Reactions of Ring-Expanded Xanthines Containing the Imidazo[4,5-*e*][1,4]diazepine Ring System

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Dedicated to the memory of Professor Roland K. Robins

4,5,7,8-Tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione underwent bromination at the 2-position with or without substituents at the 3-, 4- or 7-position, using bromine, *N*-bromosuccinimide, or acetyl hypobromite. The activation of position 6 with an ester functionality, as in **7**, did not alter the site of bromination. The base-catalyzed bromination of the ring-open precursor, diethyl 2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**5**), resulted either in introduction of an alkoxy functionality in the above aminomalonate side-chain, yielding **17** when the reaction was quenched with an alcohol, or in degradation of the side-chain, yielding 1-benzyl-5-nitroimidazole-4-carboxamide (**19**) when the reaction was quenched with water. Both **17** and **19** are formed by oxidative bromination of **5** *via* the bromo intermediate **15**. An indirect evidence for the latter was obtained by base-catalyzed methylation of **5** which gave diethyl 2-methyl-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**21**). The base-catalyzed bromination of **5** with *N*-bromosuccinimide gave rise to two products, the dimer **24a** and the monomer **24b** that contained the substituted 2,2-diaminomalonate side-chain. The structure of **24b** was confirmed by single-crystal X-ray diffraction analyses. Reduction of the 5-nitro group of **17** to the corresponding amino derivative **25**, followed by ring-closure with sodium methoxide/methanol, yielded three products, a 5:6-fused system **26** and two 5:7 fused systems **27** and **28**. The structures of **26** and **27** were confirmed by single-crystal X-ray diffraction analyses. A tentative reaction pathway for the formation of all three products has been proposed. Hydrolysis of **27** with aqueous hydrochloric acid resulted in ring-opening to form 5-amino-1-benzylimidazole-4-carboxamide (**40**). A mechanism for the hydrolysis reaction has been proposed. Catalytic hydrogenation of **5** in acetic acid yielded the aminoimidazolone derivative **11** which upon ring-closure with sodium methoxide in methanol produced imidazo[4,5-*e*][1,4]-diazepine-2,5,8-trione (**12**).

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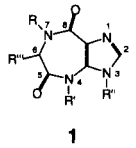
We have outlined a broad and long-term project involving synthesis, chemistry, biochemistry, and biophysical chemistry of ring-expanded ("fat") nucleic acid bases, nucleosides, and nucleotides [1-9]. As part of this project, we now report our studies on reactions of several ring-expanded xanthine analogues containing the title imidazo-[4,5-*e*][1,4]diazepine ring system (**1**).

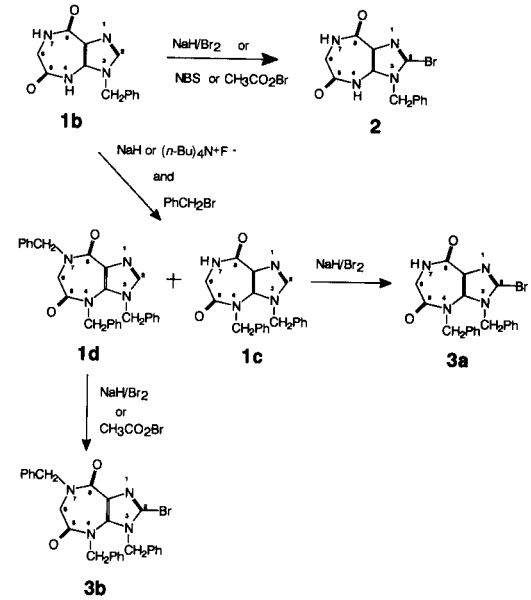


a; R = R' = R'' = R''' = H
b; R = R' = R''' = H; R'' = CH_2Ph
c; R = R''' = H; R' = R'' = CH_2Ph
d; R''' = H; R = R' = R'' = CH_2Ph

1

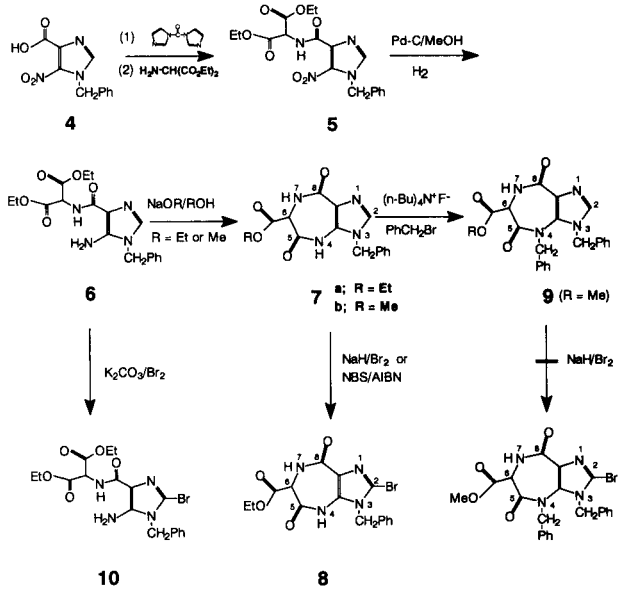
When **1b** was subjected to bromination using bromine in the presence of either sodium hydride or *n*-butyllithium, the sole product obtained was the 2-bromo derivative **2** (Scheme I). The same product was formed when *N*-bromosuccinimide or acetyl hypobromite was employed as a brominating reagent. No further bromination occurred when **1b** was treated with an excess of the brominating reagent, or when the isolated product **2** was subjected to further bromination. Apparently, the 2-position, which is conjugated with N-4 *via* resonance, is activated toward electrophilic substitution. The protection of N-4 with a benzyl group did not alter the scenario as the dibenzyl derivative **1c** or the tribenzyl derivative **1d**, obtained by benzylation of **1b**, also gave the corresponding 2-bromo derivatives **3a** or **3b**, respectively.

Scheme I



In order to enhance the chances of the 6-methylene group of **1** to effectively compete with position 2 for the site of bromination, compound **7** was synthesized. The synthesis of **7** (Scheme II) commenced with condensation of 1-benzyl-5-nitro-4-carboxylic acid (**4**) with diethyl aminomalonate, mediated by carbonyldiimidazole (CDI), which

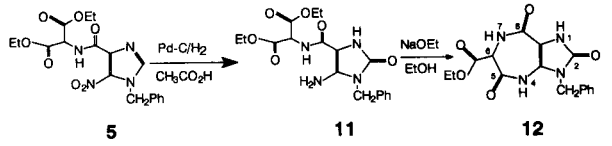
Scheme II



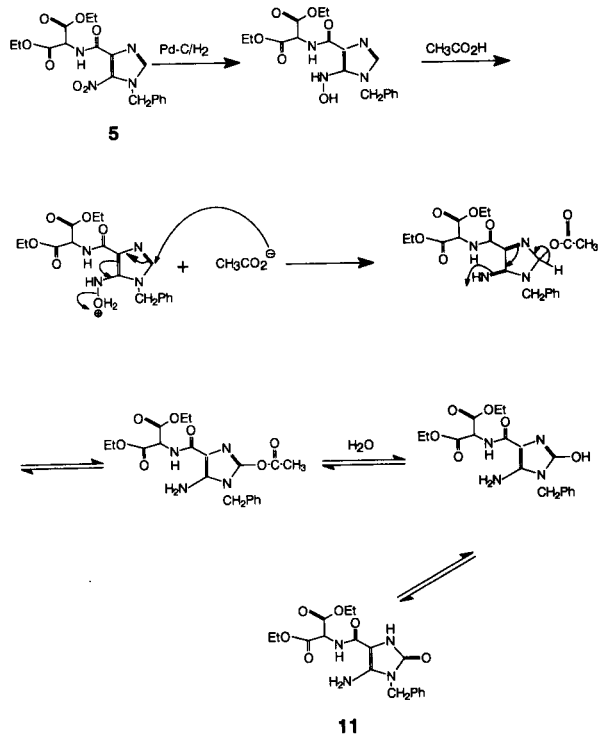
gave **5**. The latter upon catalytic hydrogenation with palladium on charcoal produced the corresponding amino compound **6**. The ring-closure of **6** with sodium alkoxide in alcohol yielded the desired **7a** or **7b**. Bromination of **7a** either with *N*-bromosuccinimide catalyzed by azobisisobutyronitrile (AIBN), or with bromine in the presence of sodium hydride, gave the corresponding 2-bromo derivative **8**. Benzylation of **7b** with benzyl bromide/tetra-*n*-butylammonium fluoride gave the dibenzyl derivative **9**. However, bromination of **9** with bromine/sodium hydride gave only an intractable material. As anticipated, bromination of **6** with bromine/potassium carbonate also gave the respective 2-bromo derivative **10**.

