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A UNIQUE DIAMINOMALONATE DERIVATIVE USEFUL FOR BUILDING NOVEL HETEROCYCLES

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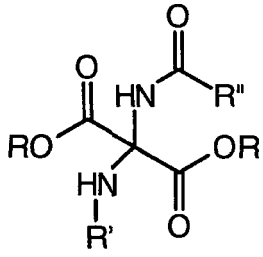
ABSTRACT: The synthetic utility of a unique diaminomalonate derivative (**1**) for constructing novel heterocycles, *e.g.* **5**, has been demonstrated.

There exists little literature precedent for a diaminomalonate derivative such as **1** that would be useful for building a variety of novel,



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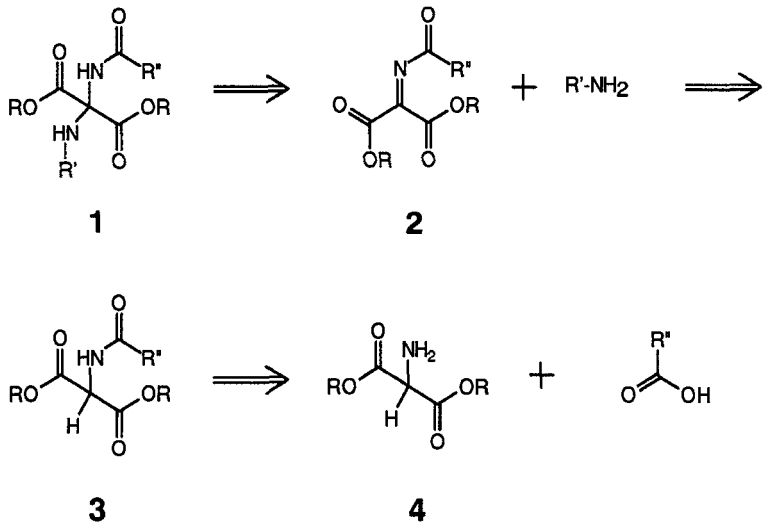
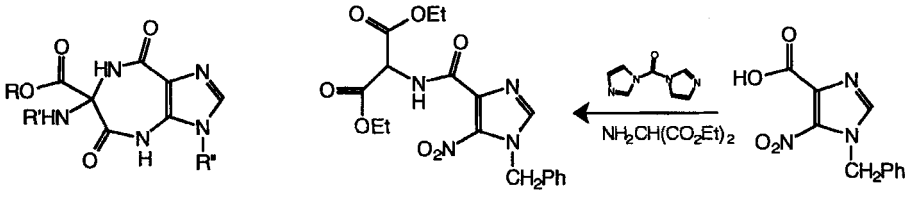
fused and unfused, heterocycles with additional functionalities. The synthesis of a reagent such as **1** appeared intriguing as it contained a unique diaminomalonate moiety whose stability and reactivity are largely unknown. We report here our preliminary results on synthetic utility of this little-explored monoacyl-diaminomalonate-diester derivative. Specifically, we demonstrate its use in the synthesis of a novel 5:7-fused heterocyclic ring system **5** which would be difficult to access by conventional methods. The method, however, would be applicable to prepare a variety of other heterocycles, including spiro ring systems.

A plausible synthetic strategy for **1** (**Scheme 1**) involves condensation of an aminomalonate **4** with an appropriate acid to obtain the corresponding acylaminomalonate **3**. The latter upon oxidation to the iminomalonate **2**, followed by conjugate addition by an amine nucleophile would yield **1**.

