Curtius Rearrangement in the 5-Phenyl-1,4-benzodiazepine Series. Unprecedented Participation by an Imine Nitrogen

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The previously unknown 3-aminomethyl-1,3-dihydro-5-(2'-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one, **3a**, was synthesized in two steps as a racemate. In the chiral series, 3(*S*)-azidocarbonylmethyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, **12b**, was prepared from N^{α}-Cbz-β-methylaspartate in five synthetic operations and subjected to Curtius rearrangement. The intermediate isocyanate was trapped intramolecularly by the 5-imine nitrogen of the benzodiazepine ring in **12b**. This unanticipated result runs counter to the generally held dictum that the isocyanate group has a strictly linear shape.

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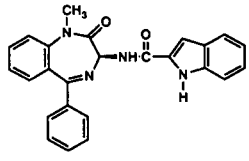
Introduction.

We recently demonstrated that the 5-phenyl-1,4-benzodiazepine ring system can serve as a useful template in the construction of ligands for peptide hormone receptors [1]. Accordingly, this benzodiazepine core structure was elaborated to afford compounds which are potent, highly specific antagonists of the gastrointestinal hormone cholecystokinin [2-6]. The most promising agent to emerge from these studies is the clinical candidate (3*S*)-(-)-*N*-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide, **1**, which was prepared from the corresponding 3-amino-1,4-benzodiazepin-2-one, **2** [7-9]. Within the context of this study, there arose the need to prepare a homologous series of compounds in an effort to ascertain which structural features of the benzodiazepine ring system and its attendant functionality are necessary for interaction with the cholecystokinin receptor(s). As a consequence, the 3-aminomethyl-1,4-benzodiazepin-2-ones, **3a** and **3c**, became key intermediates for this endeavor [10].

The widespread use of 1,4-benzodiazepine derivatives as therapeutic agents has required the development of practical and efficient processes for their preparation. Yet, in spite of an abundance of methodology for this purpose, we were surprised to find no suitable precedents which were applicable for our specific needs [11]. Nonetheless, compound **3a** could be readily prepared in racemic form *via* the two step procedure summarized in Scheme 1. Medicinal chemistry and pharmacological considerations subsequently required that both enantiomers of **3b** and **3c** be available. For this purpose, we reasoned that the enantiomers of **3b** could be assembled, as in Scheme 1, from 2-aminobenzophenone and the requisite chiral 2,3-diaminopropionic acid or 2,3-diaminopropionic acid equivalent. The latter, in turn, could be derived from the chiral pool of commonly available amino acids [12]. This general plan was followed according to Scheme 2 which details the construction of the penultimate compound, the acyl azide **12b**. Compound **12b** is poised for Curtius rearrangment



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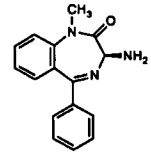

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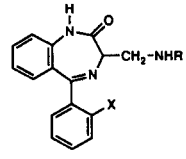
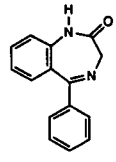


3a, R=H, X=F
3b, R=Boc, X=H
3c, R=H, X=H



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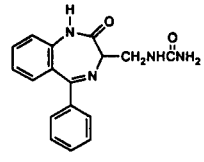

