The Synthesis of Ring-expanded Analogues of Xanthine Containing the Imidazo[4,5-*e*][1,4]diazepine Ring System

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The synthesis of 4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione and its several 1- and 3-alkyl (aralkyl) derivatives **2** has been reported. Mechanistic explorations of the final synthetic step as well as structural confirmation of a final product **2d** by single-crystal X-ray diffraction analyses have also been presented.

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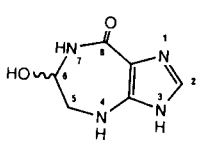
Introduction.

Ring-expanded analogues of purines have drawn considerable attention in recent years due to their potentially interesting and novel chemical, biochemical, and medicinal properties [1-5]. Chemically, they appeal in terms of synthesis and study of acid-base property, (anti/non)-aromaticity, thermodynamic (in)stability, and propensity toward opportunistic rearrangements [6-9]. Biochemically, they can be a rich source of substrates or inhibitors of enzymes of purine metabolism. The 5:7-fused nucleoside antibiotics coformycin and pentostatin, which contain the imidazo[4,5-*d*][1,3]diazepine nucleus, are the proven strongest inhibitors of adenosine deaminase ($K_i \simeq 10^{-11}$) [10]. Furthermore, because of their unique steric and conformational features, the nucleo(s/t)ides [2] derived from these heterocycles are potentially excellent probes for nucleic acid structure and function. Medicinally, ring-expanded purines can be regarded as analogues of the well-studied benzodiazepines, a family of powerful pharmaceuticals acting on the central nervous system (CNS) with a wide spectrum of activity including antianxiety, anticonvulsant, and sedative-hypnotic properties [11].

A few years ago, we communicated a general method for the synthesis of ring-expanded analogues of xanthine, guanine, and hypoxanthine, bearing the title heterocyclic ring system [1]. Since then, reports have appeared on the isolation and synthesis of a naturally occurring antitumor antibiotic, called azepinomycin (**1**), containing the same ring skeleton [12,13]. In addition, an alternative synthesis of xanthine analogues of this ring system has recently been documented [4]. The rejuvenated interest in this relatively new heterocycle, in the light of azepinomycin, has led us to scrutinize our earlier synthesis [1] of this ring system, in particular the poor-yielding final step of xanthine analogues **2**. Reported here are the results of mechanistic exploration of the mentioned synthetic step along with full experimental details of all steps leading to the final products, with procedural improvements wherever possible. The synthesis of the title parent xanthine along with its several 1- and 3-alkyl (aralkyl) derivatives, and structural confirmation of one of the final products by X-ray are presented.



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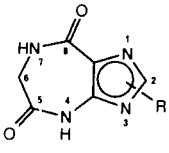

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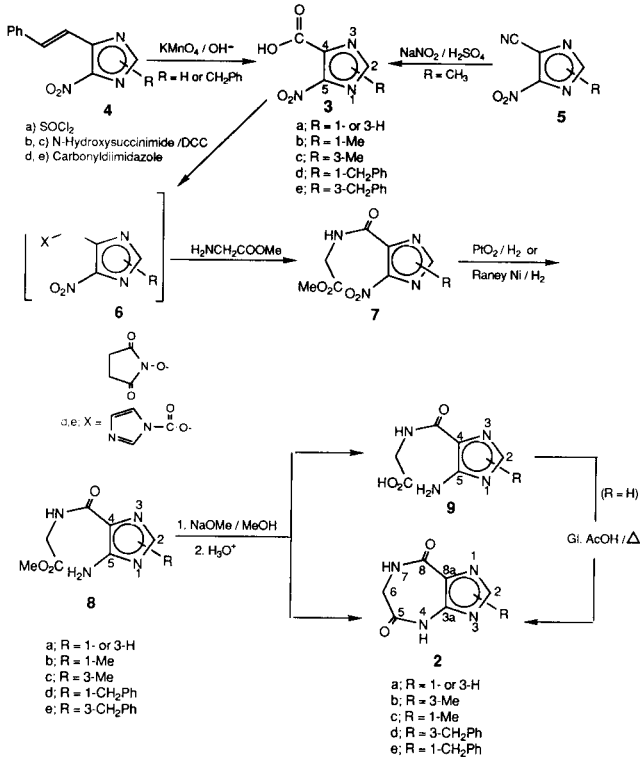
Results and Discussion.

The appropriately substituted vinylogous nitro-carboxyimidazoles **3**, the starting materials for the synthesis (Scheme I), were obtained either by oxidation of the corresponding nitrostyrylimidazoles **4** with aqueous potassium permanganate [14] or by hydrolysis of the corresponding nitro-cyanoimidazoles **5** [15] with sodium nitrite and sulfuric acid [16]. Carboxylic acids **3** were further converted either into an acid chloride **6a** by treat-

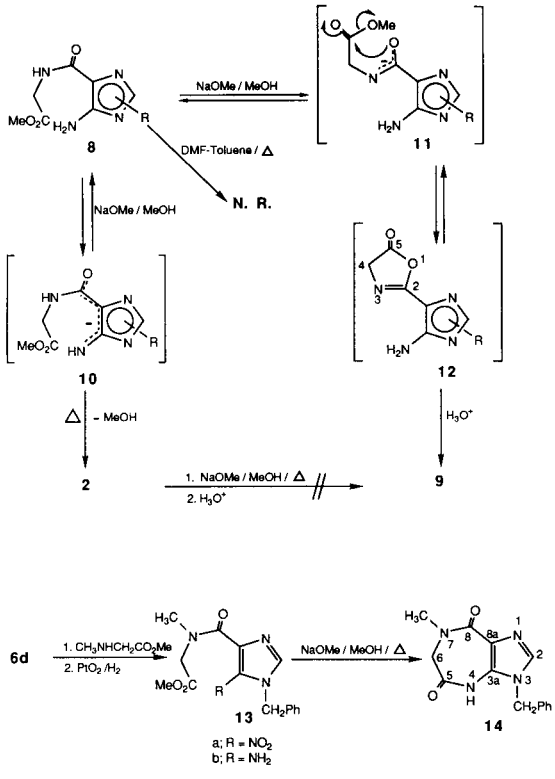
SCHEME I



ment with thionyl chloride or into *N*-hydroxysuccinimidyl or *N*-carbonylimidazolyl esters **6b-e** by condensation with *N*-hydroxysuccinimide/dicyclohexylcarbodiimide (DCC) or 1,1'-carbonyldiimidazole. Treatment of **6** with glycine methyl ester provided the corresponding amides **7** which upon catalytic hydrogenation yielded the respective amino compounds **8**. Ring closure of **8** to the desired xanthine analogues **2** was effected by treatment with sodium methoxide in methanol, followed by neutralization with acid. The above ring closure procedure, however, also provided ring-opened carboxylic acids **9**. The structure of **9a** was confirmed by its separate synthesis from **8a** by saponification. Compound **2** was the major product of the reaction of **8** with sodium methoxide. Compound **9a** could be conveniently ring-closed to form **2a** by heating in glacial acetic acid [4].