Scheme 1



We chose **5** as the target heterocycle on which to test the viability of the mentioned synthetic approach. Compound **5** is a member of the family of ring-expanded ("fat") purine analogues which are of current chemical, biochemical, and medicinal interest in this laboratory[1] and elsewhere.[2-4] Compound **5** incorporates the structural characteristics of both guanine and xanthine. Its various intra- and extranuclear functional groups in the

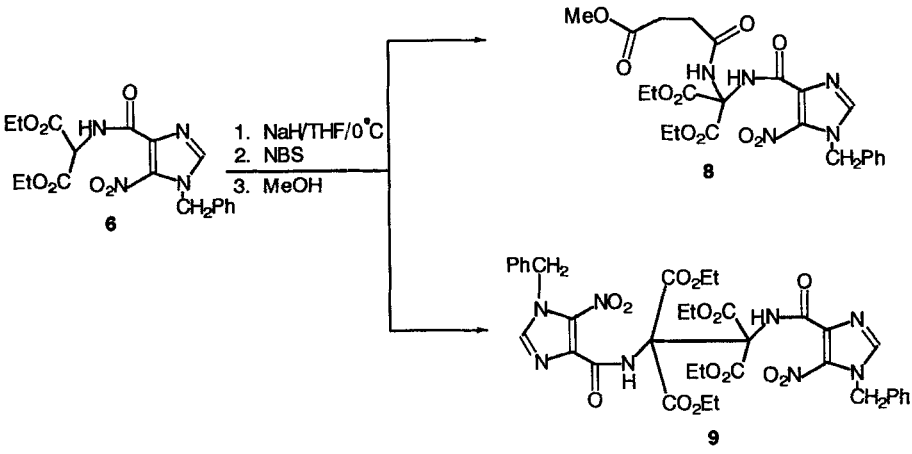


5 **6** **7**

7-membered ring can be further exploited to yield additional analogues. The necessary acylaminomalonate precursor for **5** is diethyl 2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (**6**), which parallels **3** in the synthetic strategy given in Scheme 1. The latter was prepared by condensation of 1-benzyl-5-nitroimidazole-4-carboxylic acid (**7**) with diethyl aminomalonate, mediated by 1,1'-carbonyldiimidazole.[1c] It appeared that further oxidation to the desired iminomalonate intermediate, *viz* **2**, could be accomplished by base-catalyzed bromination, followed by elimination of hydrogen bromide. Indeed, preliminary evidence for both the formation of the iminomalonate intermediate and the subsequent conjugate addition by an amine nucleophile, was provided by the reaction of **6** with *N*-bromosuccinimide in the presence of sodium hydride. One of the products isolated from this reaction, *i.e.* **8**, contained a diaminomalonate side-chain (**Scheme 2**). The structure of **8** was confirmed by single-crystal X-ray diffraction analysis. An ORTEP view of **8** along with the atom numbering scheme that was employed is shown in **Figure 1**. The atomic coordinates, bond lengths, and bond angles are collected in **Tables I** & **II**.

Compound **8** must have arisen by nucleophilic attack of the anion of *N*-bromosuccinimide on the iminomalonate **12** that was produced by the