An attempted reduction of **5** with palladium/charcoal, using acetic acid instead of methanol as a solvent, gave the imidazolone **11** instead of **6** (Scheme III). A tentative mechanism for the formation of **11** from **5** is outlined in Scheme IV. The ring-closure of **11** with sodium ethoxide/ethanol produced **12** that contained the imidazo[4,5-*e*][1,4]diazepine-2,5,8-trione ring system.

Scheme III

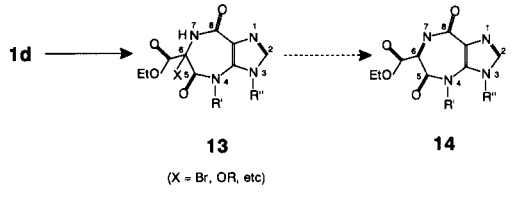


Scheme IV



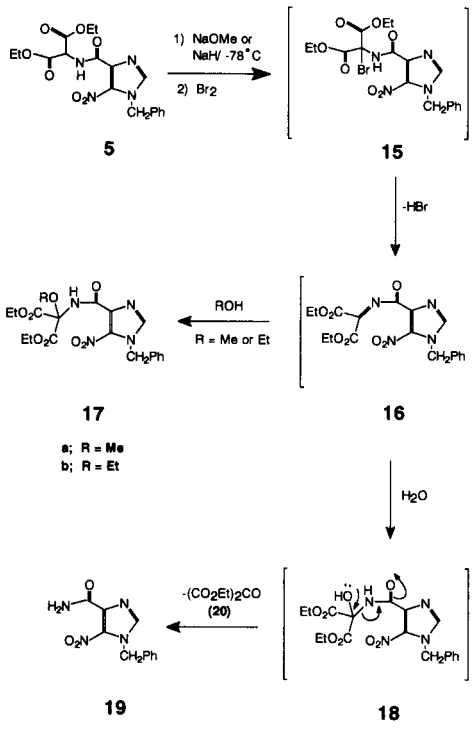
Introduction of a bromide or an alkoxide leaving group at the 6-position of **1d**, as in **13**, is a means to an oxidized ring system such as **14** (Scheme V), which is potentially aromatic by the Hückel $(4n + 2)$ π-electron rule. However, as **1d** failed to brominate at the desired 6-position, an alternative route was devised that involved bromination before the final ring-closure. To this end, compound **5** was brominated in the presence of sodium alkoxide/alcohol at $-78°$. However, the product **17** (Scheme VI) isolated from

Scheme V



this reaction contained the diethyl 2-alkoxy-2-carbonylaminomalonate side-chain. Apparently, bromination proceeds to yield sequential intermediates **15** and **16**, and the latter upon conjugate addition by alcohol yields **17**. When sodium hydride was employed in place of sodium methoxide as a base for initial bromination, and the reaction quenched with water, 1-benzyl-5-nitroimidazole-4-carboxamide **19** was the only product isolated. In this case, the addition of water to intermediate **16** produces **18** which further dissociates into **19** and **20**.

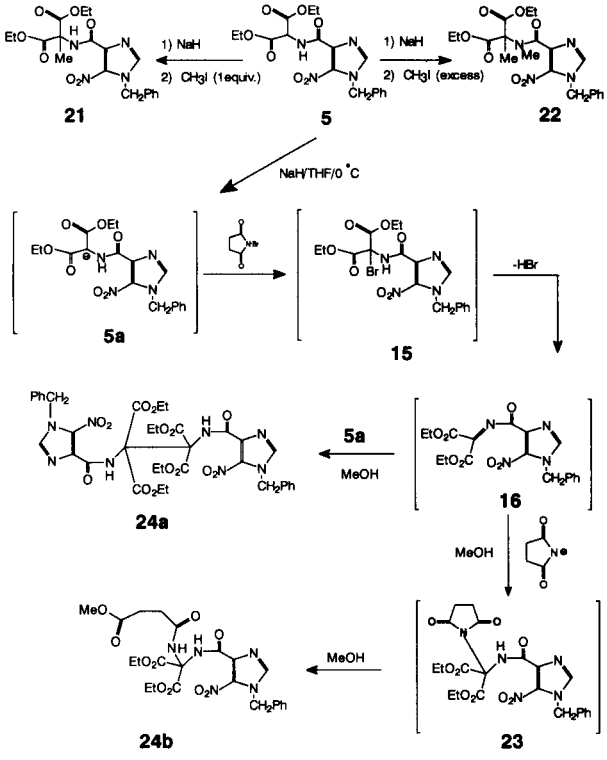
Scheme VI



5 15 17 a; R = Me b; R = Et 16 19 18

The proof that **15** is the initial intermediate formed upon bromination in the presence of a base was obtained by carrying out base-catalyzed alkylation of **5** (Scheme VII). Thus, when **5** was treated with an equivalent of sodium hydride, followed by methyl iodide, the monomethylated product **21** was formed, whereas an excess sodium hydride/methyl iodide produced the dimethyl product **22**. When bromination was carried out with *N*-bromosuccinimide (NBS) in the presence of sodium hydride, followed by quenching the reaction mixture with methanol, two products, **24a** and **24b**, were obtained. The structure of **24b** was confirmed by single-crystal X-ray diffraction analyses [10]. The reaction with NBS appears to proceed through sequential intermediates **15, 16** and **23** to form **24a** or **24b** (Scheme VII).

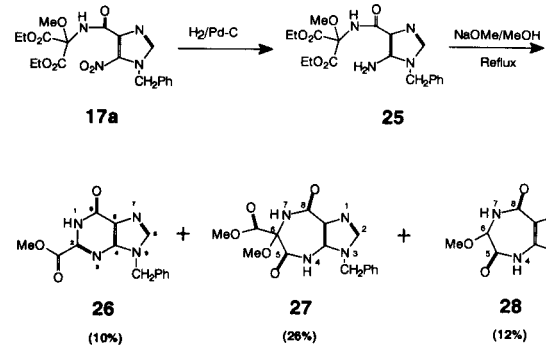
Scheme VII



21 5 22 5a 15 24a 16 24b 23

Finally, toward preparation of the intended **14**, compound **17** was reduced by catalytic hydrogenation over palladium/charcoal to obtain the corresponding amino compound **25** (Scheme VIII). The ring-closure of **25** with sodium methoxide/methanol gave three products, **26** [λ max (methanol) 308 nm], **27** [λ max (methanol) 266 nm], and **28** [λ max (methanol) 266 nm]. The structures of all three products were consistent with their analytical and spectroscopic data, and the structures of **26** and **27** were also confirmed by single-crystal X-ray diffraction analyses [10].

