, 2.2 g (5%) of **10**, and 23.1 g (50%) of **11** in this order of elution.

Compound **9** (oil) had ir (neat): 3050, 2935, 2820, 1440, 1320, 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.32 (s, 3H, NCH_3), 2.35-3.60 (m, 4H), 3.60-3.88 (m, 4H), 3.40 (m, 1H, 6-CH), 3.41 (d, J = 14, 1H, CH_2Ph), 3.58 (d, J = 14, 1H, CH_2Ph), 5.91 (br s, 1H, SO_2NH), 7.20-7.57 (m, 8H), 7.60-7.70 (m, 2H); ms: m/z 360 (MH^+), 267 (M^+-92), 203 (M^+-$PhSO_2NH$).

Compound **10** had mp 100-101° (toluene-*n*-hexane); ir (potassium bromide): 3280, 2780, 1435, 1300, 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.99 (s, 3H, NCH_3), 2.04-2.41 (m, 4H), 2.47-2.79 (m, 3H), 2.87 (dd, J = 1.5, 12, 1H), 3.11 (dd, J = 4.5, 12, 1H), 3.38 (d, J = 13.5, 1H, CH_2Ph), 3.43 (d, J = 13.5, 1H, CH_2Ph), 5.32 (br s, 1H, SO_2NH), 7.21-7.37 (m, 5H), 7.45-7.65 (m, 3H), 7.81-7.91 (m, 2H); ms: m/z 360 (MH^+), 267 (M^+-92), 189 (M^+-$PhSO_2NHCH_2$).

Anal. Calcd. for $C_{19}H_{25}N_3O_2S$: C, 63.48; H, 7.01; N, 11.69. Found: C, 63.56; H, 7.05; N, 11.60.

Compound **11** had mp 105-106° (toluene-*n*-hexane); ir (potassium bromide): 3020, 2935, 2800, 1440, 1325, 1155 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.18 (s, 3H, NCH_3), 2.08-2.37 (m, 3H), 2.40-2.68 (m, 3H), 2.78 (ddd, J = 3, 5.5, 8, 1H), 3.00 (d-like, J = 12, 1H), 3.16 (d, J = 13.5, 1H, CH_2Ph), 3.27 (dd, J = 4, 12, 1H), 3.60 (d, J = 13.5, 1H, CH_2Ph), 5.65 (br s, 1H, SO_2NH), 7.13-7.57 (m, 8H), 7.74-7.83 (m, 2H); ms: m/z 360 (MH^+), 267 (M^+-92), 189 (M^+- $PhSO_2NHCH_2$).

Anal. Calcd. for $C_{19}H_{25}N_3O_2S$: C, 63.48; H, 7.01; N, 11.69. Found: C, 63.47; H, 7.06; N, 11.55.

Method B. 2-Phenyl-4-(*p*-toluenesulfonyloxymethyl)oxazoline (**13**).

To a solution of 2-phenyloxazoline-4-methanol [6] (**12**, 5.9 g, 33 mmoles) and triethylamine (7.3 g, 72 mmoles) in chloroform (50 ml) was added *p*-toluenesulfonyl chloride (6.9 g, 36 mmoles) at 5°. The reaction mixture was stirred at room temperature for 20 hours and washed successively with water and brine. The organic layer was dried and then concentrated to dryness. The oily residue was chromatographed on silica gel with chloroform:ethyl acetate = 1:1 and recrystallized from isopropyl alcohol to give 8.4 g (76%) of **13**, mp 88-90°; ir (potassium bromide): 3040, 2880, 1640, 1345, 1170 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.42 (s, 3H, CH_3), 4.05 (m, 1H), 4.22-4.62 (m, 4H), 7.15-8.01 (m, 9H); ms: m/z 332 (MH^+).

Anal. Calcd for $C_{17}H_{17}NO_4S•1/4\ H_2O$; C, 60.79; H, 5.25; N, 4.17. Found: C, 60.89; H, 5.25; N, 4.12.

N-(1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepine-6-yl)benzamide (**14**).

A mixture of **13** (1.0 g, 3.0 mmoles) and **8a** (0.8 g, 4.9 mmoles) was heated at *ca.* 100° for 22 hours and then cooled to room temperature. The mixture was chromatographed on silica gel with chloroform:methyl alcohol = 9:1 to afford 0.3 g (31%) of **14** as an oil; ir (neat): 2930, 2800, 1640, 1470 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.41 (s, 3H, NCH_3), 1.9-2.2, 2.45-3.05 (m, 8H), 3.55 (d, J = 14, 1H, CH_2Ph), 3.72 (d, J = 14, 1H, CH_2Ph), 4.25 (m, 1H, 6-CH), 7.15-7.55, 7.65-7.75 (m, 11H); ms: m/z 324 (MH^+).