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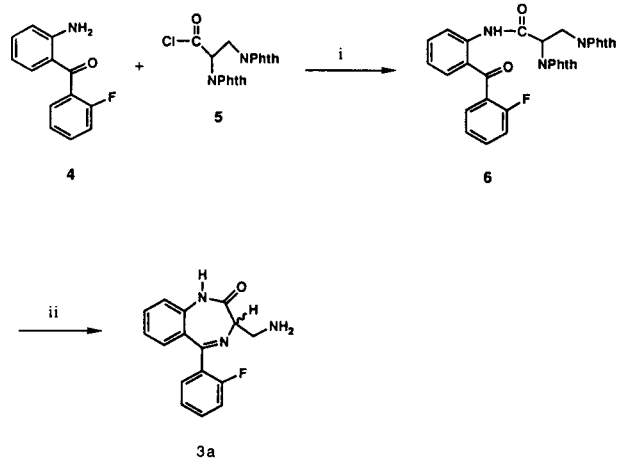
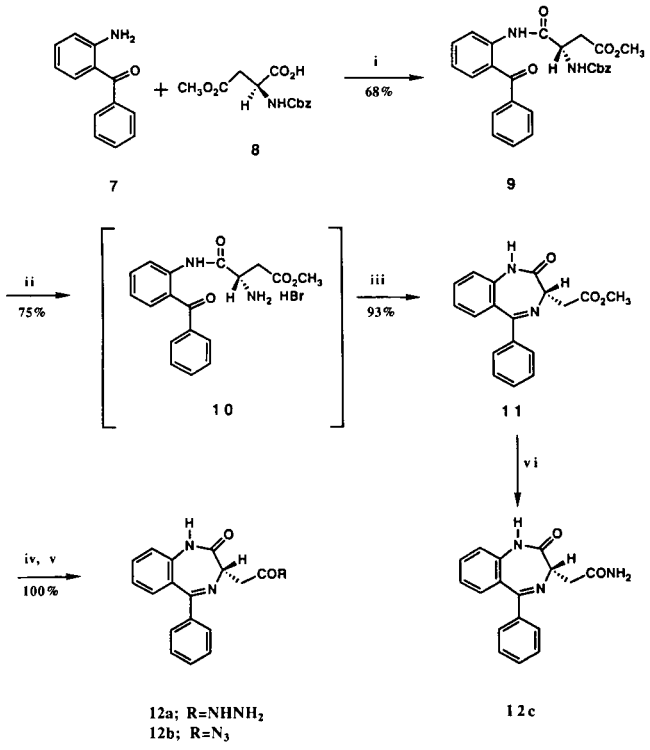
to the desired 3-aminomethyl-1,4-benzodiazepine. In this connection, we discovered that **12b** suffers the unexpected and unprecedented rearrangement which is the subject of this paper.

Scheme 1[a]



[a]Key : (i) THF, 23° C, 2.5 hr. (ii) NH_2NH_2 (95%), CH_3OH, 23 °C, 2 hr.

Scheme 2[a]



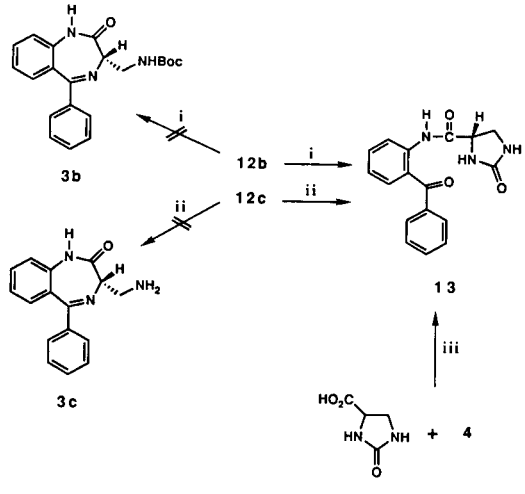
[a]Key: (i) i-BuOCOCl, NMM, 0 °C, 15 min; 41 °C, 20 min, then 23 °C, 72 hr. (ii) HBr (g), CH_2Cl_2, 23 °C, 4 hr. (iii) IPEA, CH_3OH, 23 °C, 18 hr. (iv) NH_2NH_2 (95%), CH_3OH, 23 °C, 2 hr. (v) i-AmONO, DMF, (pH 1) 0-23 °C, 30 min. (vi) NH_3, sealed tube, 36 hr.

Results and Discussion.