Scheme VIII

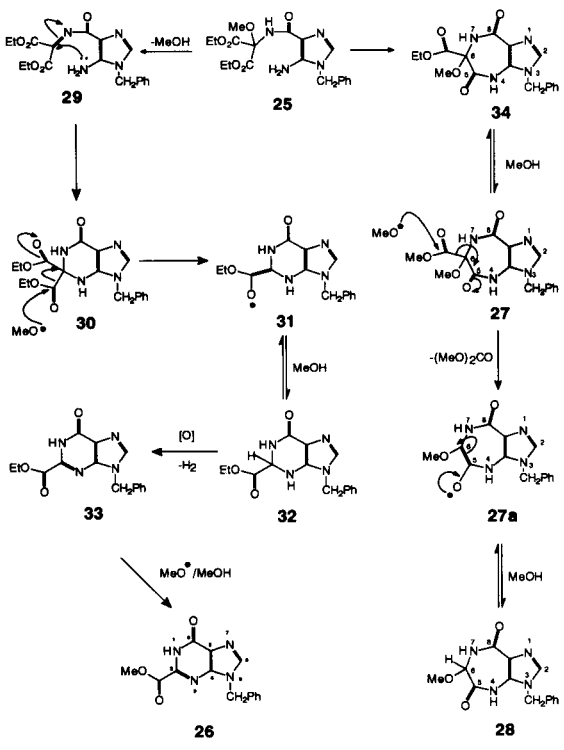


17a 25

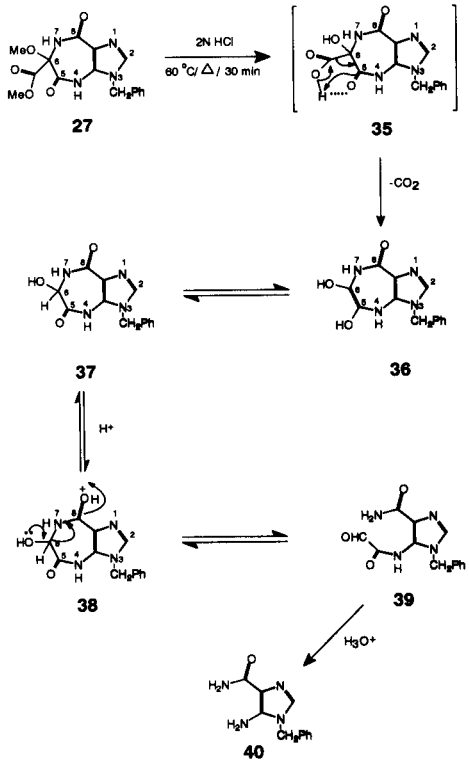
26 (10%) 27 (26%) 28 (12%)

The formation of **26** can be reconciled by invoking initial elimination of methanol from the aminomalonate bond, forming **29** (Scheme IX). The latter undergoes conjugate addition by the 5-amino group to yield the ring-closed product **30**. The attack of methoxide at one of the malonate ester carbons yields **32** which undergoes spontaneous oxidation to form **33**. An exchange of methoxide group for ethoxide at the ester functionallity of **33** (or any of its precursors) leads to **26**. It is to be noted that the mentioned OMe/OEt exchange takes place only when the reaction is carried out at reflux temperature as no such exchange was observed earlier (see Schemes VI and VII above) when similar reactions were carried out at −78°. Products **27** and **28** can be envisioned to arise from the common intermediate **34** formed upon ring-closure of **25** *via* nucleophilic attack of the 5-amino group at one of the ester carbonyls.

Scheme IX



Scheme X



An attempt to oxidize **27** to **14** by either elimination of methanol, catalyzed by a non-nucleophilic base (sodium hydride), or by simple thermolysis in toluene, only gave back the starting material. Therefore, it appears that the existence of **14** at room temperature is energetically too unfavorable, although its presence at lower temperatures can not yet be ruled out.

When **27** was heated at 60° in 2*N* hydrochloric acid for 30 minutes, 5-amino-1-benzylimidazole-4-carboxamide (**40**) was obtained (Scheme X). A tentative mechanism for the formation of **40** involves the acid-catalyzed hydrolysis of **27** to produce the corresponding hydroxy-carboxylic acid intermediate **35**. The latter being a β-keto carboxylic acid, undergoes spontaneous decarboxylation to produce **36**. The tautomerization of **36** to **37**, followed by acid-catalyzed ring-opening produces **39**, which upon acid hydrolysis yields **40**.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were recorded at 80, 300 or 500 MHz on an IBM NR/80, a GE QE-300, or a GE GN-500 spectrometer, respectively, The reported spectral data are relative to TMS as an internal reference standard. Multiplicity is designated by the abbreviation, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad, and ap = apparent. Deuterium oxide was used to verify the presence of exchangeable protons. Electron impact (EI) or chemical ionization (CI) mass spectra were recorded at 70 eV on a Hewlett Packard 5988A mass spectrometer. The fast atom bombardment (FAB) mass spectra were recorded at the Mass Spectral Facility, Department of Biochemistry, Michigan State University, East Lansing, MI. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording instrument. Ultraviolet spectra were recorded on a Gilford Response UV/VIS spectrophotomer. X-Ray diffraction analyses were carried out at the Department of Chemistry, Southern Methodist University, Dallas, TX on an automatic Nicolet R3m/V diffractometer. Elemental Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Dry solvents were prepared as follows: toluene was distilled over sodium; tetrahydrofuran was first dried over calcium hydride and then distilled over sodium. Dry solvents were stored over 4 Å molecular sieves.

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

Method A. Benzylation in the Presence of Tetra-*n*-butylammonium Fluoride.

To a suspension of **1b** [8] (2.0 g, 7.8 mmoles) in dry tetrahydrofuran (150 ml) was added tetra-*n*-butylammonium fluoride (5 ml of 1 *M* solution in tetrahydrofuran, 17.2 mmoles), followed by benzyl bromide (1.0 ml, 8.3 mmoles). The reaction mixture was stirred at room temperature for 8 hours, when a tlc (silica gel, chloroform:methanol, 4:1) showed the presence of two compounds, one major and one minor, both of which had a higher Rf

than the starting material. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of chloroform-methanol (8:1). The appropriate uv-absorbing fractions were pooled and evaporated to obtain **1c** as the major compound. It was recrystallized from 2-propanol as white flakes, yield 1.6 g (59%), mp 235°; ^{1}H nmr (DMSO-d_6): δ 8.10 (t, J = 5.5 Hz, 1H, exchangeable with deuterium oxide, NH), 7.78 (s, 1H, imidazole CH), 7.14 (m, 10H, Ph-H), 5.34 (two d, 2H, benzyl CH_2), 5.22 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 4.44 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 3.76 (dd, 1H, CH of ring CH_2), 3.46 (dd, 1H, CH of ring CH_2); ms: (CI, isobutane) m/z 347 (M^++1, 100%), 325, 297, 257, 223, 163, 155.

Anal. Calcd. for $C_{20}H_{18}N_4O_2 \cdot 0.25H_2O$: C, 68.47; H, 5.27; N, 15.97. Found: C, 68.14; H, 5.35; N, 15.83.

Method B. Benzylation in the Presence of Sodium Hydride.

This procedure yielded both **1c** and **1d** as given below.

