δ 3.60 (s, 3 H), 3.90 (s, 3 H), 5.65 (s, 2 H, $ArCH_2$), 6.20 (s, 2 H, vinyl), 7.35–7.95 (br m, 5 H, aromatic), 8.45 (s, 1 H, aromatic); MS, *m/z* 328.0947 (calcd), 328.0969 (found). Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 66.01; H, 4.92.

The same product **20** was identified by NMR, again as the major component, when the reaction was carried out in refluxing benzene. No indication of Diels–Alder adduct formation was seen in the spectra of crude reaction mixtures.

Further evidence of structure was obtained by saponifying **20** with KOH in CH_3OH; when the resulting solution was diluted with water and acidified, naphthalide **6** was obtained in 91% yield.

(b) Acetate 21. The reaction of **9** with acetic acid was observed in attempts to form cycloadducts with DMAD and AAN. Thus **9** (R = Me; 35 mg, 0.13 mmol), DMAD (0.24 mmol), and acetic acid (0.13 mmol) were refluxed in 1.5 mL of toluene for 50 h. The crude reaction mixture after vacuum evaporation showed by NMR the presence of lactone **6** and diester **21**, in approximately a 2/1 ratio. Chromatography on silica gel with a graded pentane–CH_2Cl_2 solvent gave **21**, which was recrystallized from hexane: mp 82–83 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR δ 2.10 (s, 3 H), 3.90 (s, 3 H), 5.60 (s, 2 H), 7.35–7.95 (m, 5 H), 8.50 (s, 1 H, aromatic); MS, *m/z* (relative intensity) 258 (M^+, 8), 215 (24), 183 (100). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.86; H, 5.61.

(c) Mesitoate 22. This product was detected by NMR in attempts to form a cycloadduct from **9** with DMAD by using mesitoic acid as a catalyst. To prepare a sample for subsequent use, a reaction was carried out with no dienophile present; **9** (R = Et; 50 mg, 0.19 mmol) and 0.19 mmol of mesitoic acid were refluxed for 1 h in chlorobenzene (no **9** remaining by NMR). The crude product consisted of **6** and **22** in a ratio of ca. 1/2. After removal of most of the lactone by trituration, the residue was recrystallized from $CHCl_3$–hexane to give pure **22**: mp 63–64 °C; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR (CCl_4) δ 1.40 (t, *J* = 7 Hz, 3 H), 2.25 (s, 9 H, mesitoate CH_3 protons), 4.30 (q, *J* = 7 Hz 2 H), 5.70 (s, 2 H), 6.65 (s, 2 H, mesitoate aromatic), 7.25–7.90 (m, 5 H), 8.35 (s, 1 H, aromatic); MS, *m/z* (relative intensity) 229 (50), 184 (58), 147 (100). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.37; H, 6.69.

Diester 23. Ortho ester **4** (R = Et; 50 mg, 0.24 mmol) and 0.24 mmol of mesitoic acid were heated in refluxing chlorobenzene for 0.5 h, and the solvent was then vacuum evaporated. Phthalide and **23** were formed in a ca. 1/3 ratio. Recrystallization from hexane gave pure **23**: mp 77–78 °C; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ 1.35 (t, *J* = 7 Hz, 3 H), 2.25 (s, 9 H), 4.30 (q, *J* = 7 Hz, 2 H), 5.70 (s, 2 H), 6.75 (s, 2 H), 7.1–8.0 (m, 4 H); MS, *m/z* (relative intensity) 326 (M^+,2), 147 (100), 135 (32). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.72; H, 6.88.

Amine Tetrafluoborate Salts. Commercial (Alfa) tetrafluoboric acid (62%) in ether was diluted 20-fold with anhydrous ether, and an equivalent amount of the amine (pyridine, 2,6-di-*tert*-butylpyridine, ethyldiisopropylamine) was added slowly by syringe with ice-bath cooling under nitrogen. The white crystalline precipitates were filtered and washed several times with ether in a drybox. These salts have limited solubility in chlorobenzene at room temperature but dissolve on heating.