When the Cbz-protected L-aspartic acid-β-methyl ester, **8**, isobutyl chloroformate, and *N*-methylmorpholine were combined in methylene chloride there was obtained the corresponding mixed anhydride which was then reacted *in situ* with aminobenzophenone to give the *N*-acylated aminobenzophenone **9** in 68% isolated yield. Deprotection of the α-amino group was most conveniently accomplished by saturating a solution of **9** in methylene chloride with hydrogen bromide gas. In this way, the amine salt **10** was obtained in 75% yield as an amorphous, ivory colored solid. In practice, it was expedient to treat a solution of crude **10** in methanol with Hunig's base (two equivalents) to directly give the chiral 1,4-benzodiazepine cycle **11** (93% yield). Functional group interchange of the ester **11** was accomplished in standard fashion as follows. Treatment of **11** with hydrazine (95%) in methanol yielded the acyl hydrazide **12a**. The crude product **12a** was dissolved in *N,N*-dimethylformamide and the resulting solution was treated, in succession, with tetrahydrofuran saturated with hydrogen chloride gas and isoamyl nitrite. The anticipated acyl azide **12b** was thus obtained quantitatively.

Acyl azide **12b** was then subjected to the usual protocol for effecting the Curtius rearrangement [13,14]. (Scheme 3) Within two hours there was obtained, in 47% isolated yield, a white solid the data of which was inconsistent with the expected Boc-protected 3-aminomethyl-1,4-benzodiazepine **3b**. Significantly, the ^1H nmr spectrum of the reaction product lacked the 9-proton singlet for the Boc group. The possibility that **12b** was converted directly to **3c** under the reaction conditions employed could be ruled out from both the ^1H nmr spectrum of the reaction product which showed three amide N-H protons and from the FAB mass spectrum which displayed an M+H peak at 310. Additionally, when the amide **12c** was subjected to Hofman rearrangement under a variety of conditions [15], including also use of bis(trifluoroacetoxy)phenyliodine [16,17], no trace of **3c** was detected. Instead, there was isolated a product which was identical in all respects with that obtained from the Curtius rearrangement of **12b**. A consideration of key spectral evidence pointed to structure **13** as the rearrangement product, mechanistic rationale notwithstanding. The unambiguous structure assignment of **13** was secured by virtue of its synthesis as a racemate from **4** and 2-imidazolidone-4-carboxylic acid.

Scheme 3[a]



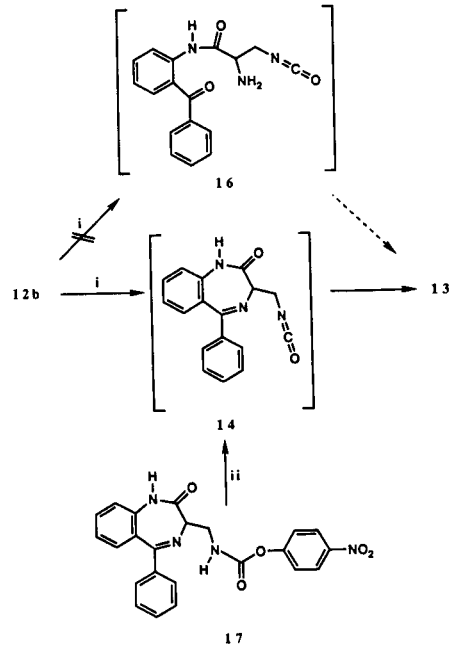
[a]Key : (i) DMF, t-BuOH, 90 °C, 2 hr. (ii) C_6H_5-I$(OCOCF_3)_2$, CH_3CN-H_2O (1:1, v/v), 23 °C, 8 hr. (iii) i-BuOCOCl, NMM, 0 °C, 15 min; 41 °C, 20 min, then 23 °C, 12 hr.

The formation of compound **13** from either **12b** or **12c** requires the intermediacy of the isocyanate **14**. As such, it appears remarkable from both a conformational and an electronic point of view that **14** does indeed lead to **13**. Inspection of molecular models suggests that the 3-methylene isocyanate appendage in **14** is not suitably disposed toward interaction with the 5-imine nitrogen atom. *A priori*, the linear nature of the isocyanate moiety seems to prevent approach of the 5-imine nitrogen to within bond

forming distance. Moreover, in a separate experiment, the intrinsic reactivity of the 5-imine nitrogen in **12b** toward isocyanates was tested using a model system and was shown to be negligible. Employing reaction conditions similar to those which produced **13** from **12b**, the 1,4-benzodiazepine **15** was recovered unchanged after prolonged heating with ethyl isocyanate.