Scheme 2



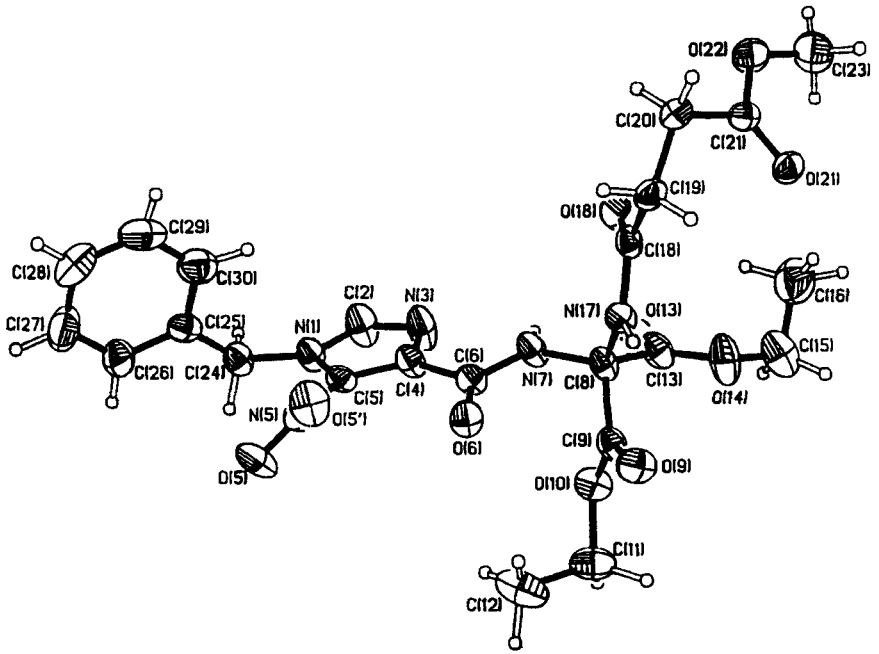


FIG. 1: ORTEP view of **8** showing the atom numbering scheme.

Table I

Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 \times 10^3$) of **8**

	x	y	z	U(eq)
N(1)	7484(2)	-135(2)	-266(2)	47(1)
C(2)	6530(3)	288(3)	-410(3)	71(2)
N(3)	6290(2)	515(3)	370(2)	71(1)
C(4)	7137(3)	194(3)	1077(2)	45(1)
C(5)	7868(2)	-200(2)	692(2)	38(1)
N(5)	8884(2)	-612(2)	1122(2)	45(1)
O(5)	9616(2)	-416(2)	795(2)	69(1)
O(5')	8968(2)	-1134(2)	1789(2)	66(1)
C(6)	7184(3)	366(2)	2074(2)	42(1)
O(6)	7965(2)	204(2)	2719(2)	52(1)
N(7)	6277(2)	731(2)	2186(2)	47(1)
C(8)	6169(2)	1028(3)	3089(2)	41(1)
C(9)	7192(3)	1497(3)	3692(3)	43(1)
O(9)	7612(2)	1286(2)	4491(2)	55(1)
O(10)	7488(2)	2184(2)	3213(2)	53(1)
C(11)	8509(3)	2649(3)	3675(3)	66(2)
C(12)	9417(4)	2097(4)	3533(5)	96(3)
C(13)	5286(3)	1782(3)	2891(3)	54(2)
O(13)	4874(2)	2094(2)	2122(2)	69(1)
O(14)	5114(2)	2068(2)	3686(2)	74(1)
C(15)	4324(4)	2860(4)	3635(4)	91(2)
C(16)	3297(5)	2432(4)	3403(4)	95(3)
N(17)	5921(2)	247(2)	3630(2)	39(1)
C(18)	4985(3)	-214(3)	3349(2)	39(1)
O(18)	4332(2)	-11(2)	2607(2)	57(1)
C(19)	4806(3)	-997(3)	3976(2)	42(1)
C(20)	3649(3)	-1307(3)	3723(3)	48(1)
C(21)	2922(3)	-530(3)	3820(2)	41(1)
O(21)	3181(2)	161(2)	4305(2)	45(1)
O(22)	1919(2)	-684(2)	3312(2)	59(1)
C(23)	1151(4)	1(4)	3439(4)	76(2)
C(24)	7960(3)	-469(3)	-1002(3)	50(2)
C(25)	8239(3)	-1502(3)	-927(2)	47(1)
C(26)	9141(3)	-1811(3)	-1157(3)	65(2)
C(27)	9401(5)	-2753(4)	-1139(3)	83(2)
C(28)	8747(5)	-3405(4)	-900(3)	85(2)
C(29)	7872(4)	-3118(4)	-650(4)	84(2)
C(30)	7607(3)	-2169(4)	-669(3)	67(2)

*Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

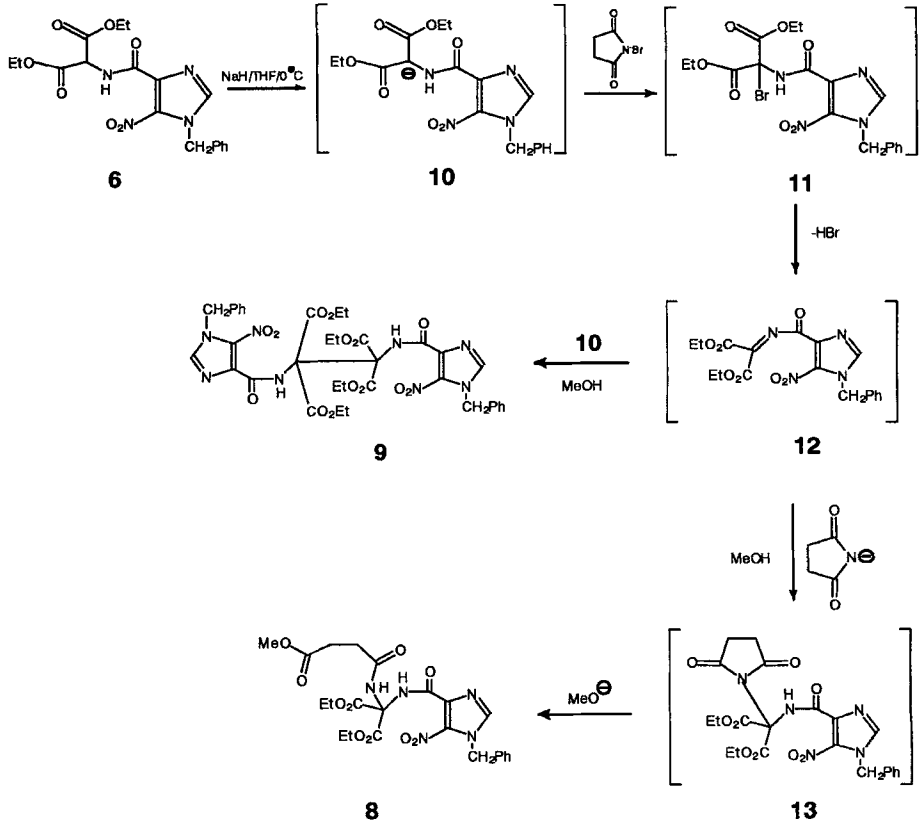
Table II

Bond lengths (Å) and bond angles (°) of **8**

N(1)-C(2)	1.346(5)	N(1)-C(5)	1.374(4)
N(1)-C(24)	1.473(5)	C(2)-N(3)	1.319(6)
N(3)-C(4)	1.377(4)	C(4)-C(5)	1.360(5)
C(4)-C(6)	1.481(5)	C(5)-N(5)	1.430(4)
N(5)-O(5)	1.217(4)	N(5)-O(5')	1.215(4)
C(6)-O(6)	1.214(4)	C(6)-N(7)	1.346(5)
N(7)-C(8)	1.446(4)	C(8)-C(9)	1.540(4)
C(8)-C(13)	1.539(5)	C(8)-N(17)	1.452(5)
C(9)-O(9)	1.198(4)	C(9)-O(10)	1.321(5)
O(10)-C(11)	1.477(5)	C(11)-C(12)	1.483(8)
C(13)-O(13)	1.203(5)	C(13)-O(14)	1.322(5)
O(14)-C(15)	1.510(6)	C(15)-C(16)	1.426(8)
N(17)-C(18)	1.347(4)	C(18)-O(18)	1.228(4)
C(18)-C(19)	1.504(5)	C(19)-C(20)	1.520(5)
C(20)-C(21)	1.486(5)	C(21)-O(21)	1.205(4)
C(21)-O(22)	1.339(4)	O(22)-C(23)	1.443(6)
C(24)-C(25)	1.501(6)	C(25)-C(26)	1.385(6)
C(25)-C(30)	1.376(6)	C(26)-C(27)	1.372(7)
C(27)-C(28)	1.368(9)	C(28)-C(29)	1.358(9)
C(C29)-C(30)	1.383(8)	C(28)-C(29)	1.358(9)
C(2)-N(1)-C(5)	104.7(3)	C(2)-N(1)-C(24)	125.8(3)
C(5)-N(1)-C(24)	129.5(3)	N(1)-C(2)-N(3)	113.7(3)
C(2)-N(3)-C(4)	104.6(3)	N(3)-C(4)-C(5)	109.1(3)
N(3)-C(4)-C(6)	120.7(3)	C(5)-C(4)-C(6)	130.1(3)