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

To a suspension of 60% sodium hydride (0.65 g, 16.25 mmoles) in dry dimethylformamide (50 ml) was added **1b** [8] (2.0 g, 7.8 mmoles). The reaction mixture was stirred at room temperature for 30 minutes, and benzyl bromide (2.0 ml, 16.3 mmoles) was introduced through a syringe needle. The reaction mixture was stirred at ambient temperature for 24 hours, when a tlc (silica gel, chloroform:methanol, 4:1) showed the presence of two uv-absorbing compounds, both of which had a higher Rf than the starting material. The reaction mixture was evaporated to dryness on a rotary evaporator and the residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of chloroform-methanol (10:1). Compound **1d**, which eluted first, was obtained as a white solid upon pooling and evaporation of appropriate uv-absorbing fractions. It was recrystallized from 2-propanol as white crystals, yield 0.74 g (43%), mp 170-172°; ^{1}H nmr (DMSO-d_6): δ 7.79 (s, 1H, imidazole CH), 7.05 (m, 15H, Ph-H), 5.35 (two d, 2H, benzyl CH_2), 5.20 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 4.62 (two d, 2H, benzyl CH_2), 4.39 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 4.10 (d, J = 14.5 Hz, 1H, CH of ring CH_2), 3.70 (d, J = 14.5 Hz, 1H, CH of ring CH_2); ms: (CI, isobutane) m/z 437 (M^++1, 100%), 376, 347, 303, 257, 226, 195, 154, 107.

Anal. Calcd. for $C_{27}H_{24}N_4O_2$: C, 74.29; H, 5.53; N, 12.83. Found: C, 74.02; H, 5.59; N, 12.67.

Compound **1c**, which eluted after **1d**, was recrystallized from 2-propanol as white flakes, yield 0.55 g (41%). The melting point and spectral data of this compound were identical to those of **1c** obtained by benzylation using tetra-*n*-butylammonium fluoride method described above.

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

To a suspension of 60% sodium hydride (0.18 g, 4.5 mmoles) in dry dimethylformamide (50 ml) was added **1b** [8] (1.0 g, 3.9 mmoles). The reaction mixture was stirred at room temperature for 15 minutes, and bromine (0.28 ml, 4.8 mmoles) was introduced through a syringe needle. The reaction mixture was heated at 50° for 10 hours, cooled, and evaporated to dryness on a rotary evaporator. The residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of chloroform-methanol (6:1) to afford a pale yellow solid. The solid was recrystallized from acetonitrile as a pale yellow powder, yield 0.92 g (70%), mp >280°; ^{1}H nmr (DMSO-d_6): δ 11.08 (br s, 1H, exchangeable with deuterium oxide, NH), 7.93 (br s, 1H, exchangeable with deuterium oxide, NH), 7.15 (m, 5H, Ph-H), 5.27 (s, 2H, benzyl CH_2), 3.66 (m, 2H, ring CH_2).

Anal. Calcd. for $C_{13}H_{11}N_4O_2Br$: C, 46.58; H, 3.30; N, 16.71; Br, 23.84. Found: C, 46.42; H, 3.29; N, 16.69; Br, 23.73.

3,4-Dibenzyl-2-bromo-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]-diazepin-5,8-dione (**3a**).

Method A. Bromination Using Acetyl Hypobromite.

To a solution of **1c** (0.3 g, 0.86 mmole) in dry acetone (15 ml) was added a freshly prepared solution of acetyl hypobromite [11] (3.0 mmoles) in carbon tetrachloride (10 ml). The reaction mixture was stirred at room temperature for 24 hours, and the white solid that separated was filtered and dried. It was recrystallized from acetone as pale yellow crystals, yield 0.33 g (90%), mp 239-241°; ^{1}H nmr (DMSO-d_6): δ 8.24 (br s, 1H, NH), 7.11 (m, 10H, Ph-H), 5.30 (s, 2H, benzyl CH_2), 5.16 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 4.35 (d, J = 15.5 Hz, 1H, CH of benzyl CH_2), 4.11 (m, 1H, CH of ring CH_2), 3.50 (m, 1H, CH of ring CH_2); ms: (CI, isobutane) m/z 427, 425 (M^++1), 347, 298, 257, 239, 213.

Anal. Calcd. for $C_{20}H_{17}N_4O_2Br$: C, 56.48; H, 4.02; N, 13.17; Br, 18.79. Found: C, 56.48; H, 4.05; N, 13.15; Br, 18.84.

Method B. Bromination Using Sodium Hydride/Bromine.

Compound **1c** (0.5 g, 1.4 mmoles) was added to a suspension of 60% sodium hydride (75 mg, 1.8 mmoles) in dry dimethylformamide (12 ml). The mixture was stirred for 30 minutes, and bromine (0.1 ml, 1.9 mmoles) was introduced through a syringe needle. The reaction mixture was stirred for 24 hours, when a tlc (silica gel, chloroform:methanol, 4:1) indicated the formation of a compound with a higher Rf than the starting material. The mixture was evaporated to dryness, and the residue was purified by rotating disc chromatography on a Chromatotron plate made of silica gel (particle size 15 μm, thickness 2 mm), eluting with a mixture of chloroform-methanol (100:1). The appropriate uv-absorbing fractions were pooled and evaporated, and the solid obtained was recrystallized from acetone as light yellow crystals, yield 0.32 g (52%). The melting point and spectral data of this compound were identical to those of **3a** obtained by Method A described above.

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

Method A. Bromination Using Acetyl Hypobromite.

To a solution of **1d** (0.2 g, 0.45 mmole) in dry acetone (10 ml) was added a freshly prepared solution of acetyl hypobromite [11] (2.0 mmoles) in carbon tetrachloride (10 ml). The reaction mixture, which was stirred at room temperature, first became brown, and over a period of 4 hours turned colorless. The white solid that separated was filtered and dried. It was recrystallized from acetone as off-white crystals, yield 0.21 g (87%), mp 174-176°; ^{1}H nmr (DMSO-d_6): δ 7.0 (m, 15H, Ph-H), 5.30 (s, 2H, benzyl CH_2), 5.12 (d, J = 5.0 Hz, 1H, CH of CH_2), 4.62 (two d, 2H, CH_2), 4.28 (m, 2H, CH_2), 3.74 (d, J = 5.0 Hz, 1H, CH of CH_2); ms: (CI, isobutane) m/z 517, 515 (M^++1), 437, 363, 347, 273, 241, 170.

Anal. Calcd. for $C_{27}H_{23}N_4O_2Br$: C, 62.92; H, 4.49; N, 10.87; Br, 15.50. Found: C, 62.82; H, 4.48; N, 10.77; Br, 15.44.

Method B. Bromination Using Sodium Hydride/Bromine.

Compound **1d** (0.5 g, 1.1 mmoles) was added to a suspension of 60% sodium hydride (55 mg, 1.3 mmoles) in dry dimethylformamide (12 ml). The reaction mixture was stirred at room temperature for 30 minutes, and bromine (0.065 ml, 1.2 mmoles) was introduced through a syringe needle. The reaction mixture was stirred at room temperature for 24 hours, evaporated to dryness on a rotary evaporator, and the residue was purified by rotating disk chromatography on a Chromatotron plate (silica gel, particle size 15μm, thickness 2 mm), eluting with chloroform. The solid obtained after pooling and evaporation of appropriate uv-absorbing fractions was recrystallized from acetone as light yellow crystals, yield 0.31 g (52%). The melting point and spectral data of this compound were identical to those of **3b** obtained by Method A described above.

Diethyl 2-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**5**) [or 1-Benzyl-4-[*N*-((bis(ethoxycarbonyl)methyl)carbamoyl]-5-nitroimidazole] (**5**).