Deuterium Analyses. A standard reference solution was prepared by dissolving 8.0 μL of cyclohexane-d_{12} in 60 mL of CCl_4. The density of perdeuteriocyclohexane (0.89) was assumed to be that of cyclohexane (0.778) corrected by the ratio of molecular weights. This solution thus contained 1.5 × 10^{-5} mol of deuterium/mL, with the reference ^2H signal appearing at 1.385 ppm. For most samples examined, the solution was used directly, while for others appropriate dilutions were used to give comparable sample/reference peak sizes. The samples, after treatment as described in the text, were evaporated to constant weight and taken up in a measured volume, usually 2.0 mL, of the reference solvent. The ^2H singlets (proton decoupled) appeared as follows: for acetal **2** (R = Me), 6.10 (acetal), 5.10 (methylene D presumed trans to methoxy), and 4.94 ppm (methylene D presumed cis to methoxy), based on assumed W coupling in the proton spectrum of undeuterated material;[8] for **18**, 5.01 ppm; for **19**, 5.07 ppm. These chemical shifts all are in good agreement with those of the corresponding protons in the ^1H NMR spectra.

Acknowledgment. Support by a grant from the University of California Cancer Research Coordinating Committee is gratefully acknowledged. We thank Prof. J. T. Gerig and Allan Kerschaw for their help in obtaining ^2H NMR spectra on an instrument partly funded by NSF, Jaime Cornejo for a careful reading of the manuscript, and Dr. Hugh Webb for obtaining mass spectra.

Registry No. 1, 268-51-9; **2E**, 75802-19-6; **2M**, 67536-29-2; **4E**, 70103-17-2; **6**, 4711-50-6; **8E**, 85827-93-6; **8M**, 85827-94-7; **9E**, 85827-95-8; **9M**, 85828-02-0; *endo*-**10**, 85827-96-9; *exo*-**10**, 85880-59-7; 11, 85827-97-0; *endo*-**12**, 85827-98-1; *exo*-**12**, 85880-60-0; *endo*-**13**, 85827-99-2; *exo*-**13**, 85880-61-1; 14, 85880-62-2; **15**, 85828-00-8; *endo*-**16**, 85880-64-4; *exo*-**16**, 85880-63-3; **20**, 85828-03-1; 21, 85849-60-1; **22**, 85828-04-2; **23**, 85828-05-3; MA, 108-31-6; DMAD, 762-42-5; BL, 497-23-4; AAN, 3061-65-2; NB, 498-66-8; cyclohexene, 110-83-8; dimethyl 1,4-dihydro-1,4-oxy-2,3-naphthalenedicarboxylate, 85828-01-9; mesitoic acid, 480-63-7.

Selective Reductions of 3-Substituted Hydantoins to 4-Hydroxy-2-imidazolidinones and Vicinal Diamines[1]

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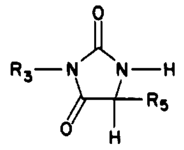
Received October 20, 1982

N^3-Substituted hydantoins (1) have been shown to undergo $LiAlH_4$ reduction (THF, room temperature, 2 days) to give 4-hydroxy-2-imidazolidinones (**3**) in good yields. Reduction of 3,5-disubstituted hydantoins in which an aliphatic substituent was present at nitrogen 3 led to the preferential formation of the cis adduct **3**. Conversely, disubstituted hydantoins possessing an aryl moiety at nitrogen 3 gave the trans derivative **3** as the major product. Treatment of the N^3-substituted hydantoins (**1**) under more vigorous conditions (THF, reflux, 3 days) led to selective ring opening of **1** to yield *N*-methylethylenediamines (**7**). The scope of both of these reductive processes has been explored, and explanations are offered to account for the observed results. Full spectral (infrared, ^1H and ^{13}C NMR, and mass spectra) data on all three classes of compounds (**1**, **3**, and **7**) have been collected. Together this information provides a consistent data set which is useful in structure elucidation. Moreover, various NMR aids have been discerned for the isomeric *cis*- and *trans*-4-hydroxy-2-imidazolidinones (**3**) which permitted stereochemical assignments for these compounds.

