Synthesis of Novel, Substituted 4*H*-Imidazo[1,5-*a*][1,4]benzodiazepines

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Synthetic approaches to novel, substituted 4*H*-imidazo[1,5-*a*][1,4]benzodiazepines are described. The compounds prepared are, in general, derivatives of known ring systems and structures were assigned on the basis of spectroscopic evidence.

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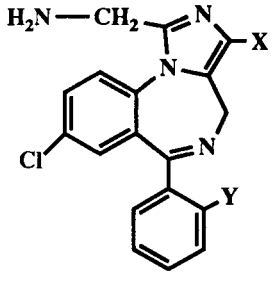
One aspect of our current research interests has been to develop novel imidazo-1,4-benzodiazepine haptens which incorporate structural requirements that define biological activities at the benzodiazepine (BZ) receptor (*e.g.* agonist and antagonist). These requirements are based on our previously reported structure-activity relationship [1,2]. These studies have pointed out that the imidazo-1,4-benzodiazepine structural skeleton has the capability of exhibiting biological activity as either a full agonist or a full antagonist depending upon the number and type of substituent present [3-5]. Therefore, by using this ring system as a template and adding the appropriate substituents, the two hapten compounds **8** and **17** were designed. A functionalized side chain has also been incorporated into each hapten structure, so that they may be used a) to couple directly to a carrier protein in order to raise specific antibodies [6,7], or b) by the addition of an appropriate spacer group such as adipic acid, to prepare affinity chromatography columns [8]. The result of the antibody work will be reported in due course, elsewhere.

The synthesis of compound **7b** has been reported in the literature [9]. Presumeably, this synthesis could be used (with minor modification) to prepare **7a**. The 3-carboxy ester derivative, **7c** could be hydrolyzed and decarboxylated to give **7a**. However, the synthetic sequence is very lengthy and time consuming and therefore an alternative approach for the synthesis of **7a** was investigated.

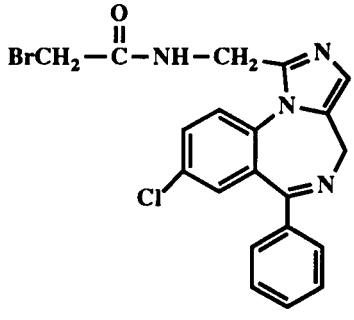
We have developed an approach to the synthesis of **7a**, in which a protected glycyl residue would react with the primary amine of the known intermediate **1** [10,11], to afford compound **2a** as its hydrochloride salt. Ring closure of this intermediate was expected to give the dihydro imidazo ring bearing a protected aminomethyl side chain at the 1-position. Thus, compound **1** was synthesized according to literature methods and was converted to compound **2a** as shown in Scheme I. Cyclization of the free base **2b** (triethylamine/ethanol) in polyphosphoric acid gave the dihydroimidazole **3** as well as the by-product **4**.

The propensity of 1,4-BZs to undergo different types of skeletal rearrangements under either acidic or basic conditions is well known [12], it was therefore felt necessary to fully characterize compound **3**. Proton nmr showed that it was difficult to assign the chemical shifts, and we decided to use proton decoupling techniques and 2-D nmr (COSY) in order to provide more detailed structural information. When the 3a-position proton, a multiplet centered at 4.7 ppm was irradiated, both the doublet-doublet patterns centered at 3.4 ppm and 3.9 ppm respectively collapsed to



7a-c

a:	**X = Y = H**
b:	**X = CO_2Me; Y= Cl**
c:	**X = CO_2Me; Y= H**



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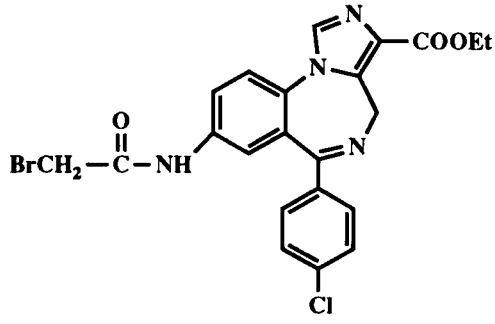

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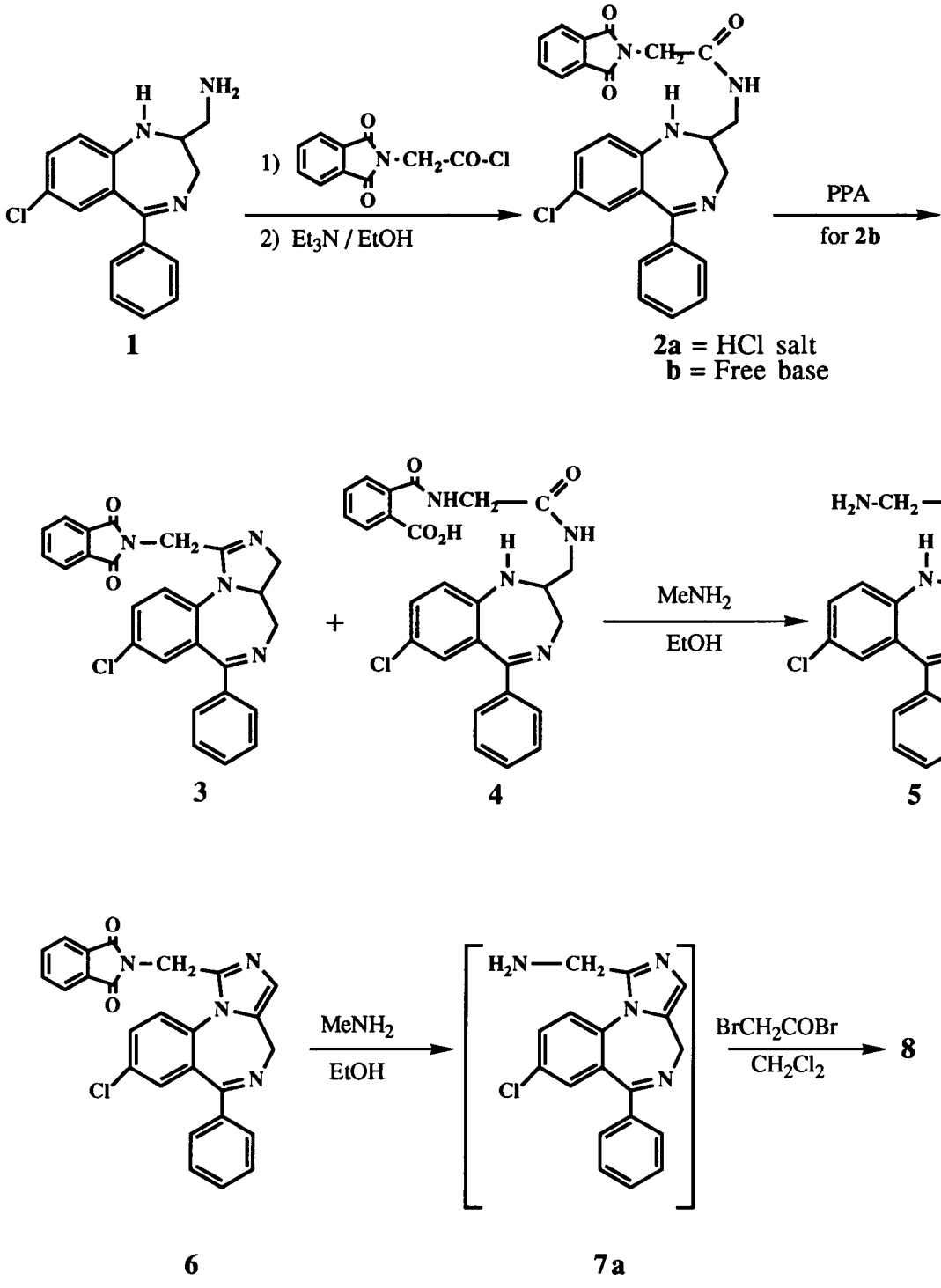
Scheme I