The formation of acid **9** as a side-product in the conversion **8** → **2** could not be avoided even after carefully excluding adventitious moisture from the reactants and the reaction medium. A possibility that **2** might ring open to produce **9** during the final acid work-up was ruled out by separately treating **2** with the same lot of sodium methoxide/methanol used for the initial ring closure, followed by acid neutralization, which resulted in complete recovery of the starting material. The ring-closure reaction failed to proceed in the absence of sodium methoxide/methanol; an attempted thermolysis of **8c** in a mixture of dimethylformamide-toluene showed no change

SCHEME II



even after several hours. Likewise, an attempted ring closure of **8b** in glacial acetic acid yielded mostly the unreacted starting material with only a trace of **2**. These results, along with a tentative reaction pathway for the formation of **9** and **2** from **8**, are summarized in Scheme II. Presumably, **8** is in equilibrium with anionic species **10** and **11**. While **10** ring-closes to form **2** upon heating, **11** produces the azlactone (oxazolone) **12**. The latter could ring-open to **9** during the acid work-up. The facile ring opening reactions of 2-substituted-5(4*H*)-oxazolones by a variety of nucleophiles at both C-5 (C=O) and C-2 (C=N) junctions are well documented [17-19]. While we did not attempt to isolate **12**, indirect support for the role of such an intermediate was obtained by replacing **8** with **13b** whose methyl group would block the formation of **11** (and, in turn, **12** and **9**). Indeed, when **13b**, prepared by reaction of **6d** with sarcosine methyl ester (to give **13a**), followed by reduction with platinum dioxide/hydrogen, was treated with sodium methoxide/methanol, the xanthine analogue **14** was the sole product.

Finally, the structure of **2d** was confirmed by single-crystal X-ray diffraction analyses. In view of a number of alleged seven-membered ring heterocycles whose structures were later found to be in error [20-22], structural confirmation of at least one of the final products by X-ray was especially warranted. The ORTEP view along with the employed atom numbering scheme for **2d** is shown in Figure 1. As anticipated, the 7-ring in **2d** is puckered, with the two lactam N-C(=O) bonds deviating about 33° from planarity, and the C1-N1-C2-C3 torsional angle being 82° ± 0.5.

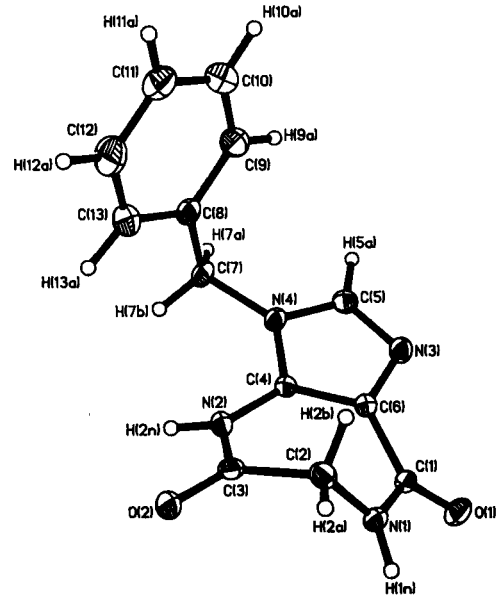


Figure 1. ORTEP view of **2d** showing the atom numbering scheme and thermal ellipsoids at the 30% probability level.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary metling point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on either an IBM NR/80 (80 MHz) or a General Electric GN-500 (500 MHz) spectrometer. The data are reported in the following format: chemical shift (all relative to TMS), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, br = broad, m = multiplet), integration, and coupling constants. ^{13}C nmr spectra were recorded on a General Electric GN-500 instrument, operating at 125 MHz. Chemical shifts are reported relative to TMS. Multiplicity, when reported, is based on off-resonance ^{1}H decoupled spectra. The 70 eV electron impact (EI) and chemical ionization (CI) mass spectra were recorded either at the School of Pharmacy, University of Maryland at Baltimore, on a Du Pont 21-490 mass spectrometer with a 21-094 data system and an Extranuclear Simulscan GC/MS instrument, or at UMBC on a Hewlett-Packard 5988A mass spectrometer. Unless stated otherwise, the reported mass spectral fragments are for the EI mode. The CI mass spectra were obtained using either methane or isobutane as the reagent gas. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording instrument. Ultraviolet (uv) spectra were recorded on either a Carey 219 UV/Vis or a Gilford Response UV/Vis spectrometer. Elemental microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. X-ray crystal structure analyses were performed at the Department of Chemistry, Southern Methodist University, Dallas, Texas, on an automatic Nicolet R_{3m}/V diffractometer at room temperature, using graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. Dry solvents were prepared as follows: methanol, ether, toluene, and xylene were distilled over sodium metal; acetonitrile was distilled from calcium hydride, followed by distillation from phosphorus pentoxide; dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled at reduced pressure from calcium hydride; tetrahydrofuran (THF) was first dried over potassium hydroxide and then distilled from lithium aluminum hydride. All Dry solvents were stored over 3 or 4Å molecular sieves.

5(4)-Nitro-1(3)*H*-imidazole-4(5)-carboxylic Acid (**3a**).

It was prepared by an improvement of the literature procedure [14]. 5(4)-Nitro-4(5)-styryl-1(3)*H*-imidazole (**4a**) [23] (22 g, 0.10 mole) was dissolved in 150 ml of 1 *N* sodium hydroxide in a 3-L flask fitted with a mechanical stirrer. Water (150 ml) was added and the flask was heated with a heat gun to 40° to make a clear solution. Crushed ice (900 g) was added slowly. The temperature inside the flask was maintained between 0-5°. A solution of potassium permanganate (60 g, 0.38 mole) in 600 ml of water was added dropwise through a dropping funnel over a period of 2 hours. The flask was sufficiently cooled to avoid any vigorous reaction. The reaction was continued for 24 hours. It was filtered, the manganese dioxide sludge was washed with a liter of boiling water, and the pale yellow filtrate was acidified with concentrated hydrochloric acid to *p*H 3. A solid (benzoic acid) started separating which was discarded. The filtrate was rotary evaporated to a volume of 50 ml. The pale yellow solid which separated was filtered *in vacuo*, washed with 25 ml of water to remove inorganic salts, and air dried. The yellow solid was triturated with ether (100 ml) to remove benzoic acid, filtered *in vacuo*, and the precipitate was washed with ether and dried over phosphorus pentoxide in a vacuum oven to obtain **3a** as an off-white, amorphous powder, yield 12.85 g (80%). It was recrystallized from boiling water as white shining flakes, mp >280° (lit [14] 303° dec); ^{1}H nmr (DMSO-d_6): δ 11.66 (br, 1H, COOH, exchangeable with deuterium oxide), 7.69 (s, 1H, imidazole CH); ir (potassium bromide): 3390, 1720, 1690 cm^{-1}; ms: (CI) m/z 158 (M^+ + 1), 157 (M^+), 113, 89; uv (methanol): λ max 294.5 nm.