N(1)-C(5)-C(4)	107.9(3)	N(1)-C(5)-N(5)	121.2(3)
C(4)-C(5)-N(5)	130.8(3)	C(5)-N(5)-O(5)	117.8(3)
C(5)-N(5)-O(5')	118.3(3)	O(5)-N(5)-O(5')	123.9(3)
C(4)-C(6)-O(6)	123.4(3)	C(4)-C(6)-N(7)	112.9(3)
O(6)-C(6)-N(7)	123.7(3)	C(6)-N(7)-C(8)	122.6(2)
N(7)-C(8)-C(9)	111.9(3)	N(7)-C(8)-C(13)	106.4(3)
C(9)-C(8)-C(13)	107.4(3)	N(7)-C(8)-N(17)	112.6(3)
C(9)-C(8)-N(17)	107.2(2)	C(13)-C(8)-N(17)	111.2(3)
C(8)-C(9)-O(9)	123.8(3)	C(8)-C(9)-O(10)	109.9(3)
O(9)-C(9)-O(10)	126.3(3)	C(9)-O(10)-C(11)	116.0(3)
O(10)-C(11)-C(12)	111.0(4)	C(8)-C(13)-O(13)	123.5(4)
C(8)-C(13)-O(14)	110.1(3)	O(13)-C(13)-O(14)	126.3(4)
C(13)-O(14)-C(15)	117.6(3)	O(14)-C(15)-C(16)	106.5(5)
C(8)-N(17)-C(18)	121.2(2)	N(17)-C(18)-O(18)	121.0(3)
N(17)-C(18)-C(19)	116.5(3)	O(18)-C(18)-C(19)	122.5(3)
C(18)-C(19)-C(20)	111.9(3)	C(19)-C(20)-C(21)	112.6(3)
C(20)-C(21)-O(21)	125.0(3)	C(20)-C(21)-O(22)	112.3(3)
O(21)-C(21)-O(22)	122.7(3)	C(21)-O(22)-C(23)	115.2(3)
N(1)-C(24)-C(25)	113.6(3)	C(24)-C(25)-C(26)	119.6(4)
C(24)-C(25)-C(30)	122.3(4)	C(26)-C(25)-C(30)	118.0(4)
C(25)-C(26)-C(27)	121.6(5)	C(26)-C(27)-C(28)	119.3(6)
C(27)-C(28)-C(29)	120.1(5)	C(28)-C(29)-C(30)	120.7(5)
C(25)-C(30)-C(29)	120.2(5)		