the single-doublet patterns while the doublet centered at 4.02 ppm collapsed to a singlet. It was noted that there was no observable effect on the other two protons centered at 4.04 ppm and 4.14 ppm, indicating that these two protons may belong to the 1-methylene substituent. The data from proton 2-D nmr (COSY) support the above relationships. Furthermore, one of these methylene proton showed an interesting doublet-triplet pattern, indicating that the two

protons are not equivalent due to the bulk of the phthalimido group, and have hindered rotation about the carbon-carbon bond (doublet) and also have long-range ^5J coupling to the proton at the 3-position of the imidazo ring (triplet). The other proton only gave a doublet pattern and no long-range coupling was observed, which may be due to its different geometric position. The two protons on the 3-position are almost equivalent and no AB pattern was observed. The doublet at 4.02 ppm in proton nmr, collapsed to a singlet when the proton at 3a-position (centered at 4.7 ppm) was irradiated with decoupling frequency. Protons on the methylene group of the 7-membered ring (4-position) showed an ABX type pattern, since they were not only coupled to each other but also coupled to the proton on 3a-position. One of the 4-position protons probably has an approximate dihedral angle of 70° to the 3a-position proton (estimated from the Karplus relationship diagram), since a very small coupling constant (J = 0.88 Hz) was observed. Broad-band proton-decoupled ^{13}C nmr (DEPT) was also carried out to determine the number of hydrogen atoms attached to carbons. The result was consistent with the proposed structure **3**.

The very polar by-product **4**, (thin layer chromatograph) formed in the cyclization reaction of **2b**, was isolated by column chromatography, and without further characterization was deprotected with ethanolic methylamine to afford **5**. The assigned structure for **5** was consistent with all of the spectral and analytical data.

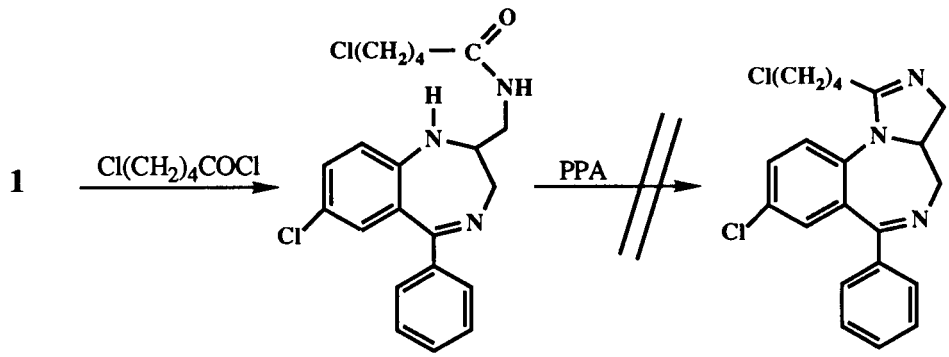
The 1-substituted imidazo-1,4-BZ, **6** was obtained by oxidation of **3** with manganese dioxide in refluxing toluene. The proton nmr of **6**, now showed only one proton at the 3-position, shifted downfield to 6.95 ppm, as one of the aromatic protons. No signal corresponding to the 3a-position proton seen for **3** was present. This provides further evidence for **3** being cyclized to the imidazolidine structure. Deprotection of **6** with methylamine in ethanol afforded the primary amine compound **7** which without further characterization was then treated with bromoacetyl bromide to give the target compound **8**.

An attempt to use this same synthetic sequence to prepare a similar hapten, containing 1-(4-chloro-*n*-butyl) as the side chain was not successful. Treatment of **1** with 5-chlorovaleryl chloride afforded the expected open chain compound **18**, but under conditions previously used for imidazole formation (PPA), ring closure did not take place.

The second target compound **17** required the incorporation of a *para*-substituent on the 6-phenyl ring in order to define its *in vivo* biological profile as that of an antagonist ligand [1,2]. The synthetic strategy employed 2-amino-4'-chlorobenzophenone **9** as a starting material. Compound **9** was obtained by means of a Grignard reaction, carried out with *p*-chlorophenylmagnesium bromide and anthranilonitrile followed by hydrolysis of the resulting imine (Scheme II). This method [13] proved to be easily workable and afforded compound **9** in relatively high overall yield (64%, *vs*, 45% reported for an alternate method [14]).

Compound **9** was then condensed with bromoacetyl bromide to form **10** using a Schotten-Baumann procedure. The acetanilide was subsequently allowed to react with liquid ammonia to give the corresponding uncharacterized 2-benzoyl-2'-aminoacetanilide derivative **11**. An ethanol solution of **11** was heated under reflux to accomplish the ring closure to **12** [15]. The corresponding 7-nitro derivative **13** was then prepared by direct nitration using 1.2 equivalents of nitrating agent following procedures described in other work [16]. In this instance, the 7-position is the most activated due to the *ortho*/*para* directing acylamino group, while steric hindrance prevents reaction at the *ortho* position [17].

The imidazo ester **15** was obtained from the enol phosphate **14** by treatment with ethyl isocyanoacetate and potassium *tert*-butoxide [18]. The enol phosphate was prepared from the benzodiazepin-2-one **13**, by treatment with diethylchlorophosphate [19] (Scheme III). Analysis of the proton nmr spectrum for **15** allows for the assignment of the ethyl group protons as a triplet and a multiplet centered at 1.55 ppm and 4.45 ppm respectively. The multi-