An alternate mechanistic pathway to **13** (Scheme 4), wherein [4,5] -imine bond hydrolysis of **14** (adventitious traces of water) produces **16** and therefrom **13**, can be ruled out based on the following observation. 4-Nitrophenylcarbonate **17**, obtained from **3c** and 4-nitrophenyl chloroformate, was heated in dry *N,N*-dimethylformamide with triethylamine under an inert atmosphere and yielded **13** and 4-nitrophenol. This alternative method of generation **14** and the scrupulously anhydrous reaction conditions which were employed in this reaction effectively preclude the formation of **16**.

Scheme 4[a]



[a]Key: (i) according to Scheme 3. (ii) NEt_3, DMF, 85° C, 2.5 hr.

How does one account for the formation of **13**? Recent findings indicate that it is more appropriate to classify molecules like HCNO as being quasilinear rather than rigidly linear [18]. In this regard, *ab initio* calculated bond angles for the isomers of HCNO have been determined with the result that the HAB bond angle for HCNO has been found to deviate substantially from linearity (141 [18] and 157.8 [20] degrees). It is not unreasonable to extrapolate these results to the present case and invoke a quasilinear shape for the isocyanate functional group in **14**. The interception of such an isocyanate moiety by an imine nitrogen, a reaction for which we have found no precedence in the literature, is then driven, in the case of **14**, by the intramolecularity of the event.

EXPERIMENTAL

Melting points were determined in open capillaries on an Electrothermal melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H nmr) were recorded on a Varian XL300 (300 MHz, FT mode) spectrometer and a Nicolet NT-360 (360 MHz, FT mode) spectrometer, both instruments with an internal lock on the deuterium resonance of the solvent. Data are reported as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment). Fast atom bombardment (FAB) mass spectra were run on a Finnigan-MAT 731 instrument and electron impact (EI) mass spectra were determined on a VG 7035 spectrometer. The ir spectra were obtained on a Perkin-Elmer 1420 spectrophotometer.

Flash chromatography was performed on silica gel (E. Merck 40-63μ). Thin-layer chromatography (tlc) and preparative thick-layer chromatography (plc) were carried out on E. Merck 60F-254 precoated silica gel plates (0.25, 0.5, and 2 mm thickness) by using uv light, iodine vapors or 5% phosphomolybdic acid reagent in 95% ethanol to visualize the chromatograms.

All reactions, except those performed in aqueous solvents, were carried out with use of standard techniques for the exclusion of moisture. Commercial chemicals were used as obtained without further purification, except for solvents, which were purified and dried, where appropriate, before use by standard methods.

N-(Benzoylphenyl)-2,3-diphthalylaminopropionylamide **6**.

2-Amino-2′-fluorobenzophenone (2.10 g, 9.80 mmoles) and 2,3-diphthalylaminopropionyl chloride (5.0 g, 9.80 mmoles) were combined in 100 ml of tetrahydrofuran at room temperature and stirred for 2.5 hours. The solvent was removed under reduced pressure and the residual foam was heated in 6*N* hydrochloric acid solution. The resulting off-white solid was collected, air dried, and recrystallized from ethyl acetate to give 4.95 g (90%) of **6**, mp 210.5-211.5°; ^{1}H nmr (perdeuteriomethanol/DMSO-d_6): δ 4.25 (m, 1H), 4.45 (m, 1H), 4.94 (dd, 1H, 11 and 4 Hz), 7.27 (m, 3H), 7.41 (t, 1H, 6 Hz), 7.51 (d, 1H, 8 Hz), 7.60 (m, 1H), 7.66 (t, 1H, 8 Hz), 7.77 (m, 4H), 7.83 (m, 4H), 8.09 (d, 1H, 8 Hz); ms: FAB 562 (M + H).