Hydantoins (**1**, Chart I) are important medicinal and synthetic compounds.[3] Although much is known about their chemical reactivity, surprisingly little is known about their reactions with hydride reducing agents.[4-7] Lithium

Table I. Summary of Selected Physical and Spectral Properties of Substituted Hydantoins 1

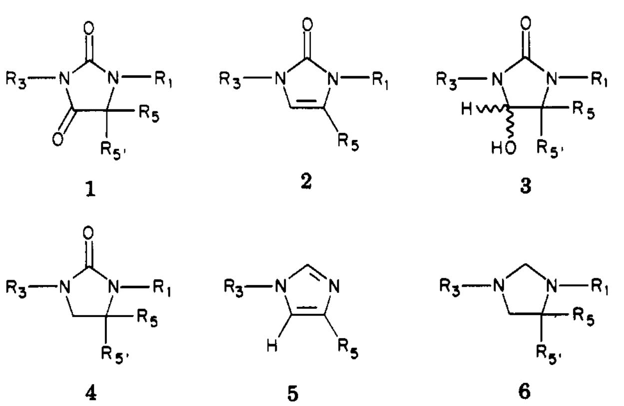


1

					^{1}H NMR[c]			^{13}C NMR[d]		
no.	R_3	R_5	mp,[a] °C	IR[b] (C=O)	R^3	C^5-H	R^5	C^2=O	C^4=O	C^5
1a	H	H	221–223[e]	1780, 1700[f]		3.89 (s)		159.0 (s)	174.4 (s)	47.7 (t, 145)
1b	H	CH_3	148–150[g]	1730, 1690		3.97 (q, 7)	1.33 (d, 7)	156.9 (s)	175.9 (s)	53.1 (d, 144)
1c	H	Ph	181–182[h]	1770, 1730		5.15 (d, 1)	7.37 (s)	157.5 (s)	174.2 (s)	61.2 (d, 148)
1d	CH_3	H	181–183[i]	1770, 1720	2.97 (s)	3.87 (s)		157.7 (s)	172.0 (s)	45.9 (t, 147)[j]
1e	CH_3	CH_3	110–112[k]	1790, 1730	3.03 (s)[l]	4.09 (dq, 7, 1)	1.47 (d, 7)	157.8 (s)[l]	174.8 (s)	52.9 (d, 144)
1f	CH_3	Ph	162–164[m]	1780, 1720	2.98 (s)	5.00 (s)	7.37 (s)	157.0 (s)	172.0 (s)	60.0 (d, 145)
1g	Bn[n]	H	139–140[o]	1770, 1720	4.63 (s)[l,p]	3.90 (s)		158.3 (s)[l]	171.0 (s)	46.4 (t, 146)
1h	Bn[n]	CH_3	113–115[q]	1770, 1725	4.52 (s)[p]	4.17 (q, 7)	1.26 (d, 7)	157.4 (s)[l]	174.4 (s)	52.8 (d, 145)
1i	Bn[n]	Ph	171–173[r]	1770, 1715	4.58 (s)[s]	5.30 (s)	7.38 (s)[t]	156.6 (s)	171.7 (s)	60.1 (d, 145)
1j	Ph	H	155–156[u]	1775, 1720	7.40 (s)	4.02 (s)		158.7 (s)[v]	172.8 (s)	47.6 (t, 147)
1k	Ph	CH_3	169–170[w]	1780, 1720	7.40 (s)	4.13 (q, 7)	1.47 (d, 7)	155.2 (s)	174.0 (s)	52.0 (d, 146)
1l	Ph	Ph	192–193[x]	1790, 1725	7.39 (s)	5.15 (s)	7.39 (s)	156.6 (s)	171.5 (s)	59.9 (d, 148)