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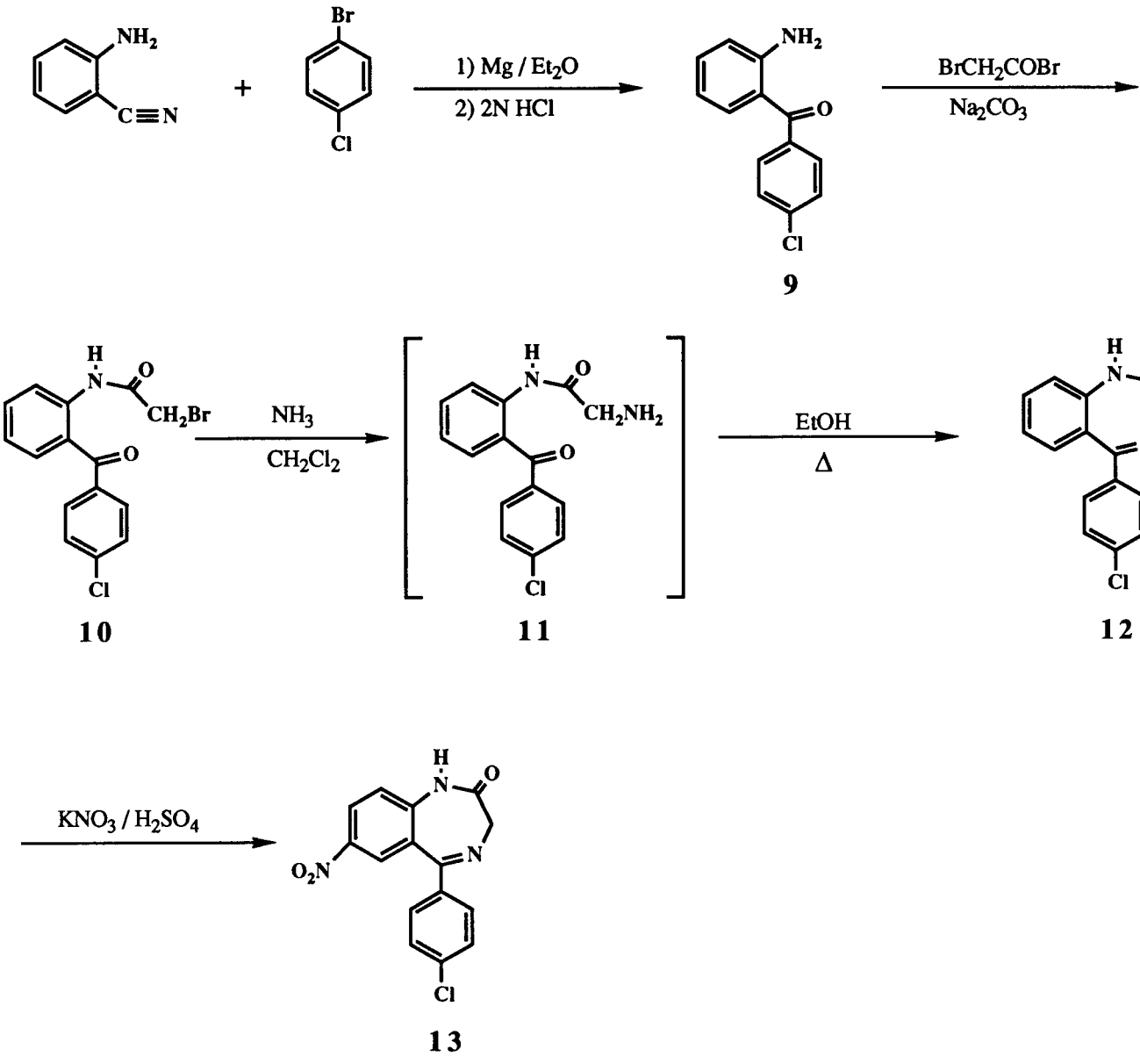
Scheme II

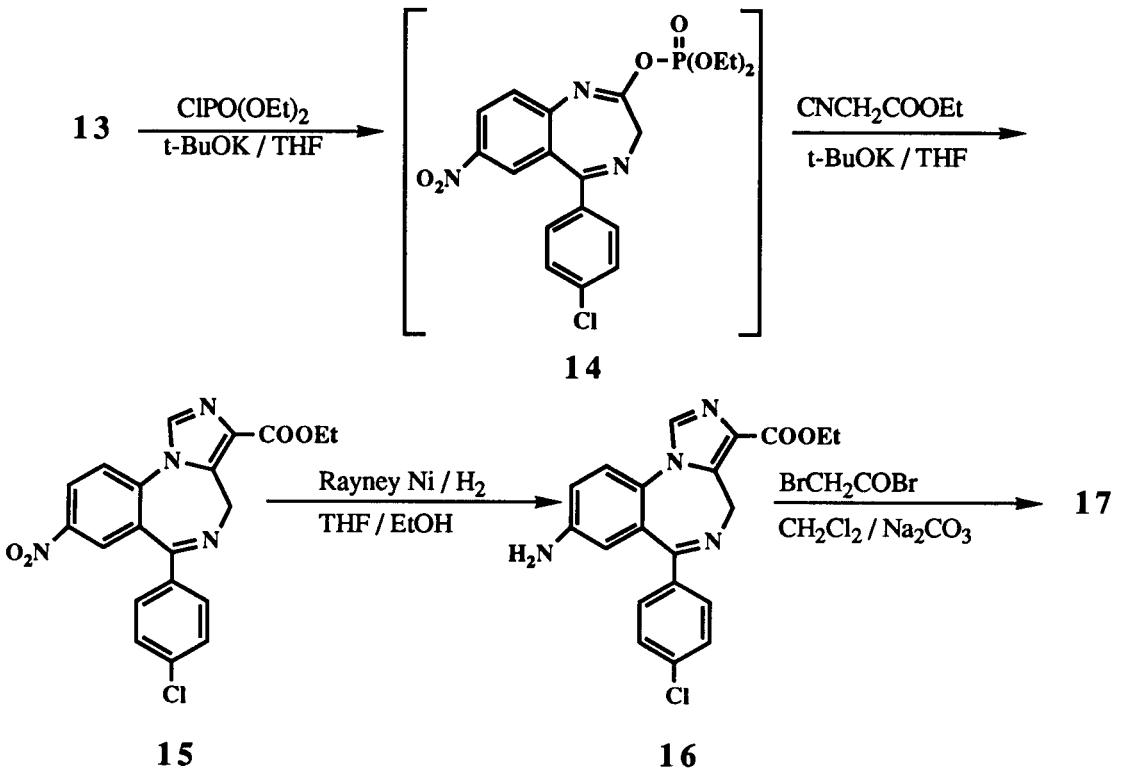


9 **10** **11** **12** **13**

plicity of the CH_2 proton signal from the ethyl group is probably due to the environmental differences between the two protons. The imidazo proton at the 1-position was displayed characteristically at 7.85 ppm, even more downfield than the aromatic protons from the benzene rings (methine carbon attached to 2 nitrogen atoms). Catalytic reduction of the nitro group, using hydrogen and Raney nickel catalyst, afforded the corresponding primary amine **16**. A comparison of the proton nmr spectrum of this compound with that of **15**, showed the additional (expected) two characteristic NH protons at 3.95 ppm which were exchangeable in deuterium oxide. The methylene protons at the 4-position also exhibited an AB quartet pattern as for compound **15**, almost 2 ppm apart.