Anal. Calcd. for $C_{32}H_{20}FN_3O_6$: C, 68.42; H, 3.73; N, 7.72. Found: C, 68.45; H, 3.59; N, 7.48.

3(*R,S*)-Aminomethyl-1,3-dihydro-5-(2′-fluorophenyl)-2*H*-1,4-benzodiazepin-2-one **3**.

To a suspension of methanol (15 ml) containing 1.34 g (2.38 mmoles) of **6** was added 1 ml of 95% hydrazine. The reaction was protected from moisture and stirred at room temperature overnight. The reaction was filtered and the filter cake was washed with 40 ml of methanol. Chromatography (plc) of the crude reaction product (chloroform-methanol concentrated ammonium hydroxide, 90:10:1, v/v R_f = 0.26) gave, after trituration with ether, 514 mg (90%) of the analytical product, mp 168-169°; ^{1}H nmr (deuteriochloroform): δ 3.47 (d, 1H, 6 Hz, C*H*-NH_2) 3.49 (d, 1H, 6 Hz, C*H*-NH_2), 3.67 (t, 1H, 6 Hz, C*H*-CH_2-NH_2), 7.05 (t, 1H, 9 Hz), 7.10 (d, 1H, 8 Hz), 7.15 (d, 1H, 8 Hz), 7.25 (m, 3H, N*H*-CO and Ar), 7.44 (m, 1H), 7.49 (t, 1H, 8 Hz), 7.58 (t, 1H, 8 Hz), 8.1 (br

s, 2H, NH_2); ms: FAB 284 (M + H).

Anal. Calcd. for $C_{16}H_{14}FN_3O \cdot 0.2H_2O$: C, 66.98; H, 5.06; N, 14.65. Found: C, 66.93; H, 5.20; N, 14.65.

N^{α}-Cbz-β-carboxymethyl-*N*-(benzoylphenyl)aspartamide **9**.

A 250 ml three-necked flask, fitted with an addition funnel, reflux condenser and nitrogen inlet was charged with N^{α}-Cbz-L-aspartic acid-β-methyl ester (1.89, 6.72 mmoles) in 45 ml of methylene chloride. The solution was cooled to 0° and treated in succession with *N*-methylmorpholine (886 μl, 8.06 mmoles) and isobutylchloroformate (1.04 ml, 8.06 mmoles). The reaction was warmed to room temperature over 10 minutes and then heated to reflux. A solution of aminobenzophenone in 30 ml of methylene chloride was then added dropwise to the refluxing reaction mixture. Heating was continued for 20 minutes more. The reaction mixture was then cooled to room temperature, stirred for 69 hours, and diluted with methylene chloride to 325 ml. The organic phase was washed with 10% citric acid solution (2 x 40 ml), saturated sodium bicarbonate solution (2 x 40 ml), and brine. The dried (sodium sulfate) organic extracts were concentrated under reduced pressure to afford 3.8 g of an oil. Flash chromatography of the crude product on silica gel employing hexane-ethyl acetate (initially 3:1, then 1:1 v/v) yielded 1.98 g (69%) of the analytical product, mp 48-50°; ^{1}H nmr (DMSO-d_6): δ 2.5 (m, 2H, C*H*$_2$-CO_2Me), 3.48 (br s, 1H, NH-Cbz), 3.54 (s, 3H, CO_2Me), 4.46 (m, 1H, α-H), 5.00 (d, 1H, 15 Hz, Cbz), 5.05 (d, 1H, 15 Hz, Cbz), 7.32 (m, 5H, Ar), 7.46 (dd, 1H, 12 and 2 Hz), 7.54 (t, 2H, 12 Hz), 7.66 (m, 4H), 7.84 (d, 1H, 12 Hz), 7.99 (d, 1H, 12 Hz), 10.80 (s, 1H, N*H*-CO); ms: FAB 461 (M + H), 417, 288.

Anal. Calcd. for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 68.16; H, 5.28; N, 6.02.