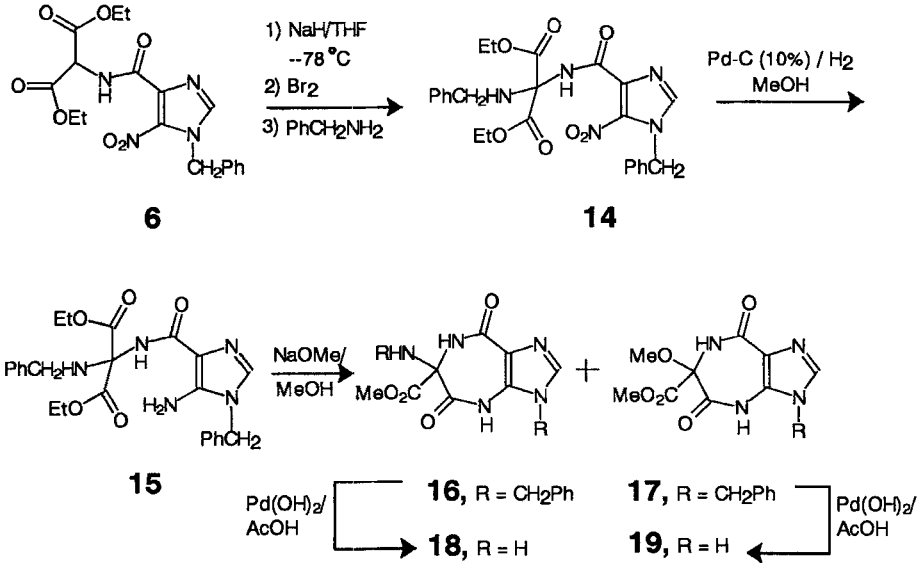
elimination of hydrogen bromide from the initially formed bromomalonate intermediate **11** (**Scheme 3**). Not surprisingly, this reaction also yielded the dimeric by-product **9** that was formed by conjugate addition of the anion of the starting material, **10**, on the iminomalonate intermediate **12**.

Scheme 3



Encouraged by the above results, Compound **6** was subjected, in a one-pot reaction, to bromination in the presence of sodium hydride, followed by treatment with benzylamine (**Scheme 4**). The product **14**,

Scheme 4



representing **1**, was further reduced by catalytic hydrogenation over palladium/charcoal to obtain the corresponding amino compound **15**. Treatment of **15** with sodium methoxide in refluxing methanol resulted in ring-closure with concomitant exchange of the ester ethoxide group with a methoxide to produce **16**. The above reaction also gave a by-product, **17**. The formation of the latter can be reconciled by the nucleophilic attack of methoxide on the putative intermediate **12** produced by base-catalyzed elimination of benzylamine from **15**. The formation of **17** could perhaps be avoided by using a non-nucleophilic base such as sodium hydride. Since the R_f values of **16** and **17** were very close in a variety of TLC solvent systems, it was more convenient to use the mixture itself for the next step wherein the two compounds could be easily separated by chromatography. Thus, debenzylation of **16** and **17** by catalytic hydrogenation over palladium hydroxide in acetic acid provided **18** and **19**, respectively, and

were separated by silica gel flash chromatography using a gradient of chloroform-methanol as eluent (6:1→4:1). The spectral and microanalytical data of **18** and **19** were consistent with the assigned structures. The structure **18** was also confirmed by single-crystal X-ray diffraction analysis.

In conclusion, a synthetic strategy has been realized for building a novel diaminomalonate derivative **1** that is useful to construct a variety of heterocycles with unique structural features.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 300 MHz on a General Electric QE-300 NMR spectrometer. The reported spectral data are relative to Me_4Si 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, and br = broad. The fast atom bombardment (FAB) mass spectra were recorded at the Mass Spectral Facility, Department of Biochemistry, Michigan State University, East Lansing, MI. X-Ray diffraction analyses were carried out on an automatic Siemens 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 tetrahydrofuran was prepared by first drying over calcium hydride and then distilling over sodium, and then storing over 4 Å molecular sieves.

Diethyl 2-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)amino]-2-[(2-methoxycarbonyl)ethylcarbonyl)amino]malonate (8) 2,2'-Bis[diethyl 2-[*N*-(1-Benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate] (9).

A flame-dried, three-necked, round-bottomed flask, maintained under N_2, was charged with compound **6**[1c] (1.0 g, 2.4 mmol) and dry

tetrahydrofuran (30 mL). The reaction mixture was stirrred 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 mmol) 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 mmol) 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 **9**, yield 0.42 g (21%), mp 253-256 °C; ^{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 **9** 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, **9** (minor component) and another (**8**) (major) that had a lower R_f than **9**. 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 **8**, yield 0.25 g (19%), mp 150 °C; ^{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, **9** was formed exclusively.)