The bromoacetyl side chain was attached to the amino group of **16** by treatment with bromoacetyl bromide, to afford the target compound **17**. The amide proton from **17** was displayed at 8.75 ppm in the nmr spectrum, exchangeable with deuterium oxide. The additional methylene group from the attached bromoacetyl side chain, was observed as a singlet, otherwise the spectrum was comparable to that of its precursor.

Scheme III



EXPERIMENTAL

General.

Unless otherwise specified, melting points were determined with Mel-Temp apparatus and are uncorrected unless specified. Infrared spectra were obtained by using Nicolet Model 2DX Fourier infrared Spectrophotometer. Mass spectra were recorded on Hewlett Packard HP5890 gas chromatography-Finnigan Mat Incos 50 mass spectrometer (70 eV). The ^{1}H nmr spectra were determined at 200 MHz Bruker Model WP 200 or at 400 MHz Bruker Model AM 400 Fourier transform spectrometers. Correlated spectroscopy (COSY) of ^{1}H nmr and ^{13}C nmr spectra were taken at 400 MHz Bruker Model AM 400 Fourier transform spectrometer. Spectra were recorded in deuteriochloroform or DMSO-d_6 and chemical shifts are expressed in parts per million (ppm) on the δ scale relative to a TMS internal standard. The ^{1}H nmr spectra are reported as follows: (solvent) chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad], coupling constant in Hz, interpretation). Broad-band proton decoupled and distortionless enhancement by polarization transfer (DEPT) spectra of ^{13}C nmr was collected for a few selected compounds. DEPT ^{13}C nmr spectra are reported as follows: (solvent) chemical shift (CH_3 = methyl carbon, CH_2 = methylene carbon, CH = methyne carbon and C = quaternary carbon). Fast atom bombardment (FAB) mass spectrum and microanalyses were performed at Hoffmann-La Roche, Inc., Nutley, New Jersey.

Unless specified otherwise, commercially available solvents from Fisher Scientific Co. and reagents from Aldrich Chemical Co. were used as received. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Purification by column chromatography was accomplished on 230-400 mesh silica gel, Merck, grade 60 (Aldrich), ~150 mesh neutral aluminum oxide, Brockmann I (Aldrich) and 80-200 mesh neutral alumina, Brockman activity 1 (Fisher). Thin layer chromatography was carried out using DC-Plastikfolien Kieselgel 60 F_{254} (Art. 5735) and DC-Plastikfolien Aluminiumoxid 60 F_{254} neutral (Typ E, Art. 5581) plates, obtained from Alltech Associates, Inc. In work-up of reactions, brine, routinely used as the final wash of organic solutions, refers to a saturated aqueous sodium chloride solution.

It should be noted while compounds **9**, **12** and **13** have been previously reported in the literature [14,15 and 16] respectively, no supporting spectral data were given. Compound **9** was previously prepared by an alternate synthetic procedure.

2-Aminomethyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine Dimaleate (**1**).

Compound **1** (from ethanol, mp 166-168°) was obtained from 7-chloro-1,3-dihydro-2-nitromethylene-5-phenyl-2*H*-[1,4]-benzodiazepine 4-Oxide [10], using the Raney nickel hydrogenation procedures reported for the synthesis of related analogs [11]; ^{1}H-nmr (DMSO-d_6): 7.92 (br s, 2H, NH_2, exchanges with deuterium oxide), 7.52 (m, 5H, Ar-H), 7.42 (dd, J = 8.9 and 2.3 Hz, 1H, Ar-H), 7.15 (br s, 1H, NH, exchanges with deuterium oxide), 7.05 (d, J = 8.9 Hz, 1H, Ar-H), 6.85 (d, J = 2.3 Hz, 1H, Ar-H), 6.11 (s, 4H, maleate CH=CH), 4.2 (m, 1H, C_2-H), 4.0 (dd, J = 12.1 and 5.6 Hz, 1H, C_3-H), 3.76 (d, J = 12.1 Hz, 1H, C_3-H), 3.0 (dd, J = 12.7 and 5.2 Hz, 1H, C_2-CH), 2.85 (dd, J = 12.7 and 7.2 Hz, 1H, C_2-CH); ir (potassium bromide): 3375, 3280, 3030, 2980, 1699, 1621, 1470, 1450, 1150 cm^{-1}.

2-Phthalimidoacetylaminomethyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (**2a**).

Compound **1** (3.88 g, 7.5 mmoles) was partitioned between 50 ml of methylene chloride and 50 ml of aqueous ammonium hydroxide solution (20%). After separation, the aqueous phase was extracted with methylene chloride. The combined organic phase was washed twice with water, once with brine, dried (magnesium sulfate) and filtered. The organic layer was then placed into a flask containing 5.9 g of phthalimidoacetyl chloride, prepared, first by refluxing a mixture of 5 g (24 mmoles) of *N*-phthaloylglycine, 10 ml of thionyl chloride and 60 ml of benzene and then followed by the removal of solvents at reduced pressure. After the reaction mixture was refluxed for 2 hours, the yellow precipitate which formed was collected by filtration and was recrystallized from methanol to afford 3.2 g (84%) of **2a** as yellow crystals, mp 262-264°; ir (potassium bromide): 3465, 3310, 3070, 3030, 2830, 1770, 1680, 1617, 1450, 1210, 586 cm^{-1}.

Anal. Calcd. for $C_{26}H_{22}N_4O_3Cl_2 \cdot CH_3OH$: C, 59.90; H, 4.84; N, 10.35. Found: C, 59.93; H, 4.88; N, 10.37.

2-Phthalimidoacetylaminomethyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine Hemihydrate (**2b**).

A solution of 3.2 g (6.3 mmoles) of **2a** in a mixture of 3 ml of triethylamine and 100 ml of ethanol was refluxed until the solution became clear yellow (about 2 hours). The solvent was removed *in vacuo* to afford a yellow oil, which was crystallized from methanol to yield 2.5 g (5.2 mmoles, 83%) of **2b** as fine yellow needles, mp 130-132°; ^{1}H-nmr (deuteriochloroform): 7.68-7.92 (m, 4H, Ar-H), 7.3-7.55 (m, 5H, Ar-H), 7.15 (br s, 1H, NH, exchanges with deuterium oxide), 7.1 (dd, J = 8.7 and 2.5 Hz, 1H, Ar-H), 6.92 (d, J = 2.4 Hz, 1H, Ar-H), 6.7 (d, J = 8.7 Hz, 1H, Ar-H), 4.68 (br s, 1H, NH, exchanges with deuterium oxide), 4.3 (s, 2H, CH_2-CON), 4.2 (m, 1H, C_2-H), 3.88 (dd, J = 11.5 and 5.4 Hz, 1H, C_3-H), 3.74 (dd, J = 11.5 and 2.8 Hz, 1H, C_3-H), 3.4 (m, 2H, C_2-CH_2); ir (potassium bromide): 3330, 3080, 2950, 1773, 1719, 1660, 1617, 1430, 1170, 680 cm^{-1}; ms: m/z (relative intensity) 472 (M^+, 6), 415 (12), 413 (12), 288 (23), 287 (22), 269 (22), 259 (36), 255 (22), 253 (14), 241 (20), 240 (12), 230 (16), 205 (13), 161 (62), 160 (100), 133 (19), 105 (25), 104 (32), 77 (49), 76 (48), 50 (38).