A 250-ml three-necked, round-bottomed flask, equipped with a reflux condenser, was charged with 1-benzyl-5-nitroimidazole-4-carboxylic acid [8] (5.0 g, 20 mmoles), 1,1'-carbonyldiimidazole (CDI) (4.5 g, 27 mmoles), and dry tetrahydrofuran (THF) (150 ml). The mixture was heated at reflux for 4 hours, when a clear solution was formed. The solution was cooled to room temperature, and a freshly prepared solution of diethyl aminomalonate from its hydrochloride salt (5.71 g, 27 mmoles) by treatment with triethylamine (4.0 ml, 28.7 mmoles) in 100 ml of methylene chloride, was added. The reaction mixture was stirred at room temperature for 1 hour, when a tlc (silica gel, chloroform:methanol, 8:1) showed the formation of a new compound which had a higher Rf than the starting material. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residual gum was suspended in ice-water, and stirred overnight on a magnetic stirrer. A pale yellow solid that separated was filtered, washed with 2 x 100 ml of water, and dried. The compound was recrystallized from methanol into pale yellow flakes, yield 7.9 g (96%), mp 88°; ^{1}H nmr (DMSO-d_6): δ 9.27 (d, J = 7.0 Hz, 1H, exchangeable with deuterium oxide, NH), 8.28 (s, 1H, imidazole CH), 7.38-7.19 (m, 5H, Ph-H), 5.54 (s, 2H, benzyl CH_2), 5.23 (d, J = 7.5 Hz, 1H, CH), 4.22-4.14 (q, 4H, two ester CH_2), 1.21-1.18 (t, 6H, two ester CH_3); ms (EI): m/z 331 (M^+ - CO_2Et), 303, 259, 230.

Anal. Calcd. for $C_{18}H_{20}N_4O_7$: C, 53.48; H, 4.98; N, 13.85. Found: C, 53.50; H, 5.03; N, 13.91.

Diethyl 2-[*N*-(5-Amino-1-benzylimidazolyl-4-carbonyl)amino]malonate (**6**) [or 5-Amino-1-benzyl-4-[*N*-((bis(ethoxycarbonyl)methyl)-carbamoyl]imidazole (**6**).

A mixture of **5** (2.0 g, 4.9 mmoles) and 10% Pd-C (200 mg) in absolute methanol (150 ml) was hydrogenated in a Parr hydrogenator at 40 psi for 2 hours. The reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The residual semi-solid was triturated with ether to obtain a white solid. The solid was filtered, dried, and recrystallized from methanol-ether as shiny, colorless needles, yield 1.52 g (82%), mp 102-104°; ^{1}H nmr (DMSO-d_6): δ 7.49 (d, J = 6.9 Hz, 1H, exchangeable with deuterium oxide, NH), 7.26 (m, 6H, imidazole CH + Ph-H), 5.91 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.10 (d, J = 6.9 Hz, 1H, CH), 5.09 (s, 2H, CH_2), 4.18 (q, J = 7.0 Hz, 4H, two ester CH_2), 1.19 (t, J = 6.9 Hz, 6H, two ester CH_3); ms (EI) m/z 374 (M^+), 301, 282, 227, 200.

Anal. Calcd. for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.91; N, 14.96. Found: C, 57.68; H, 5.88; N, 14.99.

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

Absolute ethanol (50 ml) was introduced through a syringe needle to a three-necked, round-bottomed flask maintained under nitrogen. Freshly cut and cleaned sodium metal (80 mg, 3.47 mg-atoms) was added with stirring to form a clear solution. Compound **6** (1.0 g, 2.6 mmoles) was added, and the reaction mixture was heated at reflux for 3-4 hours when a tlc (silica gel, choroform:methanol, 4:1) showed the complete absence of the starting material. The reaction mixture was cooled in an ice-water bath and the *p*H was adjusted to 6.5 with 2*N* hydrochloric acid. When an additional 10 ml of water was added to the reaction mixture, a black gummy solid separated out which was filtered off. The filtrate upon standing at room temperature for sometime yielded a solid which was recrystallized from methanol-water into colorless crystals, yield 620 mg (69%), mp 235-236°; ^{1}H nmr (DMSO-d_6): δ 11.14 (s, 1H, exchangeable with deuterium oxide, NH), 8.08 (br s, 1H, exchangeable with deuterium oxide, NH), 7.60 (s, 1H, imidazole CH), 7.35-7.15 (m, 5H, Ph-H), 5.21 (two d, 2H, CH_2), 4.61 (d, J = 6.0 Hz, 1H, CH), 3.87 (br s, 1H, one H of CH_2), 3.61 (br s, 1H, one H of CH_2), 0.77 (t, 3H, Me); ms: (EI) m/z 328 (M^+), 284, 255, 200.

Anal. Calcd. for $C_{16}H_{16}N_4O_4 \cdot 0.75H_2O$: C, 56.17; H, 5.15; N, 16.38. Found: C, 56.10; H, 5.17; N, 16.46.

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

This compound was prepared by using an analogous procedure described above for compound **7a**, substituting methanol for ethanol, mp 190°; ^{1}H nmr (DMSO-d_6): δ 11.19 (s, 1H, exchangeable with deuterium oxide, NH), 8.12 (d, J = 7.8 Hz, 1H, exchangeable with deuterium oxide, NH), 7.71 (s, 1H, imidazole CH), 7.28-7.11 (m, 5H, Ph-H), 5.25 (two d, 2H, benzyl CH_2), 4.63 (d, J = 7.8 Hz, 1H, CH), 3.20 (s, 3H, Me).

Anal. Calcd. for $C_{15}H_{14}N_4O_4 \cdot 1H_2O$: C, 54.21; H, 4.85; N, 16.85. Found: C, 54.47; H, 4.92; N, 16.67.

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

Method A. Bromination Using *N*-Bromosuccinimide.

A 50-ml round-bottomed flask was charged with dry dimethylformamide (25 ml). Compound **7b** (0.5 g, 1.52 mmoles) was added, followed by *N*-bromosuccinimide (0.3 g, 1.69 mmoles) and azobisisobutyronitrile (AIBN) (25 mg). The reaction mixture was stirred at room temperature for 3 hours when a tlc (silica gel, chloroform:methanol, 4:1) indicated a new uv-absorbing compound with a higher Rf than the starting material. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was purified by rotating disk chromatography on a Chromatotron plate (silica gel, particle size 15 μm, thickness 2mm), eluting first with a mixture of chloroform-acetone (8:1), then with chloroform-acetone (1:1). Appropriate uv-absorbing fractions were pooled and evaporated. The residue was recrystal-

lized from acetonitrile into off-white crystals, yield 0.36 g (58%), mp 273-275°; ^{1}H nmr (DMSO-d_6): δ 11.31 (br s, 1H, exchangeable with deuterium oxide, NH), 8.1 (d, 1H, exchangeable with deuterium oxide, NH), 7.43-6.97 (m, 5H, Ph-H), 5.24 (two d, 2H, CH_2), 4.71 (d, 1H, CH), 4.00-3.70 (m, 2H, CH_2), 1.09 (t, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{15}N_4O_4Br$: C, 47.19; H, 3.70; N, 13.75. Found: C, 47.29; H, 3.75; N, 13.81.

Method B. Bromination Using Sodium Hydride and Bromine.

A dry 50-ml flask was charged with 15 ml of dry dimethylformamide. Compound **7b** (400 mg, 1.21 mmoles) was added, and the mixture was cooled at 0° in an ice-water bath. Sodium hydride (60%) (58 mg, 1.45 mmoles) was added, and the reaction mixture was stirred at room temperature for 1 hour. The light yellow solution was transferred, under nitrogen, to a solution of bromine (0.2 g, 1.25 mmoles) in tetrahydrofuran, maintained at 0°, over a period of 45 minutes. The reaction mixture was stirred for 30 minutes, and evaporated to dryness. The residue was triturated with water to obtain a solid which was filtered, dried, and recrystallized from acetonitrile, yield 243 mg (49%). The melting point, Rf, and nmr data of this compound were superimposable with those of **8** obtained by Method A.