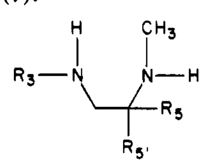
[a] Melting points are uncorrected. [b] Infrared peak positions recorded in reciprocal centimeters vs. the 1601-cm^{-1} band in polystyrene and were taken in KBr disks. [c] ^{1}H NMR spectrum were taken in Me_2SO-d_6 or Me_2SO-d_6-$CDCl_3$ unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si, followed by the multiplicity of the signal, followed by the coupling constant(s) in hertz. [d] The solvent used was Me_2SO-d_6 or Me_2SO-d_6-$CDCl_3$ unless otherwise indicated. The initial number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si, followed by the multiplicity of the signal and the coupling constant in hertz. [e] Compound obtained from Aldrich Chemical Co. [f] Data taken from: Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Co: Milwaukee, WI, 1978; p 424. [g] Lit.[10a] mp 150–152 °C. [h] Lit.[10b] mp 180 °C. [i] Lit.[10c] mp 181–182 °C. [j] The coupling constants were obtained from a spectrum taken in CD_3CN. [k] Lit.[10d] mp 110–113 °C. [l] Spectrum taken in $CDCl_3$. [m] Lit.[10b] mp 162–163 °C. [n] Bn = benzyl. [o] Lit.[10a] mp 140–141 °C. [p] The assignment reported is for the methylene moiety of the benzyl group. The aromatic signal was observed at δ 7.27 (s). [q] Lit.[10a] mp 112–114 °C. [r] Lit.[10e] mp 170–173 °C. [s] The assignment reported is for the methylene moiety of the benzyl group. The aromatic signal was observed at δ 7.30 (s). [t] The assignments for the two sets of aromatic protons present in this compound are tentative and may be reversed. [u] Lit.[10a] mp 154–155 °C. [v] Spectrum taken in CD_3NO_2. [w] Lit.[10f] mp 170.5–171.5 °C. [x] Lit.[10b] mp 189 °C.

Chart I



aluminum hydride ($LiAlH_4$) reductions[8] of hydantoins (1) have been reported to yield a variety of products. Earlier studies have indicated that imidazolones 2[4] and 4-hydroxy-2-imidazolidinones 3[6,9] were formed from room-temperature reductions, while use of slightly more vigorous conditions (reflux, ether or THF) gave 4-hydroxy-2-imidazolidinones (3),[6] 2-imidazolidinones (4)[5,6] imidazoles (5),[4] and imidazolidines (6).[4]

In light of previous findings, we were surprised to observe that 3-substituted hydantoins (1, R_1 = H) cleanly underwent reduction at room temperature to give synthetically useful yields of 4-hydroxy-2-imidazolidinones (3, R_1 = H), while more vigorous conditions (reflux, THF) led to selective ring opening of 1 to produce N-methylethylenediamines (7).



7

In this paper, we outline the synthetic methods adopted in our studies, define the scope of these processes, and describe key spectral properties observed for all three classes of compounds examined (1, 3, and 7).

Results and Discussion

Nine representative examples of 3-substituted hydantoins[10] (1d–l, Table I) were selected for reduction with

(1) Presented, in part, at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, Apr 1982, Abstract ORGN 204.

(2) Alfred P. Sloan Foundation, 1977–1981. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977–1982.

(3) *Kirk-Othmer Encycl. Chem. Technol., 3rd Ed.*, **1978**, *12*, 692–711. Ware, E. *Chem. Rev.* **1950**, *46*, 403–470.

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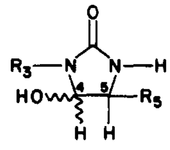
(8) Reduction of 3-substituted hydantoins 1 with bis(2-methoxyethoxy)aluminum hydride at room temperature (THF) has been reported to yield 2[7] and 3,[6] while the 2-imidazolidinone 4 was obtained under reflux conditions.[6]

(9) Numbering for 3 conforms to that used for the starting hydantoins 1 in an effort to facilitate the comparison of these two classes of compounds.