β-Carboxymethyl-*N*-(benzoylphenyl)aspartamide Hydrobromide **10**.

Hydrogen bromide gas was passed into a solution of methylene chloride (100 ml), containing 1.0 g (2.17 mmoles) of **9**, for 20 minutes at room temperature. The reaction vessel was capped and the solution was stirred for 4 hours more. Solvent and excess hydrogen bromide were rotoevaporated to give an oily residue. Toluene was added to the oil and the mixture was concentrated. This cycle was reported twice. The crude oily product was crystallized from 50 ml of methylene chloride containing 1 ml of methanol to give 660 mg (75%) of a white solid, mp 161°; ^{1}H nmr (DMSO-d_6): δ 5.49 (d, 2H, 7 Hz, C*H*$_2$$CO_2$Me), 3.57 (s, 3H, CO_2Me), 4.50 (dd, 1H, 14 and 6 Hz, α-H), 7.45 (m, 2H), 7.52 (m, 4H), 7.58 (m, 3H), 8.26 (br s, 3H, NH_3^+), 10.63 (s, 1H, NH-CO); ms: FAB 327 (M + H, -HBr), 197.

Anal. Calcd. for $C_{16}H_{19}BrN_2O_2O_4 \cdot 0.6CH_2Cl_2$: C, 48.75; H, 4.44; N, 6.11. Found: C, 48.78; H, 4.30; N, 6.11.

3(*S*)-Carboxymethyl-1,3-dihydro-5-(phenyl)-2*H*-1,4-benzodiazepin-2-one **11**.

Compound **10** (200 mg, 0.49 mmole) in 20 ml of methanol was treated with 130 μl (0.74 mmole) of diisopropylethylamine. After 18 hours at room temperature, the solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 0.5 *N* hydrochloric acid solution. The organic phase was washed with brine and dried (sodium sulfate), then rotoevaporated to yield 160 mg of an oil. Plc (hexane-ethyl acetate, 1:1, v/v) gave 140 mg (93%) of **11** as an oil which was crystallized from ethyl acetate (slow evaporation) to afford a white solid, mp 180-182°; $[\alpha]_D$ = +89.8° (c = 0.275, chloroform); ^{1}H nmr (deuteriochloroform): δ 3.22 (dd, 1H, 17 and 7 Hz, C*H*$_2$$CO_2$Me), 3.46 (dd, 1H, 17 and 7 Hz, C*H*$_2$$CO_2$Me), 3.74 (s, 3H, CO_2Me), 4.19 (t, 1H, 7 Hz, C*H*-CH_2-CO_2Me), 7.15 (d, 1H, 8 Hz), 7.17 (t, 1H, 7.5 Hz), 7.37 (m, 3H), 7.44 (m, 1H), 7.52 (m, 3H), 8.51 (br s, 1H, NH); ms: (EI, 14 ev) m/e 308 (M^+, 100%), 276 (38.8%), 265 (60.7%), 249 (45.3%), 248 (81.9%), 206 (22.6%).

Anal. Calcd. for $C_{18}H_{16}N_2O_3 \cdot 0.35H_2O$: C, 68.71; H, 5.35; N, 8.90. Found: C, 68.76; H, 5.14; N, 9.18.

Curtius Rearrangement of 3(*S*)-Azidocarbonylmethyl-1,3-dihydro-5-(phenyl)-2*H*-1,4-benzodiazepin-2-one **12b**.