3,4-Dibenzyl-4,5,7,8-tetrahydro-6-methoxycarbonyl-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**9**).

To a suspension of **7b** (1.0 g, 3.1 mmoles) in 50 ml of tetrahydrofuran was added 2 ml of a 1*M* solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran. Benzyl bromide (0.42 ml, 3.5 mmoles) was added to the clear solution, and the reaction mixture was stirred at room temperature for 8 hours. A tlc (silica gel, chloroform:methanol, 6:1) indicated the formation of a major uv-absorbing compound along with a trace of another that had higher Rf than the major compound. The reaction mixture was evaporated to dryness, and the residue was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting first with a mixture of chloroform-methanol (6:1) to remove trace impurities, followed by a mixture of chloroform-methanol (5:1) to afford the major compound. The appropriate uv-absorbing fractions were pooled and evaporated to obtain a white solid which was recrystallized from 2-propanol, yield 0.6 g (47%), mp 186-188°; ^{1}H nmr (DMSO-d_6): δ 8.58 (d, J = 7.8 Hz, 1H, exchangeable with deuterium oxide, NH), 7.69 (s, 1H, imidazole CH), 7.0 (m, 10H, Ph-H), 5.26 (m, 3H, benzyl CH_2 + CH of benzyl CH_2), 4.85 (d, J = 7.8 Hz, 1H, H-6), 4.47 (d, J = 15.6 Hz, 1H, CH of benzyl CH_2), 3.29 (s, 3H, CO_2Me); ms: (EI) m/z 404 (M^+), 346, 313, 288, 226, 198.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.28; H, 5.00; N, 13.73.

Diethyl 2-[*N*-(5-Amino-1-benzyl-2-bromoimidazolyl-4-carbonyl)-amino]malonate (**10**) [or 5-Amino-1-benzyl-2-bromo-4-[*N*-((bis(ethoxycarbonyl)methyl)carbamoyl]imidazole (**10**).

To a solution of compound **6** (320 mg, 0.85 mmole) in dry tetrahydrofuran (30 ml) was added potassium carbonate (5.0 g). The reaction mixture was stirred at room temperature under nitrogen, and bromine (0.1 ml, 1.9 mmoles) was added. The bromine color began to discharge slowly, and after 1 hour, a tlc (silica gel, chloroform:acetone, 9:1) showed the complete conversion of the starting material into a new, uv-absorbing compound. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was washed with water, and the gummy substance obtained was dissolved in chloroform, and the solution was dried over anhydrous magnesium sulfate. Filtration and evaporation gave a syrup which upon trituration with ether solidified into off-white powder, yield 282 mg (73%), mp 115-117°; ^{1}H nmr (DMSO-d_6): δ 7.63 (d, 1H, J = 6.9 Hz, exchangeable with deuterium oxide, NH), 7.3-7.0 (m, 5H, Ph-H), 6.20 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.10 (s, 2H, benzyl CH_2), 5.08 (d, J = 7.2 Hz, 1H, becomes a singlet upon deuterium oxide exchange, malonate CH), 4.15 (m, 4H, two ester CH_2), 1.9 (t, 6H, two ester CH_3).

Anal. Calcd. for $C_{18}H_{21}N_4O_5Br$: C, 47.69; H, 4.67; N, 12.36; Br, 17.62. Found: C, 47.80; H, 4.66; N, 12.28; Br, 17.70.

Diethyl 2-[*N*-(5-Amino-1-benzyl-2-imidazolonyl-4-carbonyl)amino]-malonate (**11**) [or 5-Amino-1-benzyl-4-[*N*-((bis(ethoxycarbonyl)-methyl)carbamoyl]imidazol-2-one] (**11**).

A mixture of **5** (2.0 g, 4.9 mmoles) and 10% Pd-C (200 mg) in glacial acetic acid (150 ml) was hydrogenated in a Parr apparatus at 40 psi for 1 hour. The reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The residue was co-evaporated with toluene (2 x 20 ml) to obtain a brown powder. A tlc of the powder [silica gel, chloroform-methanol (8:1)] showed that it was a mixture of two compounds, one of which--the faster moving--was readily identified as **6**. The two compounds were separated by rotating disk chromatography on a Chromatotron plate (silica gel, particle size 15 μm, thickness 4mm), eluting first with a mixture of chloroform-methanol (10:1) to collect **6**, and then with a mixture of chloroform-methanol (8:1) to obtain **11**. The spectral and analytical data of the faster-eluting compound, yield 132 mg (7%), were consistent with those of **6** obtained above from Pd-C/H_2 reduction of **5** in methanol.

The appropriate fractions of the slower-moving compound were pooled and evaporated to obtain a solid, which was recrystallized from methanol, yield 1.58 g (83%), mp 204-206°; ^{1}H nmr (DMSO-d_6): δ 9.8 (s, 1H, exchangeable with deuterium oxide, NH), 7.58 (d, J = 7.5 Hz, 1H, exchangeable with deuterium oxide, NH), 7.34-7.21 (m, 5H, Ph-H), 6.33 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.21 (d, J = 7.5 Hz, 1H, malonate CH), 4.78 (s, 2H, benzyl CH_2), 4.20 (m, 4H, two ester CH_2), 1.19 (t, J = 7.2 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.67; N, 14.35. Found: C, 55.29; H, 5.69; N, 14.40.

3-Benzyl-6-ethoxycarbonyl-1,2,4,5,7,8-hexahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-2,5,8-trione (**12**).

Dry ethanol (50 ml) was introduced to a three-necked, round-bottomed flask, maintained under nitrogen. Freshly cut and cleaned sodium metal (80 mg, 3.4 mg.atoms) was added with stirring. To the clear solution was added **11** (1.0 g, 2.56 mmoles), and the reaction mixture was heated at reflux for 4 hours. After cooling and adjusting the *p*H to 6 with 0.5 *N* hydrochloric acid, the reaction mixture was evaporated to dryness. The residue, upon trituration with water, yielded a brown solid which was recrystallized from methanol-water into pale yellow powder, yield 0.68 g (77%), mp >275°; ^{1}H nmr (DMSO-d_6): δ 10.62 (br s, 1H, exchangeable with deuterium oxide, NH), 8.13 (d, J = 7.8 Hz, 1H, exchangeable with deuterium oxide), 7.35-7.14 (m, 5H, Ph-H), 4.87 (s, 2H, benzyl CH_2), 4.66 (d, J = 7.8 Hz, 1H, CH), 3.86 (m, 2H, ester CH_2), 0.87 (t, J = 7.0 Hz, 3H, ester CH_3).

Anal. Calcd. for $C_{16}H_{17}N_4O_5$: C, 55.65; H, 4.95; N, 16.22.

Found: C, 55.74; H, 4.72; N, 16.25.

Diethyl 2-Methoxy-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)-amino]malonate (**17a**).