1-Methyl-5-nitroimidazole-4-carboxylic Acid (**3b**).

A mixture of 4-cyano-1-methyl-5-nitroimidazole (**5b**) [15] (2.4 g, 15.7 mmoles) and 13 ml of concentrated sulfuric acid, in a dry three-neck round bottom flask fitted with a guard tube, was heated at 100° for 2 hours and then cooled in an ice-salt bath. To the light brown reaction mixture, maintained at 0°, was added dropwise and with caution, a solution of sodium nitrite (1.2 g, 17.3 mmoles) in 5 ml of water through a Pasteur pipette, taking care that the end of the pipette was under acid solution all the time. The reaction was very vigorous, giving out effervescence and brown fumes. The temperature of the reaction mixture was maintained ≤30° during the addition. When the addition was complete, the reaction mixture was heated in a steam bath for 1.5-2 hours. The reaction mixture was cooled and poured into 100 g of ice, when a light yellow crystalline solid separated out. It was kept overnight in a freezer, filtered *in vacuo*, washed with water, and dried. It was recrystallized from methanol-water as colorless needles of **3b**, yield 2.35 g (89%), mp 146-148°; ^{1}H nmr (DMSO-d_6): δ 8.51 (br, s, 1H, COOH), 7.89 (s, 1H, CH), 3.84 (s, 3H, Me); ir (potassium bromide): 3400-2700 (br, OH), 1710-1700 (C=O) cm^{-1}; ms: m/z 171 (M^+), 127, 110, 80; uv (methanol): λ max 295 nm.

Anal. Calcd. for $C_5H_5N_3O_4$: C, 35.10; H, 2.95; N, 24.56. Found: C, 35.13; H, 3.01; N, 24.49.

1-Methyl-4-nitroimidazole-5-carboxylic Acid (**3c**).

It was prepared from 5-cyano-1-methyl-4-nitroimidazole (**5c**) [15] (2.5 g, 16.4 mmoles), using the procedure described above for **3b**, colorless needles from methanol-water, yield 2.45 g (90%), mp 165° (lit [16] 163°); ^{1}H nmr (DMSO-d_6): δ 9.77 (br s, 1H, COOH, exchangeable with deuterium oxide), 7.92 (s, 1H, CH); 3.82 (s, 3H, Me); ir (potassium bromide): 3400-2700 (br, OH), 1710-1700 (C=O) cm^{-1}; ms: m/z 171 (M^+), 127, 110, 97; uv (methanol): λ max 286 nm.

1-Benzyl-5-nitroimidazole-4-carboxylic Acid (**3d**) and 1-Benzyl-4-nitroimidazole-5-carboxylic Acid (**3e**).

A finely ground mixture of 1-benzyl-5(4)-nitro-4(5)-styrylimidazoles, **4d** and **4e** (2 g, 6.5 mmoles), obtained by benzylation [24] of 5(4)-nitro-4(5)-styryl-1(3)*H*-imidazole (**4a**) with benzyl chloride/sodium carbonate/DMF, was placed in a 250-ml round bottom flask equipped with a magnetic stirrer. Ice-cold water (25 ml) was added, followed by 2 *N* sodium hydroxide (5 ml) and crushed ice (50 g). The temperature inside the flask was maintained between 0-5°. Finely powdered potassium permanganate (4 g) was added slowly over a period of 1 hour and the reaction mixture was stirred vigorously for 36 hours. The dark brown reaction mixture was filtered *in vacuo* and the solid sludge (manganese dioxide) was thoroughly washed with hot water. The light yellow filtrate was acidified with concentrated hydrochloric acid to *p*H 1, when a light yellow solid precipitated out. The solid was filtered, air dried for 24 hours, and suspended in ether (50 ml)

with stirring for a few minutes to dissolve the by-product, benzoic acid. An off-white solid which remained was filtered *in vacuo*, washed with ether, and dried over phosphorus pentoxide for 24 hours to obtain **3d**, yield 0.72 g (45%), mp 154-156° (lit [24] 155-156°); ^{1}H nmr (DMSO-d_6): δ 13.35 (br s, 1H, COOH), 8.25 (s, 1H, imidazole CH), 7.31 (m, 5H, Ph), 5.52 (s, 2H, CH_2); ir (potassium bromide): 3100-2500 (br), 1680, 1500 cm^{-1}; ms: m/z 247 (M^+), 203, 178, 141, 105, 91; uv (methanol): λ max 288, 281 nm, (pH <1) 289, 281.5, (pH >10) 309.5.

The original aqueous filtrate from the hydrochloric acid acidification was concentrated to 20 ml *in vacuo* when a white solid separated. The solid was filtered, washed with water (2 x 20 ml) to remove inorganic salts, and dried. The white solid was suspended in 50 ml of ether, the mixture was stirred, and filtered to remove benzoic acid. The buff solid was dried over phosphorus pentoxide in a vacuum oven to obtain **3e**, yield (0.7 g), 45%, mp 132-134°; ^{1}H nmr (DMSO-d_6): δ 8.19 (s, 1H, imidazole CH), 7.33 (m, 5H, Ph), 5.48 (s, 2H, CH_2): ir (potassium bromide): 3300-2500, 1710, 1535 cm^{-1}; ms: m/z 247 (M^+), 203, 141, 91; uv (methanol): λ max 288 nm, (*p*H <1) 287.5, (*p*H >10) 306.5.

5(4)-Nitro-1(3)*H*-imidazole-4(5)-carboxoyl Chloride (**6a**).

In a flame-dried three-neck round bottom flask, fitted with a guard tube, was placed **3a** (5 g, 31.8 mmoles). Thionyl chloride (20 ml, 0.27 mole) was introduced through a serum cap and the reaction mixture was heated to 50° with continuous stirring for 24 hours. The compound never went into solution but as the reaction progressed the color became dark yellow. It was rotary evaporated under anhydrous conditions, and the residue was co-evaporated with dry toluene three times, when a highly hygroscopic yellow powder of **6a** was obtained. Without further purification, it was employed for the next step.

N-Succinimidyl 1-Methyl-5-nitroimidazole-4-carboxylate (**6b**).