Diethyl 2-Benzylamino-2-[*N*-(1-benzyl-5-nitroimidazolyl-4-carbonyl)amino]malonate (14)

Compound **6**[1c] (1.0 g, 2.47 mmol) was added to a stirred solution of NaH (60%) (200 mg, 5.0 mmol) in dry THF at -78 °C, followed by the addition of bromine (0.25 mL, 4.3 mmol). It was stirred for 10 minutes, and a solution of benzylamine (0.4 mL, 3.6 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred for an additional hour, and was slowly brought to room temperature. The solvents were evaporated on a rotary evaporator under reduced pressure, and the residue was taken in 50 mL of water. The pH of the solution was adjusted to 7, and it was extracted with chloroform (2 x 125 mL). The combined organic extracts were successively washed with dilute hydrochloric acid and water, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated to dryness. The residue was triturated with ether when an off-white solid separated. The solid was filtered and dried, yield 0.83 g (66%), mp 100-101 °C; ^{1}H NMR (DMSO-d_6): δ 9.09 (s, 1H, exchangeable with deuterium oxide, NH), 8.2 (s, 1H, imidazole CH), 7.40-7.10 (m, 10H, 2 x Ph-H), 5.54 (s, 2H, benzyl CH_2), 4.14 (q, J = 7.0 Hz, 4H, two ester CH_2), 3.65 (d, J = 6.6 Hz, $C\underline{H}_2NH$), 3.36 (t, J = 6.6 Hz, 1H, exchangeable with deuterium oxide, NH), 1.14 (t, J = 7.0 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{25}H_{27}N_5O_7$: C, 58.92; H, 5.34; N, 13.74. Found: C, 59.02; H, 5.36; N, 13.77.

Diethyl 2-Benzylamino-2-[*N*-(5-amino-1-benzylimidazolyl-4-carbonyl)amino]malonate (15)

A mixture of **14** (1.0 g, 1.9 mmol) and Pd-C (10%) (100 mg) in absolute methanol (100 mL) was hydrogenated in a Parr hydogenator at 40 psi for 35 minutes. The reaction mixture was filtered through Celite, and

the filtrate evaporated to dryness on a rotary evaporator. The residual semi-solid was triturated with ether to obtain a white solid. The solid was filtered and dried, yield 0.74 g (79%), mp 121-123 °C; ^{1}H NMR (DMSO-d_6): δ 7.85 (s, 1H, imidazole CH), 7.37-7.19 (m, 11H, 2 x Ph-H + NH), 5.96 (s, 2H, exchangeable with deuterium oxide, NH_2), 5.08 (s, 2H, benzyl CH_2), 4.10 (q, J = 7.0 Hz, 4H, two ester CH_2), 3.55 (d, J = 6.0 Hz, $C\underline{H}_2NH$), 3.20 (m, 1H, exchangeable with deuterium oxide, $N\underline{H}CH_2$), 1.10 (t, J = 7.0 Hz, 6H, two ester CH_3).

Anal. Calcd. for $C_{25}H_{29}N_5O_5$: C, 62.61; H, 6.09; N, 14.60. Found: C, 62.47; H, 6.12; N, 14.57.

6-Amino-6-methoxycarbonyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (18) and 6-Methoxy-6-methoxycarbonyl-4,5,7,8-tetrahydro-6*H*-imidazo[4,5-*e*][1,4]diazepine-5,8-dione (19)