A 300 ml three-necked, round-bottomed flask, equipped with a nitrogen inlet, was charged with 150 ml of dry methanol. Clean, freshly cut sodium metal (0.5 g, 21.74 mg.atoms) was added, and the mixture was stirred under nitrogen atmosphere to form a clear solution. The flask was cooled in an acetone-dry ice bath to −78°, and compound **5** (5.0 g, 12.37 mmoles) was added when the color of the reaction mixture changed to dark brown. Bromine (0.9 ml, 17 mmoles) was introduced through a syringe when the color of the solution changed to off-white, and some solid started separating. After 1 hour, the *p*H of the reaction mixture was adjusting to 6.5 with 2*N* hydrochloric acid, and the mixture was evaporated to dryness on a rotary evaporator. The residue was suspended in water and extracted with chloroform (2 x 250 ml). The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated to dryness. The residue was suspended in ether and the off-white solid that separated was recrystallized from ether, yield 4.7 g (88%), mp 126-127°; ^{1}H nmr (DMSO-d_6): δ 9.42 (s, 1H, exchangeable with deuterium oxide, NH), 8.30 (s, 1H, imidazole CH), 7.37-7.23 (m, 5H, Ph-H), 5.55 (s, 2H, benzyl CH_2), 4.19 (q, J = 7.1 Hz, 4H, two ester CH_2), 3.25 (s, 3H, OMe), 1.65 (t, J = 6.9 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{19}H_{22}N_4O_8$: C, 52.53; H, 5.10; N, 12.89. Found: C, 52.47; H, 5.11; N, 12.87.

Diethyl 2-Ethoxy-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**17b**).

The procedure is analogous to the one given above for **17a** except that ethanol was used in place of methanol. It was recrystallized from ether, mp 105-107°; ^{1}H nmr (DMSO-d_6): δ 9.4 (s, 1H, exchangeable with deuterium oxide, NH), 8.2 (s, 1H, imidazole CH), 7.25 (m, 5H, Ph-H), 5.50 (s, 2H, benzyl CH_2), 4.15 (m, 4H, two ester CH_2), 3.52 (q, 2H, OCH_2), 1.19 (m, 9H, three CH_3).

Anal. Calcd. for $C_{20}H_{24}N_4O_8$: C, 53.57; H, 5.38; N, 12.49. Found: C, 53.36; H, 5.40; N, 12.40.

1-Benzyl-5-nitroimidazole-4-carboxamide (**19**).

To a solution of **5** (1.0 g, 2.4 mmoles) in dry tetrahydrofuran (25 ml), maintained at −78°, was added 60% sodium hydride (125 mg, 3.1 mmoles). The reaction mixture was stirred for 10 minutes, and bromine (0.17 ml, 2.9 mmoles) was added. After 15 minutes, 5 ml of water was added, and the temperature was gradually raised to 0°. The reaction mixture was neutrallized to *p*H 7 with 1*N* hydrochloric acid, and was concentrated to approximately 5 ml by evaporation under reduced pressure. The concentrate was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of chloroform-methanol (5:1). Evaporation of appropriate uv-absorbing fractions gave a solid that was recrystallized from acetone to yield off-white crystals, yield 240 mg (40%), mp 200-202°; ^{1}H nmr (DMSO-d_6): δ 8.24 (s, 1H, imidazole CH), 7.92 (br s, 1H, exchangeable with deuterium oxide, NH), 7.63 (br s, 1H, exchangeable with deuterium oxide, NH), 7.35 (m, 5H, Ph-H), 5.52 (s, 2H, benzyl CH_2).

Diethyl 2-Methyl-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**21**) and Diethyl 2-Methyl-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)-*N*-methylamino]malonate (**22**).

To a solution of **5** (1.0 g, 2.4 mmoles) in dry tetrahydrofuran (100 ml), maintained at 0° in an ice-water bath, was added sodium hydride (65 mg, 2.7 mmoles). After stirring for 1.5 hours, methyl iodide (0.2 ml, 3.2 mmoles) was added, and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was triturated with water. The gummy mass that separated was washed with excess water, dried by co-evaporation with toluene, dissolved in methanol, and purified by flash chromatography on a silica gel column, eluting first with a mixture of chloroform-acetone (9:1), followed by chloroform-acetone (8:1). The appropriate uv-absorbing fractions were pooled and evaporated to obtain two new compounds - the faster eluting **21** and the slower eluting **22** - which were characterized as follows:

Compounds **21**.

Recrystallized from ether into white crystals, yield 0.6 g (58%), mp 118-120°; ^{1}H nmr (DMSO-d_6): δ 8.79 (s, 1H, exchangeable with deuterium oxide, NH), 8.26 (s, imidazole CH), 7.34-7.25 (m, 5H, Ph-H), 5.53 (s, 2H, benzyl CH_2), 4.17 (q, J = 7.0 Hz, 4H, two ester CH_2), 1.67 (s, 3H, CH_3), 1.16 (t, J = 7.0 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.29; N, 13.39. Found: C, 54.46; H, 5.28; N, 13.45.

Compound **22**.

Recrystallized from ether into light yellow crystals, yield 0.2 g (19%), mp 98-100°; ^{1}H nmr (DMSO-d_6): δ 8.32 (s, 1H, imidazole CH), 7.34-7.25 (m, 5H, Ph-H), 5.28 (s, 2H, benzyl CH_2), 4.13 (q, J = 7.1 Hz, 4H, two ester CH_2), 2.83 (s, 3H, N-Me), 1.68 (s, 3H, C-Me), 1.18 (t, J = 7.1 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{20}H_{24}N_4O_7$: C, 55.55; H, 5.58; N, 12.95. Found: C, 55.50; H, 5.58; N, 13.00.

2,2'-Bis[diethyl 2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate] (**24a**) and Diethyl 2-[(2-Ethoxycarbonyl)ethyl]amino-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**24b**).

A flame-dried, three-necked, round-bottomed flask, maintained under nitrogen, was charged with compound **5** (1.0 g, 2.4 mmoles) and dry tetrahydrofuran (30 ml). The reaction mixture was stirred at room temperature for 10 minutes to form a clear solution. The solution was cooled to 0° in an ice-water bath for 5 minutes, and 60% sodium hydride (120 mg, 3 mmoles) was added, when the color of the reaction mixture gradually turned to dark brown. The mixture was stirred at 0° for 30 minutes. *N*-Bromosuccinimide (0.5 g, 2.8 mmoles) was added, when the color immediately changed to colorless, and a white solid began to precipitate out. After 20 minutes, dry methanol (15 ml) was added, and the reaction mixture was stirred for another 10 minutes. The solid was filtered, washed with water, and dried. It was recrystallized from a mixture of dimethylformamide-methanol into white crystals of **24a**, yield 0.42 g (21%), mp 253-256°; ^{1}H nmr (DMSO-d_6): δ 8.70 (br s, 1H, exchangeable with deuterium oxide, NH), 8.27 (s, 1H, imidazole CH), 7.33-7.23 (m, 5H, Ph-H), 5.48 (s, 2H, benzyl CH_2), 4.06 (q, J = 7.1 Hz, 2H, ester CH_2), 1.03 (t, J = 7.0 Hz, 3H, ester CH_3); ms: (FAB-CI) m/z 807 ($M^+ + 1$), 733.

Anal. Calcd. for $C_{36}H_{38}N_8O_{14}$: C, 53.59; H, 4.74; N, 13.89. Found: C, 53.40; H, 4.75; N, 13.84.

The methanolic filtrate after the separation of **24a** was evaporated to dryness to obtain a solid whose tlc (silica gel,

chloroform:acetone, 9:1) showed it to be a mixture of two compounds, **24a** (minor component) and another, **24b** (major) that had a lower Rf than **24a**. The mixture was separated by flash chromatography on a silica gel column, eluting first with chloroform-acetone (9:1), followed by chloroform-acetone (1:1). The appropriate uv-absorbing fractions of the lower-moving compound were pooled and evaporated to obtain a solid, which was recrystallized from ethanol into light yellow crystals of **24b**, yield 0.25 g (19%), mp 150°; ^{1}H nmr (DMSO-d_6): δ 8.97 (s, 1H, exchangeable with deuterium oxide, NH), 7.72 (s, 1H, exchangeable with deuterium oxide, NH), 7.39 (s, 1H, imidazole CH), 7.33-7.22 (m, 5H, Ph-H), 5.40 (s, 2H, benzyl CH_2), 4.30 (q, J = 7.1 Hz, 4H, two ester CH_2), 3.64 (s, 3H, OMe), 2.58 (s, 4H, two CH_2), 1.25 (t, J = 7.0 Hz, 6H, two ester CH_3); ms: (FAB-CI) m/z 534 (M^+ + 1), 403, 307, 247.