1-Methyl-5-nitroimidazole-4-carboxylic acid (**3b**) (1 g, 5.8 mmoles) was suspended, under anhydrous conditions (nitrogen), in freshly dried and distilled THF (30 ml) contained in a three-neck round bottom flask. The reaction mixture was warmed with continuous stirring to form a uniform solution. It was cooled to room temperature and then 1.2 g (5.8 mmoles) of dicyclohexylcarbodiimide (DCC) was added. To the resultant clear solution, *N*-hydroxysuccinimide (0.7 g, 6 mmoles) was added and the reaction mixture was stirred for 24 hours. A tlc on silica gel (chloroform-acetone, 1:1) showed the formation of a uv (254 nm) absorbing product with a higher Rf. The precipitated solid (dicyclohexylurea) was filtered *in vacuo*, washed with dry THF, and the filtrate was rotary evaporated to dryness. The residue, a gummy solid, was employed without further purification in the next step. For characterization, a small portion of the product was recrystallized from acetonitrile-hexanes to obtain **6b** as pale yellow squares, crude yield 1.06 g (68%), mp 178-181°; ^{1}H nmr (DMSO-d_6): δ 8.20 (s, 1H, CH), 3.92 (s, 3H, Me), 2.87 (s, 4H, two CH_2); ir (potassium bromide): 1770, 1740, 1700 cm^{-1}; ms: (CI) m/z 269 (M^+ + 1), 255, 225, 197, 172.

N-Succinimidyl 1-Methyl-4-nitroimidazole-5-carboxylate (**6c**).

It was prepared from 1-methyl-4-nitroimidazole-5-carboxylic acid (**3c**) (1 g, 5.8 mmoles) by the procedure described above for **6b**. The crude product was directly employed for the next step. For characterization, a small sample was recrystallized from acetonitrile-hexanes as white crystals of **6c**, crude yield 1.17 g (75%), mp 133-136°; ^{1}H nmr (DMSO-d_6): δ 8.22 (s, 1H, CH), 3.91 (s, 3H, Me), 2.89 (s, 4H, two CH_2); ir (potassium bromide): 1780, 1750 cm^{-1}; ms: m/z 268 (M^+), 183, 154, 127.

N-Carbonylimidazolyl 1-Benzyl-5-nitroimidazole-4-carboxylate (**6d**).

A mixture of **3d** (1.5 g, 6 mmoles), dry THF (30 ml), and 1,1'-carbonyldiimidazole (1.1 g, 6.7 mmoles) was heated at reflux under nitrogen for 1 hour. The light brown solution was cooled to room temperature and used as such in the next step.

N-Carbonylimidazolyl 1-Benzyl-4-nitroimidazole-5-carboxylate (**6e**).

It was prepared from **3e** (1.5 g, 6 mmoles) according to the procedure given above for **6d** and used directly for the next step.

5(4)-Nitro-4(5)-(*N*-methoxycarbonylmethyl)carbamoyl-1(3)*H*-imidazole (**7a**).

Crude compound **6a** obtained above was placed in a three-neck round bottom flask, maintained under nitrogen. Dry acetonitrile (15 ml) was added, followed by the addition of a cold methylene chloride solution of glycine methyl ester (3 g, 33 mmoles) which was freshly liberated from the corresponding hydrochloride salt in 20 ml of methylene chloride by treatment with triethylamine at 0°. The reaction mixture was stirred at room temperature for 10 hours. Some solid had separated. The mixture was evaporated to dryness on a rotary evaporator, and the residue was dissolved in boiling methanol (100 ml), treated with decolorizing charcoal, and filtered. Concentration and cooling of the filtrate afforded a solid which was recrystallized from methanol as off-white shining crystals of **7a**, yield 5.5 g (76%), mp 221-223°; ^{1}H nmr (DMSO-d_6): δ 9.21 (t, J = 4.5 Hz, 1H, NH, exchangeable with deuterium oxide), 7.88 (s, 1H, imidazole CH); 4.11 (d, J = 5.5 Hz, 2H, CH_2), 3.67 (s, 3H, Me); ir (potassium bromide): 3318, 1732, 1656, 1510, 1508 cm^{-1}; ms: m/z 228 (M^+), 197, 169, 140; uv (methanol): λ max 303 nm.

Anal. Calcd. for $C_7H_8N_4O_5$: C, 36.85; H, 3.53; N, 24.56. Found: C, 36.76; H, 3.55; N, 24.48.

4-(*N*-Methoxycarbonylmethyl)carbamoyl-1-methyl-5-nitroimidazole (**7b**).

The gummy solid **6b**, obtained above, was suspended in dry THF (15-20 ml) in a three-neck flask protected from moisture (nitrogen). A cold solution of glycine methyl ester in 25 ml of methylene chloride, which was freshly liberated from the corresponding hydrochloride salt (0.75 g, 5.9 mmoles) by treatment with triethylamine (0.61 g, 6.0 mmoles) at 0°, was introduced through a serum cap. The reaction mixture was stirred for 3 hours, evaporated to dryness, and the residue was triturated with 15 ml of water to dissolve the liberated *N*-hydroxy succinimide. After filtration and drying, the solid was repeatedly recrystallized from chloroform-petroleum ether (60-80°) to obtain pure **7b**, yield 1.19 g (85%), mp 124-127°; ^{1}H nmr (DMSO-d_6): δ 8.8 (t, J = 5.6 Hz, 1H, NH, exchangeable with deuterium oxide), 8.01 (s, 1H, CH), 4.0 (d, J = 5.6 Hz, 2H, CH_2), 3.86 (s, 3H, N-Me), 3.65 (s, 3H, O-Me); ir (potassium bromide): 3320, 1740, 1680 cm^{-1}; ms: m/z 242 (M^+), 211, 183, 154; uv (methanol): λ max 296 nm.

Anal. Calcd. for $C_8H_{10}N_4O_5$: C, 39.67; H, 4.16; N, 23.13. Found: C, 39.73; H, 4.17; N, 23.09.

5-(*N*-Methoxycarbonylmethyl)carbamoyl-1-methyl-4-nitroimidazole (**7c**).

It was prepared from **6c** (1.0 g, 3.7 mmoles) by an analogous procedure described above for **7b** except for the following changes: The reaction mixture was stirred overnight, evaporated to dryness, and the residue was purified by flash chromatography on silica gel (40-63 μm), using chloroform-acetone (4:1) as the eluting solvent system. It was recrystallized from chloroform as white needles of **7c**, yield 0.64 g (71%), mp 132-134°; ^{1}H nmr (DMSO-d_6): δ 7.80 (s, 1H, CH), 4.03 (d, J = 5.6 Hz, 2H, CH_2), 3.7 (s, 3H, N-Me), 3.69 (s, 3H, O-Me); ir (potassium bromide): 3300, 1740, 1640 cm^{-1}; ms: m/z 242 (M^+), 224, 183, 154, 143; uv (methanol): λ max 292.5 nm.

Anal. Calcd. for $C_8H_{10}N_4O_5$: C, 39.67; H, 4.16; N, 23.13. Found: C, 39.74; H, 4.20; N, 23.09.