Table II. Summary of Selected Physical and Spectral Properties of 3-Substituted 4-Hydroxy-2-imidazolidinones (3)[a]

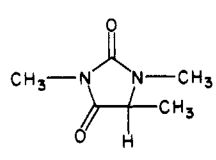


3

no.	R_3	R_5	yield,[b] %	mp,[c] °C	IR,[d] (C=O)	^{1}H NMR[e] C^4-H	C^5-H$_a$	C^5-H$_b$	^{13}C NMR[f] C^4	C^5
3d	CH_3	H	78 (56)	90-92[g]	1690	5.03 (dd, 7, 3)	2.97 (dd, 10, 3)	3.44 (dd, 10, 7)	80.3	46.5
cis-3e[h]	CH_3	CH_3	78 (62)[i,j]	113-114	1690	4.82 (dd, 7, 7)		3.57 (qd, 7, 7)	81.9 (d, 165)	49.8 (d, 140)
trans-3e[k]	CH_3	CH_3		*l*	*l*	4.48 (dd, 7, 3)	3.21 (qd, 6, 3)		87.3 (d, 161)	53.8 (d, 143)
3f[h]	CH_3	Ph	94 (46)	227 dec[m]	1695	5.05 (dd, 7, 6)		4.65 (d, 6)	82.1	58.8
3g	Bn[n]	H	80 (65)	126-128[o]	1690	5.02 (ddd, 7, 7, 3)	3.17 (dd, 10, 3)	3.52 (dd, 10, 7)	78.0 (d, 164)	46.7 (d, 142)
cis-3h[h]	Bn[n]	CH_3	92 (71)[i,p]	123-125	1690	4.75 (br t, 6)		3.61 (qd, 7, 6)	79.5 (d, 164)	49.9 (d, 140)
trans-3h[k]	Bn[n]	CH_3		*l*	*l*	*l*	*l*		84.7 (d, 160)	53.9 (d, 146)
3i[h]	Bn[n]	Ph	75 (50)	257 dec[q]	1680	5.00 (br d, 6)		4.75 (d, 6)	79.8 (d, 168)	58.9 (d, 141)
3j	Ph	H	66 (56)	112-114[r]	1700	5.60 (m, 8, 7, 2)	3.27 (m, 10, 2)	3.67 (dd, 10, 7)	79.4	46.6
cis-3k[h]	Ph	CH_3	89 (46)[s,t]	140-143	1715	5.60 (dd, 9, 6)[u]		3.92 (qd, 7, 6)	82.9 (d, 166)[u]	51.2 (d, 140)
trans-3k[k]	Ph	CH_3		104-107	1695	5.05 (dd, 9, 2)	3.47 (qd, 7, 2)		87.5 (d, 170)[u]	55.2 (d, 145)
3l[k]	Ph	Ph	95 (67)	173-176[v]	1685	5.27 (dd, 8, 2)	4.53 (m, 2)		87.0 (d, 165)	61.7 (d, 143)