Method C. 1-Benzyl-4-methylhexahydro-1*H*-1,4-diazepine-6-carboxylic Acid (**16**).

To a solution of β,β-dibromoisobutyric acid [7] (**15**, 24.6 g, 0.10 mole) in chloroform (300 ml) was added dropwise a solution of **8a** (16.4 g, 0.10 mole) and triethylamine (22.2 g, 0.22 mole) in chloroform (100 ml) at 10°. The mixture was heated to reflux for 3.5 hours and then cooled to room temperature. After the solvent was evaporated, the residue was dissolved in a small amount of acetone. The resulting precipitates were filtered off, and the filtrate was kept at room temperature. The resulting precipitates were collected by filtration. Three recrystallizations of the crystals from isopropyl alcohol provided 19.5 g (79%) of **16**, mp 150-153°; ir (potassium bromide): 3400, 3015, 2930, 2770, 1585, 1355 cm^{-1}; ^1H-nmr (dimethyl sulfoxide-d_6): δ 2.37 (s, 3H, NCH_3), 2.55-2.80 (m, 5H), 2.80-3.10 (m, 4H), 3.61 (d, J = 14, 1H, CH_2Ph), 3.78 (d, J = 14, 1H, CH_2Ph), 7.18-7.38 (m, 5H), 12.15 (br s, 1H, COOH); ms: m/z 249 (MH^+).

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.65; H, 8.08; N, 11.31.

Compound **16** was converted in the usual manner to the corresponding dihydrochloride, **16**•dihydrochloride, mp 185-190° (5% aqueous ethyl alcohol).

Anal. Calcd. for $C_{14}H_{20}N_2O_2•2HCl$: C, 52.34; H, 6.90; N, 8.72. Found: C, 52.30; H, 6.74; N, 8.65.

The Curtius Rearrangement of **16**.

A mixture of **16** (4.0 g, 16 mmoles), diphenylphosphoryl azide (DPPA, 4.4 g, 16 mmoles), triethylamine (1.6 g, 16 mmoles), and *tert*-butyl alcohol (100 ml) was heated to reflux for 15 hours, cooled to room temperature, and concentrated to dryness. The residue was dissolved in chloroform and washed successively with water and brine. The solvent was evaporated to leave an oil, which was chromatographed on silica gel with chloroform:methyl alcohol = 19:1 to give 0.4 g (8%) of 1-benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepine (**17**) as an oil; ir (neat): 1690 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.40 (s, 9H, $COOC(CH_3)_3$), 2.3-3.0, (m, 6H), 2.35 (s, 3H, NCH_3), 3.2-3.4 (m, 2H), 3.56 (d, J = 13, 1H, CH_2Ph), 3.69 (d, J = 13, 1H, CH_2Ph), 3.75 (m, 1H), 5.45 (br d, J = 9, 1H, NHCO), 7.15-7.45 (m, 5H, arom H); ms: m/z 320 (MH+).

Method D. Methyl N^3-(2-Benzylaminoethyl)-N^2-*tert*-butoxycarbonyl-N^3-methyl-2,3-diaminopropionate (**19a**).

A mixture of methyl 2-*tert*-butoxycarbonylaminopropenate [8] (**18**, 4.0 g, 20 mmoles) and **8a** (16.0 g, 98 mmoles) was stirred at room temperature for 16 hours. The reaction mixture was chromatographed on silica gel with chloroform:methyl alcohol = 9:1 to give 6.0 g (83%) of **19a** as an oil; ir (neat): 1740, 1700 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.45 (s, 9H, $COO(CH_3)_3$), 1.83 (br s, 1H), 2.24 (s, 3H, NCH_3), 2.52-2.77 (m, 6H), 3.72 (s, 3H, $COOCH_3$), 3.83 (s, 2H, CH_2Ph), 4.30 (m, 1H, 2-CH), 5.88 (m, 1H, NH), 7.20-7.39 (m, 5H, arom H); ms: m/z 366 (MH^+).

1-Benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepin-7-one (**20a**) and 1-Benzyl-6-methoxycarbonylamino-4-methylhexahydro-1*H*-1,4-diazepin-7-one (**21a**).

A mixture of **19a** (2.4 g, 6.6 mmoles), 28% sodium methoxide in methyl alcohol (2.8 g, 15 mmoles), and toluene (50 ml) was heated at 80° for 2 hours. The reaction mixture was cooled to room temperature and then washed successively with water and brine. The solvent was evaporated to leave an oily residue, which was chromatographed on silica gel with ethyl acetate to give 1.1 g (50%) of **20a** and 0.4 g (22%) of **21a** in this order of the elution.