1-Benzyl-4-(*N*-methoxycarbonylmethyl)carbamoyl-5-nitroimidazole (**7d**).

A methylene chloride solution (10 ml) of glycine methyl ester, freshly liberated from the corresponding hydrochloride salt (0.85 g, 6.7 mmoles) by treatment with triethylamine (0.95 ml, 6.8 mmoles) in methylene chloride at 0° and filtration, was introduced through a serum cap to the THF solution of **6d**, prepared as described above, contained in a 100 ml three-neck flask, protected from moisture (nitrogen). The reaction mixture was stirred at ambient temperature for 30 minutes, rotary evaporated to dryness, and triturated with 75 ml of water. The white solid separated was filtered *in vacuo*, washed with water, and dried. Recrystallization from methanol afforded white crystals of **7d**, yield 1.85 g (96%), mp 148-149°; ^{1}H nmr (DMSO-d_6): δ 8.88 (t, 1H, J = 5.8 Hz, NH, exchangeable with deuterium oxide), 8.26 (s, 1H, imidazole CH), 7.26 (m, 5H, Ph), 5.53 (s, 2H, CH_2), 4.00 (d, 2H, J = 5.8 Hz, CH_2), 3.65 (s, 3H, Me); ir (potassium bromide): 3370, 1740, 1670, 1520, 1475 cm^{-1}; ms: m/z 318 (M^+), 287, 259, 212, 128, 91; uv (methanol): λ max 293.5, 213 nm, (*p*H < 1) 294, (*p*H > 10) 295.5.

Anal. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.42; N, 17.60. Found: C, 52.91; H, 4.47; N, 17.54.

1-Benzyl-5-(*N*-methoxycarbonylmethyl)carbamoyl-4-nitroimidazole (**7e**).

It was prepared from **6e** according to the procedure given above for **7d**, recrystallized from water-methanol as white needles, yield 1.75 g (91%), mp 115-117°; ^{1}H nmr (DMSO-d_6): δ 9.5 (t, 1H, J = 5.5 Hz, NH, exchangeable with deuterium oxide), 8.05 (s, 1H, imidazole CH), 7.36-7.30 (m, 5H, Ph), 5.31 (s, 2H, benzyl CH_2), 4.08 (d, 2H, J = 5.5 Hz, side-chain CH_2), 3.64 (s, 3H, Me); ir (potassium bromide): 3300, 1760, 1640, 1210 cm^{-1}; ms (CI): m/z 319 (M^+ + 1), 289, 218, 188, 92; uv (methanol): λ max 291 nm, (*p*H < 1) 293, (*p*H > 10) 296.5.

Anal. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.42; N, 17.60. Found: C, 52.75; H, 4.47; N, 17.53.

5(4)-Amino-4(5)-(*N*-methoxycarbonylmethyl)carbamoyl-1(3)*H*-imidazole (**8a**).

Compound **7a** (1 g, 4.3 mmoles) was dissolved in absolute methanol (150 ml), and transferred to a 500-ml hydrogenation bottle. About 0.1 g of platinum dioxide monohydrate was added, and the bottle shaken in a Parr hydrogenation apparatus at 40 psi for 30 minutes. The reaction mixture was filtered through a pad of Celite. The filtrate was evaporated to dryness and the residue was purified by flash chromatography on silica gel (40-63 μm), using 8:1 chloroform-methanol as the eluting solvent system. The pure solid obtained was recrystallized from methanol-ether as a white amorphous powder of **8a**, yield 0.24 g (28%), mp 162-164°; ^{1}H nmr (DMSO-d_6): δ 7.62 (t, J = 6.0 Hz, 1H, NH, exchangeable with deuterium oxide), 7.04 (s, 1H, imidazole CH), 5.5 (br s, 2H, NH_2, exchangeable with deuterium oxide), 3.93 (d, J = 6.0 Hz, 2H, CH_2), 3.63 (s, 3H, Me); ir (potassium bromide): 3370, 3340, 3258, 1714, 1624, 1532 cm^{-1}; ms: m/z 198 (M^+), 166, 139, 110, 82; uv (methanol): λ max 268.5 nm.

Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.38; H, 5.10; N, 28.23.

5-Amino-4-(*N*-methoxycarbonylmethyl)carbamoyl-1-methylimidazole (**8b**).

Raney Ni (300 mg) was twice washed successively with water and methanol and transferred to a hydrogenation bottle containing a solution of **7b** (300 mg, 1.23 mmoles) in absolute methanol (15 ml). The reaction mixture was hydrogenated in a Parr hydrogenation apparatus at 43 psi for 3 hours. The reaction mixture was filtered to remove Raney Ni, and the filtrate was evaporated to dryness to obtain a solid residue. It was recrystallized from methanol-hexanes as white needles of **8b**, yield 0.2 g (77%), mp 113-115°; ^{1}H nmr (DMSO-d_6): δ 7.64 (t, J = 5.6 Hz, 1H, NH, exchangeable with deuterium oxide), 7.10 (s, 1H, CH), 5.72 (br s, 2H, NH_2, exchangeable with deuterium oxide), 3.91 (d, J = 5.6 Hz, 2H, CH_2), 3.62 (s, 3H, Me), 3.39 (s, 3H, Me); ir (potassium bromide): 3300, 3120, 1740 cm^{-1}; ms: m/z 212 (M^+), 143, 124, 98; uv (methanol): λ max 267.5 nm, (water) 268 (ε 13.3 x 10^3, (*p*H 12.9) 266 (13.0 x 10^3), (*p*H 0.6) 270.5 (10.5 x 10^3), 240.0 (8 x 10^3).

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.34; H, 5.72; N, 26.38.

4-Amino-5-(*N*-methoxycarbonylmethyl)carbamoyl-1-methylimidazole (**8c**).

It was prepared from **7c** (0.3 g, 1.23 mmoles) using the procedure described above for **8b**. The solid residue obtained after evaporation of methanol was recrystallized from methanol-hexane as white needles of **8c**, yield 0.2 g (76%), mp 128-130°; ^{1}H nmr (DMSO-d_6): δ 7.45 (t, J = 5.6 Hz, 1H, NH, exchangeable with deuterium oxide), 7.34 (s, 1H, CH), 5.14 (br s, 2H, NH_2, exchangeable with deuterium oxide), 3.94 (d, J = 5.6 Hz, 2H, CH_2), 3.64 (s, 6H, O-Me + N-Me); ir (potassium bromide): 3370, 3360, 1740, 1630 cm^{-1}; ms: m/z 212 (M^+), 143, 124, 98; uv (methanol): λ max 274 nm, (water) 273.5 (ε 13.2 x 10^3), (*p*H 13) 271.5 (13 x 10^3), (*p*H 0.65) 269 (13.0 x 10^3).

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.13; H, 5.73; N, 26.31.