The methyl ester **11** (180 mg, 0.58 mmole) was dissolved in 5 ml of methanol and treated with 1.5 ml of 95% hydrazine at room temperature. After 2 hours all volatiles were removed under reduced pressure. Toluene (10 ml) was added and the suspension was again concentrated. The oily residue was partitioned between ethyl acetate and water (25 ml, 1:1) and the organic phase was separated and washed with water once more. The dried (sodium sulfate) organic extracts were concentrated to yield 180 mg of the acyl hydrazide **12a** as a solid. Without purification, **12a** (180 mg, 0.58 mmole) was dissolved in 3 ml of dry *N,N*-dimethylformamide. The solution was cooled to 0° under nitrogen and treated with a solution of tetrahydrofuran saturated with hydrogen chloride until the *p*H of the resulting reaction mixture was approximately 1 (wet *p*H paper). Isoamylnitrite (100 μl, 0.74 mmole) was then added dropwise. The solution was warmed to room temperature for 0.5 hour. Infrared spectrophotometric analysis of an aliquot confirmed the presence of the acyl azide **12b** (film: 2150 cm^{-1}). All solvent was removed under reduced pressure and the residue was treated with a mixture of *t*-butyl alcohol/*N,N*-dimethylformamide (7:1 ml) and heated to 90° for 2 hours. Rotoevaporation of the reaction mixture afforded a semi-solid which was chromatographed (plc, chloroform-methanol-concentrated ammonium hydroxide, 90:10:1, v/v) to give 84 mg (47% overall) of **13** as a white solid after trituration with ether/petroleum ether, mp 109-111°; $[\alpha]_D$ = −10° (c = 0.11, chloroform); ir (Nujol, partial) 3250, 1660, 1260, 930 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.64 (dd, 1H, 9.6 and 6.3 Hz, CH-C*H*$_2$-NH-), 3.95 (dd, 1H, 10.5 and 9.6 Hz, CH-C*H*$_2$-NH-), 4.41 (ddd, 1H, 10.5, 6.3 and 2.7 Hz, CO-C*H*-CH_2), 5.02 (s, 1H, NH), 5.70 (br s, 1H, NH), 7.15 (dd, 1H, 8.1 and 7.5 Hz), 7.45 (dd, 2H, 8.1 and 7.5 Hz), 7.58 (m, 3H), 7.68 (m, 2H), 8.57 (d, 1H, 8.1 Hz), 10.90 (s, 1H, Ar-NH-CO); ms: (EI, 14 ev) m/e 309 (38.4%), 225 (91%), 224 (42.6%), 197 (73.8%), 85 (100%); ms: FAB 310 (M + H).

Anal. Calcd. for $C_{17}H_{15}N_3O_3 \cdot 0.35H_2O \cdot 0.20Et_2O$: C, 64.69; H, 5.40; N, 12.72. Found: C, 64.72; H, 5.16; N, 12.65.

3(*S*)-Aminocarbonylmethyl-1,3-dihydro-5-(phenyl)-2*H*-1,4-benzodiazepin-2-one **12c**.

The methyl ester **11** (308 mg, 1.00 mmole) and 30 ml of liquid ammonia were combined at −45° in a sealed tube. The reaction mixture was warmed to room temperature. After 36 hours, the vessel was vented and excess ammonia was allowed to evaporate. The residue was crystallized from ethyl acetate to give 280 mg (95%) of the amide **12c** as a white solid, mp 245°; ^{1}H nmr (DMSO-d_6): δ 2.84 (dd, 1H, 15.6 and 6.6 Hz, -C*H*$_2$-$CONH_2$), 2.97 (dd, 1H, 15.6 and 6.6 Hz, -C*H*$_2$-$CONH_2$), 3.92 (t, 1H, 6.6 Hz, C*H*-CH_2-), 6.88 (br s, 2H, CO-NH_2), 7.21 (t, 1H, 7.5 Hz), 7.27 (d, 2H, 8.1 Hz), 7.47 (m, 6H, Ar and NH-CO), 7.60 (t, 1H, 7.5 Hz); ms: FAB 294 (M + H).

Anal. Calcd. for $C_{17}H_{15}N_3O_2 \cdot 0.5H_2O$: C, 67.53; H, 5.33; N, 13.90. Found: C, 67.55; H, 5.40; N, 13.88.

Hofmann Rearrangement of **12c**.

To a solution of bis(trifluoroacetoxy)iodobenzene (516 mg, 1.2 moles) in 20 ml of acetonitrile/water (1:1, v/v) was added 200 mg (0.68 mmole) of **12c** at room temperature. The reaction mixture was stirred for 14 hours, diluted with 20 ml of water and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with brine, dried (sodium sulfate), and concentrated to give a semi-solid. Plc (chloroform-methanol-concentrated ammonium hydroxide, 90:10:1, v/v) afforded 100 mg (48%) of **13**.