Compound **20a** (oil) had ir (neat): 1700, 1645 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.46 (s, 9H, $COOC(CH_3)_3$), 2.08 (dd, J = 11, 13, 1H, 3-CH_2), 2.28 (dd, J = 12, 13, 1H, 5-CH_2), 2.40 (s, 3H, NCH_3), 2.78 (dd, J = 5, 13, 1H, 3-CH_2), 3.05 (br d, J = 12, 1H, 5-CH_2), 3.19 (dd, J = 5, 16, 1H, 2-CH_2), 3.75 (dd, J = 11, 16, 1H, 2-CH_2), 4.51 (d, J = 14, 1H, CH_2Ph), 4.63 (m, 1H, 6-CH), 4.75 (d, J = 14, 1H, CH_2Ph), 5.99 (m, 1H, NHCO), 7.2-7.4 (m, 5H, arom H); ms: m/z 334 (MH^+), 292, 278, 260.

Compound **21a** (oil) had ir (neat): 1720, 1650 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 2.00 (dd, J = 2, 12, 1H, 3-CH_2), 2.21 (dd, J = 10, 12, 1H, 5-CH_2), 2.34 (s, 3H, NCH_3), 2.73 (dd, J = 5, 12, 1H, 3-CH_2), 3.01 (br d, J = 12, 1H, 5-CH_2), 3.19 (dd, J = 5, 16, 1H, 2-CH_2), 3.62 (dd, J = 10, 16, 1H, 2-CH_2), 3.70 (s, 3H, $COOCH_3$), 4.54 (d, J = 14, 1H, CH_2Ph), 4.61 (m, 1H, 6-CH), 4.73 (d, J = 14, 1H, CH_2Ph), 6.20 (m, 1H, NHCO), 7.2-7.4 (m, 5H, arom H); ms: m/z 277 (M^+), 202 (M^+-CH_3OCONH_2), 175.

6-Amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepin-7-one (**22a**).

A solution of **20a** (3.4 g, 10 mmoles) in a mixture of methyl alcohol (20 ml) and 10% hydrochloric acid (20 ml) was heated to reflux for 1 hour and then cooled to room temperature. After the methyl alcohol was evaporated, the aqueous solution was basified with 10% sodium hydroxide solution and extracted with chloroform. The extract was washed with brine and concentrated to dryness to give 2.3 g (97%) of **22a** as an oil; ir (neat): 1640 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 1.87 (s, 2H, NH_2), 1.97 (dd, J = 2, 12, 1H, 3-CH_2), 2.25 (dd, J = 10, 12, 1H, 5-CH_2),

2.33 (s, 3H, NCH_3), 2.72 (dd, J = 5, 12, 1H, 3-CH_2), 2.83 (dd, J = 2, 12, 1H, 5-CH_2), 3.20 (ddd, J = 2, 5, 16, 1H, 2-CH_2), 3.61 (dd, J = 10, 16, 1H, 2-CH_2), 3.87 (dd, J = 2, 10, 1H, 6-CH), 4.60 (d, J = 14, 1H, CH_2Ph), 4.70 (d, J = 14, 1H, CH_2Ph), 7.2-7.4 (m, 5H, arom H); ms: m/z 233 (M^+), 190.

Method E. 1-Benzyl-6-(*tert*-butoxycarbonylamino)-4-methylhexahydro-1*H*-1,4-diazepine (**17**).

To a solution of **19a** (4.5 g, 12 mmoles) in toluene (40 ml) was added 1*M* solution of diisobutylaluminum hydride (DIBAL-H) in tetrahydrofuran (37 ml, 37 mmoles) at -70°. The mixture was stirred at the same temperature for 1 hour and the excess reagent was decomposed with methyl alcohol (40 ml) at -70°. After the mixture was then warmed to -20°, sodium borohydride (0.5 g, 13 mmoles) was gradually added. The reaction mixture was stirred at room temperature for 16 hours and then concentrated to dryness. The residue was dissolved in chloroform and washed successively with water and brine and dried. The solvent was evaporated to leave an oil, which was chromatographed on silica gel with chloroform:methyl alcohol = 19:1 to give 3.2 g (81%) of **17** as an oil, which was identified with the sample obtained the Curtius rearrangement of **16**, on the basis of tlc, ir, and ^{1}H-nmr comparisons.

6-Amino-1-benzyl-4-methylhexahydro-1*H*-1,4-diazepine (**3b**).