5-Amino-1-benzyl-4-(*N*-methoxycarbonylmethyl)carbamoylimidazole (**8d**).

It was prepared from **7d** (1 g, 3.14 mmoles) by the procedure given above for **8a** and recrystallized from chloroform-ligroin as pale yellow crystals, yield 0.63 g (70%), mp 85-88°; ^{1}H nmr (DMSO-d_6): δ 7.60 (t, J = 5.6 Hz, 1H, NH, exchangeable with deuterium oxide), 7.25 (m, 6H, imidazole CH + Ph), 5.8 (br s, 2H, NH_2, exchangeable with deuterium oxide), 5.08 (s, 2H, CH_2 of benzyl), 3.92 (d, J = 5.6 Hz, 2H, CH_2 attached to NH), 3.62 (s, 3H, Me); ir (potassium bromide): 3400, 1740, 1630, 1500 cm^{-1}; ms: m/z 288 (M^+), 256, 229, 200, 110, 91; uv (methanol): λ max 267.5 nm, (*p*H < 1) 269.5, (*p*H > 10) 267.5.

Anal. Calcd. for $C_{14}H_{16}N_4O_3 \cdot \frac{3}{4}H_2O$: C, 55.67; H, 5.83; N, 18.55. Found: C, 55.40; H, 5.87; N, 18.22.

4-Amino-1-benzyl-5-(*N*-methoxycarbonylmethyl)carbamoylimidazole (**8e**).

It was prepared from **7e** (1 g, 3.14 mmoles) according to the procedure described above for **8a**. It was recrystallized from chloroform-ligroin as shining white flakes, yield 0.82 g (90%), mp 148-150°; ^{1}H nmr (DMSO-d_6): δ 7.58 (s, 1H, imidazole CH), 7.56 (t, J = 5.5 Hz, 1H, NH, exchangeable with deuterium oxide), 7.22 (m, 5H, Ph), 5.36 (s, 2H, benzyl CH_2), 5.14 (s, 2H, NH_2, exchangeable with deuterium oxide), 3.9 (d, J = 5.5 Hz, 2H, side-chain CH_2), 3.60 (s, 3H, Me); ir (potassium bromide): 3400, 3340, 1745, 1610 cm^{-1}; ms: m/z 288 (M^+), 256, 200, 171, 110, 91; uv (methanol): λ max 273.5 nm, (*p*H < 1) 270.5, 245 sh, (*p*H > 10) 272.5.

Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.33; H, 5.58; N, 19.43. Found: C, 58.44; H, 5.63; N, 19.54.

5(4)-Amino-4(5)-(*N*-carboxymethyl)carbamoyl-1(3)*H*-imidazole (**9a**).

Method A. By Saponification of **8a**.

A mixture of **8a** (100 mg, 0.5 mmole) and 1*N* sodium hydroxide (5 ml) was stirred at room temperature for ½ hour. The reaction mixture was acidified to pH 6.5 with 1 *N* hydrochloric acid, and evaporated to dryness on a rotary evaporator. Trituration of the residue with a small amount of methanol-water (1:1) resulted in separation of a white solid. The solid was recrystallized from methanol-water into white crystals of **9a**, yield 74 mg (80%), mp 220° dec; ^{1}H nmr (DMSO-d_6): δ 7.64 (t, J = 5.5 Hz, 1H, NH, exchangeable with deuterium oxide), 7.11 (s, 1H, imidazole CH), 5.52 (br s, 2H, NH_2, exchangeable with deuterium oxide); 3.85 (d, J = 5.5 Hz, 2H, CH_2); ir (potassium bromide): 3600-3200 (br), 1650, 1632 cm^{-1}; ms: m/z 184 (M^+), 166, 137, 110, 82; uv (methanol): λ max 266.5 nm, (*p*H = 5.4) 267.0 (ε 4.9 x 10^3), (*p*H = 12.8) 275.5 (7.3 x 10^3), (*p*H = 0.5) 266.5 (5.6 x 10^3).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.47; N, 30.42. Found: C, 39.14; H, 4.37; N, 30.32.

Method B. Ring Closure of **8a**.

Compound **9a** was also isolated in 29% yield as a side product in the reaction, **8a** → **2a**, using sodium methoxide/methanol. The procedure for isolation is analogous to the one described (*vide infra*) for **2b** from **8b**.

General Procedure for the Preparation of **9** and **2**.

Dry methanol (25 ml), freshly distilled over sodium, was introduced in a three-neck flask, maintained under nitrogen. Freshly cut Na metal (110 mg, 4.8 mg-atoms) was added with stirring to form a clear solution. Compound **8** (4.7-4.8 mmoles) was added in portions and the reaction mixture was heated to reflux for 24 hours. It was cooled, neutralized with 1 *N* hydrochloric acid or glacial acetic acid, and evaporated to dryness. The residue was purified by flash chromatography on silica gel (40-63 μm), employing (a) chloroform-methanol (4:1) to collect the faster eluting **2**, followed by (b) chloroform-methanol (1:1) to obtain the slower eluting **9**. Recrystallization solvents, percentage yields, melting points, and spectral and analytical data for the compounds **9** and **2**, obtained by this method, are listed below:

5-Amino-4-(*N*-carboxymethyl)carbamoyl-1-methylimidazole (**9b**).

It was recrystallized from methanol as a white powder, yield 0.2 g (21%), mp >255° dec; ^{1}H nmr (DMSO-d_6): δ 7.15 (t, 1H, NH, exchangeable with deuterium oxide), 7.03 (s, 1H, imidazole CH), 5.64 (br s, 2H, NH_2, exchangeable with deuterium oxide), 3.40 (d + s, 5H, CH_2 and Me); ir (potassium bromide): 3400-3000 (br), 1715, 1650, 1512 cm^{-1}; ms: m/z 198 (M^+), 180, 151, 124, 96; uv (water): λ max 268 nm, (*p*H 12.6) 266, (*p*H 1.5) 268.5.

4-Amino-5-(*N*-carboxymethyl)carbamoyl-1-methylimidazole (**9c**).

It was recrystallized from methanol-ether as off-white crystals, yield 0.2 g (21%), mp >300°; ^{1}H nmr (DMSO-d_6): δ 7.31 (s, 1H, imidazole CH), 7.42 (t, J = 5.8 Hz, 1H, NH, exchangeable with deuterium oxide), 3.85 (d, J = 5.8 Hz, 2H, CH_2), 3.67 (s, 3H, Me); ir (potassium bromide): 3420-3100, 1650, 1400 cm^{-1}; ms: m/z 198 (M^+), 180, 151, 124, 96; uv (water): λ max 270.5 nm, (*p*H < 1) 266, 244.5, (*p*H 13) 271.5.

5-Amino-1-benzyl-4-(*N*-carboxymethyl)carbamoylimidazole (**9d**).