To a solution of sodium methoxide, freshly prepared by dissolving sodium metal (368 mg, 16 mg.atom) in methanol (25 mL), was added **15** (2.0 g, 4.1 mmol), when the color of the reaction mixture changed to dark brown. The mixture was heated to reflux for 2.5 hours. It was cooled, the pH adjusted to 7.5 with 1N HCl, and was evaporated to dryness on a rotary evaporator. The residue was suspended in glacial acetic acid (50 mL), and 20% $Pd(OH)_2$-C (250 mg) was added. The mixture was hydrogenated in a Parr hydrogenator for 18 hours. The reaction mixture was filtered through Celite, and the filtrate evaporated to dryness. The residue was purified by flash chromatography on a silica gel column, eluting first with a mixture of chloroform-methanol (6:1) to collect the faster moving **19**, recrystallized from MeOH-H_2O, mp >280 °C; ^{1}H NMR (DMSO-d_6) δ 12.97 (br s, 1H, exchangeable with D_2O, NH), 11.36 (br s, 1 H, exchangeable with deuterium oxide, NH), 8.66 (s, 1H, exchangeable with deuterium oxide, NH), 7.70 (s, 1H, imidazole CH), 3.73 (s, 3H, CO_2Me), 3.08 (s, 3H, OMe); MS (EI, 70 e*V*) *m/z* 254 (M^+).

Further elution of the column with a mixture of chloroform-methanol (4:1) afforded the slower moving **18**, recrystallized from MeOH as white

rhombic crystals, mp: sinters at 196 °C and decomposes at 203 °C; ^{1}H NMR (DMSO-d_6) δ 12.93 (br s, 1H, exchangeable with deuterium oxide, NH), 11.13 (br s, 1H, exchangeable with deuterium oxide, NH), 7.83 (s, 1H, exchangeable with deuterium oxide, NH), 7.67 (s, 1H, imidazole CH), 3.4 (s, 3H, CO_2Me), 3.0 (s, 2H, exchangeable with deuterium oxide, NH_2); MS (EI, 70 eV) m/z 239 (M^+).

Anal. Calcd. for $C_8H_9N_5O_4$: C, 40.17; H, 3.78; N, 29.27. Found: C, 40.06; H, 3.74; N, 29.15.

Single-Crystal X-ray Diffraction Analysis of 8

Suitable crystals were grown through slow crystallization from EtOH. The unit cell dimensions were obtained by a least-squares fit of the angles of 24 accurately centered reflections in the range of 19° <2Θ <30°. Intensity data were collected in the range of 3.5° <2Θ <42° at -43 °C, using graphite monochromated Mo Kα (λ = 0.71073 Å) radiation. The scan was θ/2θ, 3156 reflections were collected with 2848 unique with R_{int} = 0.014. Three standard reflections monitored after every 150 reflections did not show any significant change in intensity during data collection. Intensities were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using the program package SHELXTL-PLUS.[5] Full-matrix least-squares refinements were performed. Neutral atom scattering factors and anomalous scattering correction terms were taken from the International Tables for X-ray Crystallography.[6] Hydrogen atoms were located on DF maps and refined at fixed isotropic temperature factors (U = 0.08 Å^2). The weight had the form $\omega = [\sigma^2(F_o) + 0.0006(F_o)^2]^{-1}$. The final cycles of refinement converged at $R = \Sigma||F_o| - |Fc||/\Sigma|F_o| = 0.042$, $\omega R = [\Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega(F_o)^2]^{1/2} = 0.054$, GOF = 1.79 for 2162 observed [$I > 3.0\sigma(I)$] reflections. Maximum and minimum residuals, 0.29 and -0.30e/Å^3, respectively, were shown on the final difference Fourier maps. The final atomic coordinates and bond lengths/bond angles are collected in **Tables I** and **II**, respectively.

Crystallographic Data for **8**: $C_{23}H_{27}N_5O_{10}$, FW = 533.5, space group $P2_{1/c}$, a = 13.076 (3) Å, b = 14.131 (3) Å, c = 14.821 (3) Å, β = 105.91° (2), V = 2634 (1) Å^3, μ_{calcd} = 1.00 cm^{-1}. Final R = 4.2%, R_w = 5.4% for 2162 observed [$I \geq 3\sigma(I)$] reflections.

Supplementary Material Available

Anisotropic displacement coefficients, H-atom coordinates with isotropic displacement coefficients and the calculated and observed structure factors for **8** are available from the authors upon request.

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