Anal. Calcd. for $C_{26}H_{21}N_4O_3Cl \cdot 0.5H_2O$: C, 64.80; H, 4.60; N, 11.63. Found: C, 64.78; H, 4.73; N, 11.49.

8-Chloro-3a,4-dihydro-6-phenyl-1-phthalimidomethyl-3*H*-imidazo-[1,5-*a*][1,4]benzodiazepine (**3**) and 2-[2-(2-Carboxybenzamido)acetamido methyl]-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**4**).

A mixture of 1.2 g (2.5 mmoles) of **2b** and 12 g of polyphosphoric acid was heated with stirring at 150° for 2 hours. After cooling to about 50°, the mixture was dissolved in ice water. The solution was made alkaline with concentrated ammonium hydroxide and extracted with methylene chloride. The combined extracts were washed with water, brine, dried (magnesium sulfate) and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel. The product was eluted with mixture of dichloromethane:ethyl acetate:methanol (3:2:0.5; v/v/v) and crystallized from ethyl acetate to yield 0.6 g (1.3 mmoles, 52%) of **3** as pale yellow crystals mp 195-197°; ^{1}H-nmr (deuteriochloroform): 7.12-8.8 (m, 12H, Ar-H), 4.7 (m, 1H, C_{3a}-H), 4.16 (dt, J = 15.7 and 1.8 Hz, 1H, CH_2-CON), 4.04 (d, J = 15.6 Hz, 1H, CH_2-CON), 4.02 (d, J = 8.8 Hz, 2H, C_3-H), 3.9 (dd, J = 11.7 and 0.88 Hz, 1H, C_4-H), 3.4 (dd, J = 11.7 and 4.2 Hz, 1H, C_4-H); homonuclear decoupling (deuteriochloroform), irradiation at δ 4.7 collapsed the signals at δ 4.02 to a singlet and at δ 3.9 and δ 3.4 to doublets; irradiation at δ 3.4 collapsed the signals at δ 4.7 to a triplet and at δ 3.9 to a singlet, while irradiation at δ 4.16 had no observable effect on the remainder of the spectrum; ^{13}C-nmr (deuteriochloroform, broad-band proton decoupling and DEPT) 169.8 (C), 167.2 (C), 158.8 (C), 138.6 (C), 138.2 (C), 137.9 (C), 134.6 (C), 134.2 (CH), 132.2 (C), 131.6 (CH), 131.5 (CH), 131.1 (CH), 131.0 (CH), 129.2 (CH), 128.8 (CH), 123.8 (CH), 73.1 (CH), 57.8 (CH_2), 54.2 (CH_2), 35.9 (CH_2) ppm; ir (potassium bromide): 3030, 2910, 2830, 1773, 1719, 1645, 1616, 1450, 675 cm^{-1}; ms: m/z (relative intensity) 456 (19), 454 (M^+, 77), 452 (20), 428 (15), 294 (100), 292 (52), 267 (78), 266 (40), 240 (34), 227 (18), 204 (33), 191 (14), 160 (98), 104 (42), 91 (25), 77 (72), 50 (20).

Anal. Calcd. for $C_{26}H_{19}ClN_4O_2$: C, 68.65; H, 4.21; N, 12.32. Found: C, 68.39; H, 4.11; N, 12.14.

Further elution of the column with methanol gave a fraction which was concentrated *in vacuo* to give a yellow residue, which was crystallized from ethyl acetate to yield 0.3 g of **4**, mp 242-244°. This product was carried through to the next step without further characterization.

2-(2-Aminoacetamidomethyl)-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**5**).

A solution of 1.2 g (2.4 mmoles) of **4** in 25 ml of 40% aqueous methylamine and 75 ml of 95% ethanol was stirred at room temperature for 3 hours. Water (200 ml) was added and after stirring the reaction mixture for an additional hour the reaction mixture was extracted thrice with methylene chloride. The combined extracts were washed with water, brine, dried (magnesium sulfate) and filtered. After the solvent was removed at reduced pressure, the residue was crystallized from ethyl acetate to give 480 mg (1.4 mmoles, 58%) of **5** as white crystals, mp 151-153°; ^{1}H-nmr (deuteriochloroform): 7.75 (t, J = 5.0 Hz, 1H, NH, exchanges with deuterium oxide), 7.42-7.58 (m, 5H, Ar-H), 7.16 (dd, J = 8.6 and 2.5 Hz, 1H, Ar-H), 6.97 (d, J = 2.5 Hz, 1H, Ar-H), 6.75 (d, J = 8.6 Hz, 1H, Ar-H), 4.55 (br s, 1H, NH, exchanges with deuterium oxide), 4.15 (m, 1H, C_2-H), 3.95 (dd, J = 11.2 and 2.6 Hz, 1H, C_3-H), 3.75 (dd, J = 11.2 and 6.9 Hz, 1H, C_3-H), 3.6 (dd, J = 6.9 and 2.1 Hz, 1H, C_2-CH_2-N), 3.45 (dd, J = 7.0 and 2.1 Hz, 1H, C_2-CH_2-N), 3.35 (s, 2H, CH_2-CON), 1.5 (br s, 2H, NH, exchanges with deuterium oxide); ir (potassium bromide): 3340, 3310, 3010, 2950, 1661, 1611, 1482, 1202, 700 cm^{-1}; ms: m/z (relative intensity) 344 (5), 343 (4), 342 (M^+, 10), 312 (8), 270 (11), 269 (11), 268 (23), 267 (11), 257 (28), 256 (19), 255 (100), 253 (8), 240 (8), 227 (14), 205 (5), 193 (7), 165 (5), 117 (3), 30 (12).

Anal. Calcd. for $C_{18}H_{19}N_4OCl$: C, 63.06; H, 5.59; N, 16.34. Found: C, 62.86; H, 5.50; N, 16.17.

8-Chloro-6-phenyl-1-phthalimidomethyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine Hemihydrate (**6**).

A mixture of 300 mg (0.7 mmole) of **3**, 3 g of activated manganese dioxide and 50 ml of toluene was heated to reflux with stirring overnight. Another 1 g of activated manganese dioxide was added and reflux was continued for an additional 3 hours. The manganese dioxide was filtered hot through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was crystallized from ethyl acetate to yield 110 mg (34%) of **6** as fine pale yellow crystals, mp 204-206°; ^{1}H-nmr (deuteriochloroform): 7.31-7.88 (m, 12H, Ar-H), 6.95 (s, 1H, imidazo-H), 5.18 (d, J = 15.6 Hz, 1H, NCH_2-C_1), 5.08 (d, J = 12.9 Hz, 1H, C_4-H), 5.0 (d, J = 15.7

Hz, 1H, NCH_2-C_1), 4.0 (d, J = 13 Hz, 1H, C_4-H); ir (potassium bromide): 3040, 1770, 1719, 1601, 1470, 1110, 720 cm^{-1}; ms: m/z (relative intensity) 454 (16), 453 (13), 452 (M^+, 40), 304 (9), 294 (37), 293 (25), 292 (100), 265 (7), 256 (6), 202 (8), 160 (32), 150 (39), 149 (100), 121 (30), 105 (28), 104 (44), 93 (32), 77 (61), 76 (52), 65 (37), 50 (32).