Recrystallized from methanol-water as buff crystals, yield 0.36 g (27%), mp 193-195°; ^{1}H nmr (DMSO-d_6): δ 7.24 (m, 7H, Ph + imidazole CH + NH), 5.80 (br s, 3H, NH_3^+, exchangeable with deuterium oxide), 5.10 (s, 2H, CH_2 of benzyl), 3.67 (d, 2H, CH_2); ir (potassium bromide): 3420-3340, 1720, 1630, 1560 cm^{-1}; ms: m/z 256 (M^+ - 18), 178, 155, 149; uv (methanol): λ max 264.5 nm, (*p*H < 1) 264.5, 239.5 (*p*H > 10) 263.5.

Anal. Calcd. for $C_{13}H_{14}N_4O_3 \cdot \frac{1}{4}H_2O$: C, 55.96; H, 5.20; N, 20.09. Found: C, 55.76; H, 5.20; N, 19.82.

4-Amino-1-benzyl-5-(*N*-carboxymethyl)carbamoylimidazole (**9e**).

It was recrystallized from methanol-water as white crystals, yield 0.16 g (12%), mp 283-285° (lit [4] 284-286°); ^{1}H nmr (DMSO-d_6): δ 7.59 (s, 1H, imidazole CH), 7.51 (t, J = 5.7 Hz, 1H, NH, exchangeable with deuterium oxide), 7.23 (m, 5H, Ph), 5.38 (s, 2H, benzyl CH_2), 3.83 (d, J = 5.7 Hz, 2H, side-chain CH_2); ir (potassium bromide): 3360-3140 (br), 1650, 1630, 1560; ms: m/z 274 (M^+), 256, 227, 200, 171, 106, 91; uv (methanol): λ max 267.5 nm, (*p*H 12.6) 272.5, (*p*H 0.1) 268.

4,5,7,8-Tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2a**).

Method A. Ring-closure of **9a** with Glacial Acetic Acid.

Compound **9a** (300 mg, 1.63 mmoles) was dissolved in glacial acetic acid (6 ml) and the solution was heated to reflux under nitrogen for 3 hours. A tlc (silica gel, 1:1 chloroform-methanol) indicated the formation of a new uv-absorbing compound which had a higher Rf than the s.m. The solvent was evaporated to dryness and traces of the solvent were removed by azeotroping with toluene. The solid residue was recrystallized from water with treatment of decolorizing charcoal into shining needles of **2a**, yield 184 mg (68%), mp >300° (lit [4] >340°); the spectral data of the compound were identical with those of **2a** obtained by method B below.

Method B. Ring Closure of **8a** (0.95 g, 4.8 mmoles) with Sodium Methoxide/Methanol Using the General Procedure.

It was recrystallized from water as shiny needles, yield 0.54 g (68%), mp >300°; ^{1}H nmr (DMSO-d_6): δ 12.87 (s, 1H, NH, exchangeable with deuterium oxide), 10.72 (s, 1H, NH, exchangeable with deuterium oxide), 7.80 (t, J = 5.0 Hz, 1H, NH, exchangeable with deuterium oxide), 7.70 (s, 1H, imidazole CH), 3.67 (d, J = 5.2 Hz, 2H, CH_2); ^{13}C nmr (DMSO-d_6): δ 168.23 (s, C=O), 162.33 (s, C=O), 141.63 (s, C-3a), 137.13 (d, imidazole C-2), 111.37 (s, C-8a), 46.3 (t, CH_2); ir (potassium bromide): 3412, 1672, 1650 cm^{-1}; ms: m/z 166 (M^+), 137, 110, 82; uv (water): λ max 268.5 nm (ε = 7.2 x 10^3), (*p*H 12.8) 293 (7.6 x 10^3).

Anal. Calcd. for $C_6H_6N_4O_2 \cdot \frac{1}{4}H_2O$: C, 42.20; H, 3.80; N, 32.81. Found: C, 42.50; H, 3.88; N, 32.95.

3-Methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2b**).

It was prepared from **8b** (1 g, 4.7 mmoles) using the General Procedure; recrystallized from methanol-petroleum ether (40-60°), yield 0.53 g (62%), mp 292-295° dec; ^{1}H nmr (DMSO-d_6): δ 7.96 (t, J = 4.8 Hz, 1H, NH, exchangeable with deuterium oxide), 7.63 (s, 1H, CH), 3.68 (d, J = 4.8 Hz, 2H, CH_2), 3.60 (s, 3H, Me); ^{13}C nmr (DMSO-d_6): δ 169.21 (s, C=O), 164.67 (s, C=O), 135.99 (d, imidazole C-2), 133.11 (s, C-3a), 121.83 (s, C-8a), 45.80 (t, CH_2), 30.75 (q, CH_3); ir (potassium bromide): 3258, 2960, 1725, 1650 cm^{-1}; ms: m/z 180 (M^+), 150, 140, 123; uv (water): λ max 266 (7.4 x 10^3), (*p*H 13) 294.5 (8 x 10^3), 247 (8.8 x 10^3).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.67; H, 4.47; N, 31.12. Found: C, 46.61; H, 4.48; N, 31.04.

1-Methyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2c**).

It was prepared from **8c** (1 g, 4.7 mmoles) using the general procedure; recrystallized from methanol-hexanes, yield 0.32 g (38%), mp >300°; ^{1}H nmr (DMSO-d_6): δ 10.69 (br s, 1H, NH, exchangeable with deuterium oxide), 7.94 (t, J = 4.8 Hz, 1H, NH, exchangeable with deuterium oxide), 7.72 (s, 1H, CH), 3.77 (s, 3H, Me), 3.63 (d, J = 4.8 Hz, 2H, CH_2); ^{13}C nmr (DMSO-d_6): δ 168.59 (s, C=O), 162.15 (s, C=O), 142.76 (s, C-3a), 140.37 (d, imidazole C-2), 111.60 (s, C-8a), 45.92 (t, CH_2), 33.55 (q, CH_3); ir (potassium bromide): 3170, 1702, 1660 cm^{-1}; ms: m/z 180 (M^+), 151, 124; uv (water): λ max 267 nm (ε 7.4 x 10^3), (*p*H 12.9) 291 (7 x 10^3), (*p*H 0.6) 255 (12.6 x 10^3).

Anal. Calcd. for $C_7H_8N_4O_2 \cdot \frac{1}{4}H_2O$: C, 45.49; H, 4.60; N, 30.33. Found: C, 45.87; H, 4.46; N, 30.29.

3-Benzyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2d**).