Anal. Calcd. for $C_{23}H_{27}N_5O_{10}$: C, 51.78; H, 5.10; N, 13.13. Found: C, 51.96; H, 5.12; N, 13.15.

(Note: When *N*-bromosuccinimide was replaced with bromine in the above procedure, **24a** was formed exclusively.)

Diethyl 2-Methoxy-2-[*N*-(5-amino-1-benzylimidazolyl-4-carbonyl)-amino]malonate (**25**).

A mixture of **17a** (500 mg, 1.15 mmoles) and 5% Pd-C (100 mg) in absolute methanol (100 ml) was hydrogenated in a Parr hydrogenator at 40 psi for 50 minutes. The reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The residual syrup was purified by rotating disk chromatography on a Chromatotron plate, made of silica gel (particle size 15 μm, thickness 2 mm), eluting with chloroform. Appropriate uv-absorbing fractions were pooled and evaporated to afford a syrup, which upon trituration with ether gave an off-white solid. The compound was recrystallized from ether, yield 0.42 g (90%), mp 162-163°; ^{1}H nmr (DMSO-d_6): δ 7.95 (s, 1H, exchangeable with deuterium oxide, NH), 7.32-7.22 (m + s, 6H, imidazole CH + Ph-H), 6.01 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.08 (s, 2H, benzyl CH_2), 4.19 (q, J = 7.0 Hz, 4H, two ester CH_2), 3.18 (s, 3H, OMe), 1.15 (t, J = 7.0 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{19}H_{24}N_4O_6$: C, 56.42; H, 5.98; N, 13.85. Found: C, 56.35; H, 5.93; N, 13.82.

9-Benzyl-2-methoxycarbonylhypoxanthine (**26**), 3-Benzyl-4,5,7,8-tetrahydro-6-methoxy-6-methoxycarbonyl-6*H*-imidazo[4,5-*e*]-[1,4]diazepine-5,8-dione (**27**) and 3-Benzyl-4,5,7,8-tetrahydro-6-methoxy-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (**28**).

To a methanolic solution of sodium methoxide, freshly prepared from sodium (0.17 g, 7.4 mg.atoms) and methanol (25 ml), was added **25** (1.5 g, 3.7 mmoles) when the color of the reaction mixture changed to light brown. The mixture was heated at reflux for 5-7 hours, when a tlc of the reaction mixture (silica gel, chloroform:methanol, 4:1) showed uv-absorbing one major compound, **27**, and two minor compounds, **26** and **28**. The reaction mixture was cooled to room temperature, treated with 0.5*N* hydrochloric acid to adjust the *p*H to 6.5, and the light brown solution was evaporated to dryness. The residue was purified by flash chromatography on a column of silica gel (60 g, particle size 40-63 μm), eluting with chloroform. Pooling and evaporation of the appropriate uv-absorbing fractions yielded the fastest-moving **26**, which was recrystallized from acetone into pale yellow crystals, yield 100 mg (10%), mp 190-192°; ^{1}H nmr (DMSO-d_6): δ 12.65 (s, 1H, exchangeable with deuterium oxide, NH), 8.30 (s, 1H, imidazole CH), 7.25 (m, 5H, Ph-H), 5.40 (s, 2H, benzyl CH_2), 3.80 (s, 3H, OMe); ^{13}C nmr (DMSO-d_6): δ 159.9 (C=O), 156.17 (C=O), 147.07 (quaternary C), 143.37 (quaternary C), 142.42 (imidazole CH), 136.51 (quaternary C), 128.75, 127.85, 127.26 (Ph-CH), 125.76 (quaternary Ph-C), 53.45 (OMe), 46.52 (benzyl CH_2); ms: (EI, 70 eV) m/z 284 (M^+), 240, 225, 207; uv (methanol): λ max 305 nm, (*p*H 13) 305.

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.14; H, 4.25; N, 19.71. Found: C, 59.07; H, 4.28; N, 19.62.

Further elution of the column with a mixture of chloroform-methanol (100:1), followed by pooling and evaporation of the appropriate UV-absorbing fractions, afforded **27** as a syrup which crystallized into white powder upon dissolving in hot acetone and cooling, yield 450 mg (26%), mp 172-175°; ^{1}H nmr (DMSO-d_6): δ 11.49 (s, 1H, exchangeable with deuterium oxide, NH), 8.3 (s, 1H, exchangeable with deuterium oxide, NH), 7.67 (s, 1H, imidazole CH), 7.20 (m, 5H, Ph-H), 5.30 (two d, 2H, benzyl CH_2), 3.69 (s, 3H, CO_2Me), 2.98 (s, 3H, OMe); ms: (EI, 70 eV) m/z 344 (M^+), 285, 257, 242, 226, 199, 180; uv (methanol): λ max 267 nm, (*p*H 13) 303.

Anal. Calcd. for $C_{16}H_{16}N_4O_5 \cdot 0.75H_2O$: C, 53.65; H, 4.89; N, 15.65. Found: C, 53.78; H, 5.00; N, 15.45.

Further elution of the column with a mixture of chloroform-methanol (100:5), followed by pooling and evaporation of the appropriate uv-absorbing fractions, afforded **28** which was recrystallized from acetone as white crystals, yield 120 mg (12%), mp >245°; ^{1}H nmr (DMSO-d_6): δ 11.1 (s, 1H, exchangeable with deuterium oxide, NH), 8.59 (d, J = 6.9 Hz, 1H, exchangeable with deuterium oxide, NH), 7.6 (s, 1H, imidazole CH), 7.2 (m, 5H, Ph-H), 5.29 (two d, 2H, benzyl CH_2), 4.52 (d, J = 6.6 Hz, 1H, becomes a singlet upon exchange with deuterium oxide, H-6), 3.05 (s, 3H, OMe); ms: (EI, 70 eV) m/z 286 (M^+), 258, 242, 226, 199 171; uv (methanol): λ max 267 nm, (*p*H 13) 303.

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.72; H, 4.92; N, 19.57. Found: C, 58.79; H, 4.95; N, 19.48.

5-Amino-1-benzylimidazole-4-carboxamide (**40**).

A mixture of a solution of **27** (0.3 g, 0.87 mmole) in methanol (10 ml) and 1*N* hydrochloric acid (1.0 ml) was heated at reflux for 0.5 hour. The reaction mixture was cooled to room temperature and the *p*H was adjusted to 7.5 with 1*N* sodium hydroxide. The mixture was evaporated to dryness under reduced pressure, and the residue was co-evaporated with methanol (2 x 25 ml). The crude product was purified by flash chromatography on a column of silica gel (particle size 40-63 μm), eluting with a mixture of chloroform-methanol (4:1). After pooling and evaporation of the appropriate uv-absorbing fractions, a solid was obtained which was recrystallized from acetone into white crystals, yield 162 mg (86%), mp 249-251° (lit [12] 249-251°); ^{1}H nmr (DMSO-d_6): δ 7.27 (m + s, 6H, Ph-H + imidazole CH), 6.70 (br, 2H, exchangeable with deuterium oxide, amide NH_2), 5.84 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.07 (s, 2H, CH_2).

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