Anal. Calcd. for $C_{26}H_{17}N_4O_2Cl \cdot 0.5H_2O$: C, 67.61; H, 3.93; N, 12.12. Found: C, 67.87; H, 3.77; N, 12.06.

1-(2-Bromoacetamidomethyl)-8-chloro-6-phenyl-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine Dihydrobromide Hydrate (**8**).

A mixture of 100 mg (0.22 mmole) of **6**, 2 ml of 40% aqueous methylamine and 15 ml of 95% ethanol was stirred at room temperature for 3 hours. This was followed by the slow addition of 50 ml of water. After stirring another 30 minutes, the mixture was extracted thrice with methylene chloride. The combined extracts were washed with water, brine, dried (magnesium sulfate) and filtered. The filtrate was concentrated *in vacuo* to afford **7** as a yellow oil (decreased R_f value on tlc compared to **6**). Without further purification the oil **7** was dissolved in 30 ml of methylene chloride, cooled in an ice bath and treated with the dropwise addition of a solution of 0.5 ml of bromoacetyl bromide in 5 ml of methylene chloride. After stirring for 30 minutes in the ice bath, the mixture was allowed to stir at room temperature overnight and then concentrated *in vacuo*. The residue was crystallized from a mixture of methanol and ethyl acetate to afford 50 mg (51%) of **8** as the monohydrate of the dihydrobromide salt, pale yellow crystals, mp 262-264° dec; ^{1}H-nmr (DMSO-d_6): 8.95 (t, J = 4.5 Hz, 1H, NH, exchanges with deuterium oxide), 8.03 (d, J = 8.6 Hz, 1H, Ar-H), 7.9 (dd, J = 8.6 and 2.3 Hz, 1H, Ar-H), 7.85 (s, 1H, imidazo-H), 7.4-7.6 (m, 6H, Ar-H), 5.18 (d, J = 12.6 Hz, 1H, C_4-H), 4.85 (m, 2H, NCH_2-C_1), 4.15 (d, J = 12.6 Hz, 1H, C_4-H), 3.85 (s, 2H, $BrCH_2$); ir (potassium bromide): 3484, 3030, 2985, 1722, 1610, 1421, 1228 cm^{-1}; ms: m/z (relative intensity) 444 (4), 442 (M^+, 5), 384 (5), 364 (15), 363 (9), 346 (5), 328 (17), 323 (23), 321 (77), 294 (15), 293 (15), 292 (42), 286 (7), 270 (24), 250 (26), 242 (20), 228 (19), 226 (14), 203 (12), 193 (23), 184 (21), 179 (23), 165 (30), 115 (36), 91 (100), 77 (60), 61 (45).

Anal. Calcd. for $C_{20}H_{18}N_4OBr_3Cl \cdot H_2O$: C, 38.52; H, 3.23; N, 8.99. Found: C, 38.84; H, 3.08; N, 8.96.

4'-Chloro-2-aminobenzophenone (**9**).

A solution of 40 g (210 mmoles) of 4-bromochlorobenzene in 120 ml of anhydrous ethyl ether was slowly added to a stirred suspension of 7.0 g (290 mmole) of Magnesium turnings in 50 ml of anhydrous ethyl ether at a rate adjusted to keep the solution refluxing continuously. After the addition was complete the reaction mixture was refluxed for an additional 30 minutes, and then a solution of 8.3 g (70 mmoles) of anthranilonitrile in 100 ml of anhydrous ethyl ether was added dropwise and the resulting mixture was refluxed for another hour. After cooling it was slowly poured into 400 ml of ice water (precipitate formed). Then 300 ml of 3*N* hydrochloric acid was added, the mixture was stirred at room temperature for 1 hour, and the organic phase was separated. The aqueous phase was extracted with ethyl ether. The combined organic layers were washed with water, brine, dried (magnesium sulfate) and filtered. The filtrate was concentrated *in vacuo* and the residue was crystallized from ethanol to give 10.2 g (64%) of **9** as yellow prisms, mp 94-96° (lit [14] mp 98-99°); ^{1}H-nmr (deuteriochloroform): 7.25-7.6 (m, 6H, Ar-H), 6.55-6.75 (m, 2H, Ar-H), 6.1 (br s, 2H, NH_2, exchanges with deuterium oxide); ir (potassium bromide): 3476, 3372, 1637, 1611, 1584, 1470, 1304, 1297, 1246, 1156, 1088, 920 cm^{-1}; ms: m/z (relative intensity) 233 (25), 232 (40), 231 (M^+, 72), 230 (100), 214 (10), 196 (20), 195 (10), 167 (11), 141 (8), 139 (30), 120 (70), 113 (12), 111 (45), 98 (10), 92 (48), 84 (19), 75 (31), 65 (58), 50 (12), 39 (23).

2-Bromo-2'-(4-chlorobenzoyl)acetanilide (**10**).

A solution of 10.8 g (47 mmoles) of **9** in 200 ml of ethyl ether and 50 ml of water was cooled in an ice bath. The mixture was stirred while a solution of 5.0 ml (10 mmoles) of bromoacetyl bromide and an aqueous sodium carbonate solution (20%) were added alternately, keeping the solution slightly basic. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hour. The precipitate formed was collected by filtration to afford 16.2 g (98%) of **10** as a fine yellow powder, mp 143-145°; ^{1}H-nmr (deuteriochloroform): 11.4 (br s, 1H, NH, exchanges with deuterium oxide), 8.6 (d, J = 8.4 Hz, 1H, Ar-H), 7.5-7.8 (m, 6H, Ar-H), 7.15-7.25 (m, 1H, Ar-H), 4.05 (s, 2H, CH_2Br); ir (potassium bromide): 3270, 1675, 1641, 1570, 1520, 1449, 1295, 1287, 925 cm^{-1}; ms: m/z (relative intensity) 355 (10), 354 (8), 353 (35), 352 (M^+, 25), 272 (14), 260 (11), 258 (33), 242 (10), 240 (9), 233 (16), 232 (38), 231 (48), 230 (100), 214 (67), 212 (59), 201 (14), 196 (17), 195 (13), 167 (20), 166 (24), 145 (53), 141 (20), 140 (12), 139 (72), 121 (12), 120 (28), 113 (18), 111 (55), 94 (9), 93 (10), 92 (21), 90 (13), 77 (10), 76 (12), 75 (22), 65 (10), 64 (11), 63 (13), 51 (8), 50 (9), 42 (10).