It was prepared from **8d** (1.4 g, 4.8 mmoles) using the general procedure; recrystallized from ethanol as transparent flakes, yield 0.77 g (62%), mp >265° gradual dec; ^{1}H nmr (DMSO-d_6): δ 7.90 (t, 1H, NH, exchangeable with deuterium oxide), 7.67 (s, 1H, imidazole CH), 7.36-7.20 (m, 5H, Ph), 5.28 (s, 2H, CH_2 of benzyl), 3.58 (d, J = 5.0 Hz, 2H, CH_2); ir (potassium bromide): 3250, 1695, 1635, 1435 cm^{-1}; ms: m/z 256 (M^+), 228, 200, 170, 91; uv (methanol): λ max 261, 232 nm, (*p*H >10) 295.5, 251.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.71; N, 21.86. Found: C, 60.82; H, 4.75; N, 21.78.

1-Benzyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**2e**).

It was prepared from **8e** (1.4 g, 4.8 mmoles) using the general procedure; recrystallized from water-methanol as shiny white flakes, yield 0.85 g (68%), mp 284° (lit [4] 288-289°); ^{1}H nmr (DMSO-d_6): δ 10.76 (s, 1H, NH, exchangeable with deuterium oxide), 7.96 (t, J = 5.0 Hz, 1H, NH, exchangeable with deuterium oxide), 7.94 (s, 1H, imidazole CH), 7.2 (m, 5H, Ph), 5.48 (s, 2H, CH_2 of benzyl), 3.55 (d, J = 5.0 Hz, 2H, ring CH_2); ir (potassium bromide): 3270, 1710, 1655, 1400 cm^{-1}; ms: m/z 256 (M^+), 200, 171, 117, 91; uv (water): λ max 275 nm, (*p*H <1) 268.5, 245.5 sh, (*p*H >10) 294.5.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.71; N, 21.86. Found: C, 60.84; H, 4.73; N, 21.81.

1-Benzyl-4-(*N*-methoxycarbonylmethyl-*N*-methyl)carbamoyl-5-nitroimidazole (**13a**).

It was prepared according to the procedure described above for the preparation of **7d** from **6d**, substituting glycine methyl ester with sarcosine methyl ester. The crude product was purified by flash chromatography on silica gel (40-63 μm), using chloroform as the eluting solvent. The viscous material collected was triturated with ether-ligroin and refrigerated for 2 hours when an amorphous white solid separated. The solid was recrystallized from methanol-water into white crystals of **13a** as a mixture of *cis* and *trans* isomers, yield 1.43 g (71%), mp 90-92°; ^{1}H nmr (DMSO-d_6): δ 8.36, 8.28 (s, 1H, CH of imidazole), 7.34 (m, 5H, Ph), 5.61, 5.57 (s, 2H, CH_2 of benzyl), 4.29, 4.14 (s, 2H, CH_2 of side-chain), 3.69, 3.59 (s, 3H, O-Me), 3.05, 2.91 (s, 3H, N-Me); ir (potassium bromide): 3300, 3080, 1750, 1650, 1510 cm^{-1}; ms (CI): m/z 333 (M^+ + 1), 303, 211, 91; uv (methanol): λ max 299.5 nm (*p*H <1) 298.5, (*p*H >10) 300.5.

Anal. Calcd. for $C_{15}H_{16}N_4O_5$: C, 54.21; H, 4.85; N, 16.86. Found: C, 54.28; H, 4.88; N, 16.79.

5-Amino-1-benzyl-4-(*N*-methoxycarbonylmethyl-*N*-methyl)carbamoylimidazole (**13b**).

It was prepared from **13a** (1 g, 3 mmoles) by the procedure given above for **8a** from **7a**. It was recrystallized from chloroform-ether as off-white crystals, yield 0.55 g (60%), mp 125°; ^{1}H nmr (DMSO-d_6): δ 7.34-7.11 (m, 6H, imidazole CH + Ph), 6.15 (br s, 2H, NH_2, exchangeable with deuterium oxide), 5.0 (s, 2H, CH_2 of benzyl), 4.60 (s, 2H, CH_2), 3.58 (s, 3H, O-Me), 3.10 (s, 3H, N-Me); ir (potassium bromide): 3380, 3280, 1743, 1610, 1400 cm^{-1}; ms: m/z 302 (M^+), 243, 200, 173, 91; uv (methanol): λ max 274.5 nm, (*p*H <1) 271.5, 252, (*p*H >10) 292, 251.

Anal. Calcd. for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.67; H, 6.01; N, 18.60.

3-Benzyl-4,5,7,8-tetrahydro-6-methylimidazo[4,5-*e*][1,4]diazepine-5,8-dione (**14**).

It was prepared from **13b** (1 g, 3.3 moles) according to the general procedure described above for the preparation of **2** from **8** using sodium methoxide/methanol. It was recrystallized from methanol-acetonitrile as colorless crystals, yield 0.85 g (96%), mp 274-276°; ^{1}H nmr (DMSO-d_6): δ 10.93 (br s, 1H, NH, exchangeable with deuterium oxide), 7.65 (s, 1H, imidazole CH), 7.24 (m, 5H, Ph), 5.25 (s, 2H, CH_2 of benzyl), 3.80 (s, 2H, ring CH_2), 3.01 (s, 3H, Me); ir (potassium bromide): 3120, 1700, 1620, 1400 cm^{-1}; ms: m/z 270 (M^+), 241, 199, 118, 91; uv (methanol): λ max 257.5, (*p*H >10) 292.5, 250.5.

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.72. Found: C, 62.30; H, 5.24; N, 20.83.

Single Crystal X-ray Diffraction Analyses of **2d**.

Suitable crystals were grown through slow crystallization from ethanol. The unit cell dimensions were obtained by a least-squares fit of 25 centered reflections in the range of 10° <2θ <25°. Intensity data were collected by using a θ/2θ scan type in the range of 3° <2θ <45°. Three standard reflections monitored after every 100 reflections did not show any significant change in intensity during data collections. Intensities were corrected for decay and Lorentz polarization effects but not for absorption. The structure was solved and all non-hydrogen atoms were found by using results of SHELXTL-PLUS [25]. After several cycles of refinements using SHELXTL-PLUS/SHELX76

[25,26] the positions of hydrogen atoms were located on difference Fourier maps, and included in the final refinement with isotropic thermal parameters, and with geometrical constraints for CH_2 and CH protons. Refinement proceeded to converge by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where the weight, w, is $\sigma(F)^{-2}$. The discrepancy indices $R = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$ are presented below.

Crystallographic data of **2d** is $C_{13}H_{12}N_4O_2$, $M_r = 256.26$, space group $P2_12_12_1$, orthorhombic, $a = 6.051$ (5) Å, $b = 12.948$ (14) Å, $c = 15.115$ (12) Å, $V = 1184$ (2) Å^3, $Z = 4$, $D_x = 1.44$ g cm^{-3}, (Mo Kα) = 0.71073 Å, $\mu = 0.095$ mm^{-1}; Final $R = 3.57\%$, $R_w = 4.13\%$ for 1782 unique reflections with $I \geq 3\sigma(I) = 1327$.

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