A mixture of **9** (6.1 g, 17 mmoles), sodium bis(2-methoxyethoxy)aluminum hydride (24.5 g of 70% solution of toluene, 84 mmoles), and xylene (200 ml) was heated to reflux for 24 hours and then cooled to room temperature. The excess reagent was decomposed with water at 5°. After the reaction mixture was filtered through Celite, the organic layer was separated, washed with brine, dried, and concentrated to dryness. The residue was chromatographed on silica gel with chloroform:methyl alcohol = 9:1 to give 3.0 g (81%) of **3b** as an oil; ir (neat): 3300, 2920, 2790, 1440 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.25 (s, 2H, NH_2), 2.37 (s, 3H, CH_3), 2.15-2.75 (m, 6H), 2.75-2.95 (m, 2H), 3.07 (m, 1H), 3.61 (d, J = 13, 1H, CH_2Ph), 3.69 (d, J = 13, 1H, CH_2Ph), 7.15-7.45 (m, 5H, arom H); ms: m/z 220 (MH^+).

A solution of **14** (1.0 g, 3.1 mmoles) in concentrated hydrochloric acid (10 ml) was heated to reflux for 5 hours and then cooled to room temperature. After the reaction mixture was washed with diethyl ether, the aqueous solution was basified with 20% sodium hydroxide solution, and extracted with chloroform. The extract was washed with brine and evaporated to give 0.5 g (74%) of **3b** as an oil, which was identified with the sample obtained above, on the basis of tlc, ir, and ^{1}H-nmr comparisons.

A mixture of **17** (2.0 g, 6.3 mmoles) and 10% hydrochloric acid (100 ml) was heated to reflux for 3 hours and then cooled to room temperature. Following work-up similar to that described above was given 1.2 g (87%) of **3b** as an oil, which was identified with the sample obtained above, on the basis of tlc, ir, and ^{1}H-nmr comparisons.

To a solution of **22a** (2.3 g, 9.9 mmoles) in toluene (23 ml) was added dropwise a solution of 1*M* DIBAL-H in toluene (49 ml, 49 mmoles) at -5°. The reaction mixture was stirred at room temperature for 16 hours and recooled to 5°, and the excess of the reducing agent was decomposed by the addition of water. After the insoluble materials were filtered off, the filtrate was basified with 20% sodium hydroxide solution and extracted with chloroform. The extract was washed with brine and evaporated to give 1.8 g (83%) of **3b** as an oil, which was identified with the sample obtained above, on the basis of tlc, ir, and ^{1}H-nmr comparisons.

Methyl N^3-Benzyl-N^3-(2-benzylaminoethyl)-N^2-*tert*-butoxycarbonyl-2,3-diaminopropionate (**19c**).

In a similar manner to that described for **18** to **19a**, compound **19c** was prepared from *N,N'*-dibenzylethylenediamine (**8c**) and **18** in 40% yield as an oil; ir (neat): 1740, 1700 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.45 (s, 9H, $COO(CH_3)_3$), 2.60-2.92 (m, 6H), 2.82 (d, 1H, J = 6, CH_2Ph), 3.60 (d, 1H, J = 6, CH_2Ph), 3.66 (s, 3H, $COOCH_3$), 3.80 (s, 2H, CH_2Ph), 4.40 (m, 1H, 2-CH), 5.45 (m, 1H, NH), 6.00 (m, 1H, NH), 7.20-7.45 (m, 10H, arom H); ms: m/z 442 (MH^+).

6-(*tert*-Butoxycarbonylamino)-1,4-dibenzylhexahydro-1*H*-1,4-diazepine (**24c**).

In a similar manner to that described for **19a** to **17**, compound **24c** was prepared from **19c** in 53% yield as an oil; ir (neat): 1705 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.37-1.65 (m, 9H, $COOC(CH_3)_3$), 2.45-2.81 (m, 6H), 2.82-3.00 (m, 2H), 3.58 (d, J = 15, 2H, CH_2Ph x 2), 3.70 (d, J = 15, 2H, CH_2Ph x 2), 3.74 (m, 1H), 5.31 (m, 1H, NHCO), 7.15-7.45 (m, 10H, arom H); ms: m/z 396 (MH^+).

6-(*tert*-Butoxycarbonylamino)-1,4-dimethylhexahydro-1*H*-1,4-diazepin-7-one (**20b**).

In a similar manner to that described for **18** to **19a**, compound **20b** was obtained from *N,N'*-dimethylethylenediamine (**8b**) and **18** in 19% yield as an oil; ir (neat): 1720, 1650 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.45 (s, 9H, $COOC(CH_3)_3$), 2.18-2.40 (m, 2H), 2.45 (s, 3H, NCH_3), 2.75-3.10 (m, 2H), 3.05 (s, 3H, NCH_3), 3.26 (dd, J = 6, 16, 1H, 5-CH_2), 3.91 (dd, J = 11, 16, 1H, 5-CH_2), 4.59 (m, 1H, 6-CH), 5.91 (m, 1H, NHCO); ms: m/z 258 (MH^+).

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