2-Imidazolidone-4-*N*-(benzoylphenyl)carboxamide **13**.

Employing reaction conditions identical to those described for the synthesis of **9**, the mixed anhydride or 2-imidazolidone-4-carboxylic acid (100 mg, 0.77 mmole) and isobutylchloroformate was prepared and used to acylate 2-aminobenzophenone (144 mg, 0.73 mmole). In this way, 150 mg (66%) of **13** was obtained as a racemate. Recrystallization from ethyl acetate afforded a white solid which melted at 159-160° and which was identical spectroscopically and chromatographically with material obtained from the Curtius rearrangement of **12b**.

3(*R,S*)-4-Nitrophenyloxycarbonylmethyl-1,3-dihydro-5-(phenyl)-2*H*-1,4-benzodiazepin-2-one **17**.

A solution of 3 ml of tetrahydrofuran containing 455 mg (1.71 mmoles) of the 3-aminomethyl-1,4-benzodiazepine **3c** was stirred magnetically in an ice bath and treated in succession with triethylamine (132 μl, 0.95 mmole) and a solution of 4-nitrophenylchloroformate (362 mg, 1.80 mmoles) in 1 ml of tetrahydrofuran. After 15 minutes, the reaction mixture was filtered and concentrated. The residue was partitioned between ethyl acetate (25 ml) and water (25 ml). The organic layer was washed with 10% citric acid solution and brine, then dried (sodium sulfate) and concentrated to give 740 mg of a yellow foam. The analytical sample was obtained as a white solid *via* silica gel chromatography (15% ethyl ether in methylene chloride) and crystallization from methylene chloride/ether, mp 192-195°; ^{1}H nmr (deuteriochloroform): δ 3.92 (t, 1H, 6 Hz), 4.11 (t, 1H, 6 Hz), 6.14 (br s, 1H, CH_2-N*H*-CO-), 7.23 (m, 3H), 7.31 (d, 2H, 9 Hz, Ar-NO_2), 7.38 (d, 1H, 7.5 Hz), 7.44 (t, 2H, 7.5 Hz), 7.57 (m, 4H), 8.21 (d, 2H, 9 Hz, Ar-NO_2); ms: FAB 431 (M + H).

Anal. Calcd. for $C_{23}H_{18}N_4O_5$: C, 64.18; H, 4.22; N, 13.02. Found: C, 63.99; H, 4.06; N, 13.01.

In situ generation of 3(*R,S*)-Isocyanatomethyl-1,3-dihydro-5-(phenyl)-2*H*-1,4-benzodiazepin-2-one.

A flame dried 25 ml 2-necked flask was charged with a solution of dry, degassed *N,N*-dimethylformamide (1 ml) containing 4-nitrophenylcarbamate **17** (53 mg, 0.123 mmole). To this solution was added, at 23°, freshly distilled triethylamine resulting in an instantaneous yellowing of the reaction mixture (4-nitrophenoxide). The reaction flask was immersed in a preheated bath at 85° and stirred for 3.5 hours affording three products. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was chromatographed (plc) on silica gel (chloroform-methanol-concentrated ammonium hydroxide, 93:7:0.7, v/v). The reaction components were isolated and characterized. The least polar product, R_f 0.23 (chloroform-methanol-concentrated ammonium hydroxide, 90:10:1, v/v) was identical with **13** spectroscopically (^{1}H nmr and ms) and chromatographically (hplc, coinjection and tlc, three solvent systems). The reaction component with an R_f value of 0.16 was identified as 4-nitrophenol by comparison with an authentic sample. The most polar reaction product, R_f 0.10 (chloroform-methanol-concentrated ammonium hydroxide, 90:10:1, v/v) was characterized as the urea **18**, obtained as an artifact of the purification method (plc solvent system).

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