1,3-Dihydro-5-(4-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**12**).

Approximately 100 ml of anhydrous liquid ammonia was condensed from a dry-ice condenser into a stirred solution of 10 g (28.4 mmoles) of **10** in 150 ml of methylene chloride. After 3 hours of reflux the condenser was removed in order to allow the ammonia to evaporate. The solution was then washed with water until the washings were neutral, then washed with brine, dried (magnesium sulfate) and filtered. After the solvent was removed (reduced pressure), **11** was obtained as a yellow oil. Without further purification, **11** was heated to reflux in 100 ml of absolute ethanol for 3 hours in order to effect ring closure. On cooling a pale yellow crystalline precipitate was formed and was collected by filtration to give 5.6 g (73%) of **12**, mp 259-260° (lit [16] 262-263°); ^{1}H-nmr (DMSO-d_6): 10.55 (s, 1H, NH, exchanges with deuterium oxide), 7.45-7.65 (m, 5H, Ar-H), 7.1-7.3 (m, 3H, Ar-H), 4.1 (br s, 2H, CH_2); ir (potassium bromide): 3061, 2873, 2821, 1677, 1508, 1503, 1484, 1382, 1377, 837 cm^{-1}; ms: m/z (relative intensity) 272 (22), 271 (31), 270 (M^+, 62), 269 (70), 244 (34), 243 (45), 242 (100), 241 (65), 236 (16), 234 (23), 214 (10), 207 (18), 179 (10), 178 (14), 177 (10), 150 (17), 151 (18), 129 (16), 125 (10), 111 (8), 104 (21), 103 (38), 102 (16), 95 (10), 90 (21), 89 (34), 78 (12), 77 (28), 76 (32), 75 (24), 63 (17), 51 (13), 50 (8), 39 (10).

7-Nitro-1,3-dihydro-5-(4-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (**13**).

A solution of 2.4 g (24 mmoles) of potassium nitrate in 6 ml of concentrated sulfuric acid was added dropwise to a solution of 5.4 g (20 mmoles) of **12** in 12 ml of concentrated sulfuric acid kept at ice bath temperature. After addition was complete the reaction mixture was stirred continuously in the ice bath for 30 minutes and then at room temperature for 4 hours. The solution was poured into 150 ml of ice water and neutralized with concentrated ammonium hydroxide giving a yellow precipitate. The precipitate was collected by filtration and washed thoroughly

with water until the washings were neutral. The precipitate was then dissolved in 200 ml of methylene chloride and any insoluble material was removed by filtration. The filtrate was washed with water, brine, dried (magnesium sulfate) and filtered. Solvent was removed at reduced pressure and the residue was crystallized from methanol to give 4.0 g (63%) of **13** as yellow needles mp 250-251° (lit [16] mp 253-254°); ^{1}H-nmr (DMSO-d_6): 11.15 (s, 1H, NH, exchanges with deuterium oxide), 8.4 (dd, J = 9.0 and 2.6 Hz, 1H, Ar-H), 8.05 (d, J = 2.5 Hz, 1H, Ar-H), 7.4-7.7 (m, 5H, Ar-H), 4.25 (br s, 2H, CH_2); ir (potassium bromide): 3091, 3087, 2962, 1694, 1608, 1533, 1482, 1342, 1335, 1306 and 1095 cm^{-1}; ms: m/z (relative intensity) 317 (17), 316 (25), 315 (M^+, 53), 314 (55), 289 (39), 288 (46), 287 (100), 280 (16), 270 (17), 269 (13), 268 (40), 252 (13), 242 (20), 241 (28), 240 (50), 239 (23), 234 (15), 213 (12), 206 (12), 205 (21), 179 (16), 178 (22), 177 (32), 163 (8), 152 (15), 151 (28), 150 (27), 138 (11), 125 (21), 111 (18), 103 (22), 102 (24), 90 (13), 89 (36), 88 (13), 82 (12), 77 (21), 76 (25), 75 (47), 63 (19), 62 (12), 51 (16), 44 (7).

Ethyl 8-Nitro-6-(4-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (**15**).

A solution of 1.6 g (5.0 mmoles) of **13** and 1.34 g (12 mmoles) of potassium *t*-butoxide in 30 ml of dry THF was stirred in an ice bath for 10 minutes under nitrogen and was then treated with 3.5 g (20 mmoles) of diethyl chlorophosphate. After stirring for 30 minutes, 1.7 g (15 mmoles) of ethyl isocyanoacetate and 1.9 g (17 mmoles) of potassium *t*-butoxide were added (the solution turned dark brown). The mixture was continuously stirred in the ice bath for 1 hour, was allowed to stir at room temperature overnight under nitrogen and after the addition of 4.0 ml of acetic acid, was stirred for an additional 20 minutes and was then concentrated (reduced pressure). The residue was chromatographed on neutral alumina and the product was eluted with 15% acetonitrile in methylene chloride. Removal of solvent at reduced pressure afforded 900 mg (44%) of **15** as a pale brown oil; ^{1}H-nmr (deuteriochloroform): 8.55 (dd, J = 8.9 and 2.6 Hz, 1H, Ar-H), 8.3 (d, J = 2.5 Hz, 1H, Ar-H), 8.0 (s, 1H, imidazo-H), 7.8 (d, J = 8.8 Hz, 1H, Ar-H), 7.35-7.5 (m, 4H, Ar-H), 6.15 (d, J = 12.7 Hz, 1H, C_4-H), 4.45 (m, 2H, OCH_2), 4.1 (d, J = 12.7 Hz, 1H, C_4-H), 1.55 (t, J = 7.2 Hz, 3H, CH_3); ms: m/z (relative intensity) 412 (15), 410 (M^+, 35), 366 (28), 365 (23), 364 (64), 338 (35), 337 (30), 336 (100), 306 (6), 291 (14), 290 (23), 262 (5), 240 (18), 228 (12), 202 (15), 201 (19), 154 (14), 153 (25), 141 (23), 137 (23), 128 (27), 127 (21), 114 (12), 101 (23), 87 (8), 75 (15), 52 (36), 44 (16). The oil **15** was not further characterized but was used directly in the next step.

Ethyl 8-Amino-6-(4-chlorophenyl)-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate (**16**).

A solution of 900 mg (2.2 mmoles) of **15** in 40 ml of dry THF and 60 ml of ethanol was hydrogenated in a Parr bomb hydrogenator, in the presence of 1.5 g of Raney nickel and 5 drops of 20% ammonia in methanol (at an initial pressure of 40 psi) until the hydrogen consumption ceased. The catalyst was removed by filtration over Celite and the filtrates were concentrated *in vacuo*. The residue was crystallized from ethanol to give 520 mg (64%) of **16** as pale yellow needles, mp 136-138°; ^{1}H-nmr (deuteriochloroform): 7.85 (s, 1H, imidazo-H), 7.5 (dd, J = 6.8 and 1.9 Hz, 2H, Ar-H), 7.38 (d, J = 8.6 Hz, 1H, Ar-H), 7.32 (dd, J = 6.8 and 1.9 Hz, 2H, Ar-H), 6.9 (dd, J = 8.6 and 2.6 Hz, 1H, Ar-H), 6.6 (d, J = 2.6 Hz, 1H, Ar-H), 5.98 (d, J = 12.3 Hz, 1H, C_4-H), 4.4 (m, 2H, OCH_2), 4.05 (d, J = 12.4 Hz, 1H, C_4-H), 3.95 (br s, 2H, NH_2, exchanges with deuterium oxide), 1.4 (t, J = 7.2 Hz, 3H, CH_3); ir (potassium bromide): 3335, 3209, 2975, 1704, 1602, 1568, 1509, 1489, 1374, 1248, 1183, 1181 and 1089 cm^{-1}; ms: m/z (relative intensity) 382 (10), 380 (M^+, 53), 336 (10), 335 (25), 334 (50), 308 (57), 307 (42), 306 (100), 278 (10), 256 (20), 254 (12), 244 (16), 207 (17), 170 (12), 169 (42), 144 (10), 117 (23), 116 (10), 79 (11), 52 (20), 44 (17).

Anal. Calcd. for $C_{20}H_{17}N_4O_2Cl \cdot 0.1H_2O$: C, 62.78; H, 4.53; N, 14.64. Found: C, 62.43; H, 4.43; N, 14.49; and C, 62.75; H, 4.35; N, 14.32.

Ethyl 8-(2-Bromoacetamido)-6-(4-chlorophenyl)-4*H*-imidazo[1,5-*a*]-[1,4]-benzodiazepine-3-carboxylate (**17**).

A solution of 760 mg (2.0 mmoles) of **16** in 15 ml of methylene chloride and 5 ml of water was vigorously stirred while being cooled with an external ice bath. A solution of 0.5 ml (5 mmoles) of bromoacetyl bromide in 5 ml of methylene chloride, and an aqueous sodium carbonate solution (20%) were added portionwise and alternately, such that the reaction solution remained slightly basic. After completing the addition, the reaction mixture was continuously stirred in the ice bath for 10 minutes, then at room temperature overnight. After addition of 50 ml of water to the solution, the organic layer was separated and filtered to remove any inorganic precipitate. The filtrate was washed with water, brine, dried (magnesium sulfate) and filtered. After removal of the solvent at reduced pressure, the residue was crystallized from a mixture of ethanol and ethyl acetate to afford 400 mg (40%) of **17**, mp 247-248° (hot stage, microscope); ^{1}H-nmr (deuteriochloroform): 8.75 (br s, 1H, NH, exchanges with deuterium oxide), 8.05 (dd, J = 8.8 and 2.5 Hz, 1H, Ar-H), 7.95 (s, 1H, imidazo-H), 7.3-7.6 (m, 6H, Ar-H), 6.05 (d, J = 12.3 Hz, 1H, C_4-H), 4.4 (m, 2H, OCH_2), 4.1 (d, J = 12.3 Hz, 1H, C_4-H), 4.05 (s, $BrCH_2$), 1.4 (t, J = 7.1 Hz, 3H, CH_3); ir (potassium bromide): 2980, 1722, 1692, 1615, 1589, 1557, 1507, 1263, 1180, 1077 cm^{-1}; ms: (FAB), m/z 501 (MH^+); ms: m/z (relative intensity) 380 (12), 350 (19), 334 (40), 333 (18), 310 (47), 309 (46), 308 (100), 307 (65), 306 (30), 282 (27), 281 (37), 280 (62), 265 (18), 254 (18), 248 (17), 232 (100), 230 (100), 219 (47), 218 (18), 188 (70), 187 (35), 186 (82), 185 (40), 173 (32), 172 (65), 171 (50), 170 (65), 157 (34), 155 (36), 145 (42), 139 (43), 137 (100), 133 (55), 108 (100), 91 (100), 77 (100).

Anal. Calcd. for $C_{22}H_{18}N_4O_3ClBr$: C, 52.66; H, 3.62; N, 11.17. Found: C, 52.58; H, 3.59; N, 10.76.

2-(5-Chlorovalerylamidomethyl)-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride Hemihydrate (**18**).

Compound **1**, (1.3 g, 2.5 mmoles) was converted to the free base by partitioning between 30 ml of methylene chloride and 30 ml of aqueous ammonium hydroxide solution (20%). After separation, the aqueous phase was extracted twice with 30 ml portions of methylene chloride. The combined organic phase was washed thrice with 200 ml portions of water, once with 150 ml saturated brine, dried (magnesium sulfate) and filtered. The filtrate was concentrated to about 50 ml at reduced pressure (water aspirator) on a rotary evaporator and then cooled in an ice bath. After a solution of 1.0 ml (7.0 mmoles) of 5-chlorovaleryl chloride in 10 ml of methylene chloride was slowly added, the solution was stirred in the ice bath for 30 minutes and then at room temperature for 2 hours. The solvent was removed (reduced pressure) to afford an orange oil which was crystallized from methanol to give 360 mg (33% yield) of **18**, hydrochloride hemihydrate, as orange prisms, mp 225-227°; ^{1}H-nmr (DMSO-d_6): 8.7 (br s, 1H, NH, ex-

changes with deuterium oxide), 8.4 (t, J = 5.8 Hz, 1H, NH, exchanges with deuterium oxide), 7.8 (m, 1H, Ar-H), 7.6 (m, 4H, Ar-H), 7.4 (dd, J = 9.0 and 2.5 Hz, 1H, Ar-H), 7.2 (d, J = 9.0 Hz, 1H, Ar-H), 6.8 (d, J = 2.5 Hz, 1H, Ar-H), 4.1 (m, 1H, C_2-H), 3.95 (m, 2H, $CONCH_2$), 3.6 (t, J = 6.4 Hz, 2H, $ClCH_2$), 3.5 (m, 1H, C_3-H), 3.1 (m, 1H, C_3-H), 2.2 (t, J = 6.6 Hz, 2H, CH_2CON), 1.7 (m, 4H, CH_2-CH_2); ir (potassium bromide): 3285, 3212, 3110, 3048, 1666, 1622, 1470, 1210, 1170, 720 cm^{-1}; ms: m/z (relative intensity) 405 (3), 403 (M^+, 5), 369 (15), 368 (18), 367 (40), 366 (28), 350 (17), 349 (23), 348 (31), 322 (24), 309 (17), 308 (22), 296 (24), 294 (51), 269 (18), 268 (26), 267 (36), 257 (34), 255 (100), 241 (20), 240 (26), 228 (15), 227 (18), 205 (19), 204 (23), 201 (12), 185 (14), 91 (12), 77 (13), 55 (17), 36 (52).

Anal. Calcd. for $C_{21}H_{24}N_3OCl_3 \cdot 0.5H_2O$: C, 56.08; H, 5.60; N, 9.34. Found: C, 56.03; H, 5.60; N, 9.12.

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