[a] All reductions were performed in THF at room temperature for 2 days by using 4 equiv of hydride. The $LiAlH_4$-THF solution was filtered and titrated prior to use. [b] Yields based upon NMR analysis. Numbers in parentheses are purified yields. [c] Melting points are uncorrected. [d] Infrared peak positions are recorded in reciprocal centimeters vs. the 1601-cm^{-1} band in polystyrene and were taken in KBr disks. [e] ^{1}H NMR spectrum were taken in Me_2SO-d_6 or Me_2SO-d_6-$CDCl_3$ unless otherwise indicated. The number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si, followed by the multiplicity of the signal, followed by the coupling constant(s) in hertz. [f] The solvent used was Me_2SO-d_6 unless otherwise indicated. The initial number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si, followed by the multiplicity of the signal and the coupling constant in hertz when available. [g] Mol wt 116.0587 (calcd for $C_4H_8N_2O_2$, 116.0586). [h] The values reported are for the cis isomer. [i] NMR analysis of the crude product mixture indicated an approximate cis to trans ratio of 1.5:1. [j] Mol wt (mixture) 130.0746 (calcd for $C_5H_{10}N_2O_2$, 130.0742). [k] The values reported are for the trans isomer. [l] The material isolated was not sufficiently pure to permit acquisition of this information. [m] Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.52; H, 6.22; N, 14.63. [n] Bn = benzyl. [o] Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.33; H, 6.18; N, 14.66. [p] Anal. Calcd for $C_{11}H_{14}N_2O_2$ (mixture): C, 64.06; H, 6.84; N, 13.58. Found: C, 64.08; H, 6.78; N, 13.68. [q] Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.52; H, 5.94; N, 10.50. [r] Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.51; H, 5.65; N, 15.76. [s] NMR analysis of the crude product mixture indicated an approximate cis to trans ratio of 0.5:1. Anal. Calcd for $C_{10}H_{12}N_2O_2$ (mixture): C, 62.48; H, 6.29; N, 14.58. Found: C, 62.40; H, 6.23; N, 14.45. [u] NMR spectrum taken in acetone-d_6. [v] Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.69; H, 5.48; N, 10.88.

$LiAlH_4$. These compounds differed principally in the types of substituents (i.e., alkyl, aryl) present at both the 3- and 5-positions of the hydantoin ring. In addition, we have examined the reactivity of 5-methyl-[10a] (**1b**), 5-phenyl- (**1c**),[10b] and 1,3,5-trimethylhydantoin (**1m**).



1m

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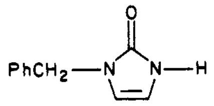
Room-Temperature Reductions. Treatment of each of the 3-substituted hydantoins listed in Table I with 4 equiv of hydride ion in THF at room temperature (2 days) gave, upon workup, moderate yields of **3** (Table II). The reactions were run for 2 days in all cases for consistency. In most instances, however, reduction was essentially complete in a few hours and was accompanied by the formation of a copious white precipitate.[11] The 4-hydroxy adducts **3** obtained were stable under neutral conditions but underwent rapid dehydration in the presence of trifluoroacetic acid to give the corresponding imidazolone **2** (i.e., **3g** → **2g**[12]). This latter observation may explain why the 2-imidazolone derivatives (**2**) and not the 4-hydroxy-2-imidazolidinone adducts (**3**) were isolated in previous

(11) For example, reductions of **1e** and **1l** for 18 h gave **3e** and **3l** in 24% ad 57% purified yields, respectively.

(12) Novák, J. J. K. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1511–1519.

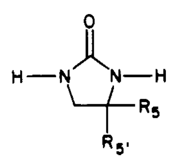


2g

studies.[4,7] In this regard, use of HCl in place of NaOH in the destruction of the excess $LiAlH_4$ in the reduction of **1g** led to the formation of imidazolone **2g**.

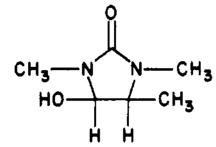
Additional information concerning the room-temperature reduction process was obtained by comparison of the cis to trans ratio of the diastereomeric 4-hydroxy-2-imidazolidinones (**3**) obtained from 3,5-disubstituted hydantoins. Consistent stereochemical trends were observed. Substrates containing an alkyl group at nitrogen 3 gave predominantly the cis adducts **3** (i.e., from hydantoins **1f** and **1i**) or an approximate 1.5:1 mixture of the cis and trans diastereomers **3**, respectively (i.e., from hydantoins **1e** and **1h**). Conversely, compounds bearing a phenyl substituent at nitrogen 3 (i.e., **1k** and **1l**) yielded the trans adduct **3** as the major product. A variety of potential explanations exist for these observations. In this regard, epimerization at carbon 5 in **3** is not a significant process either during the reaction or workup. $LiAlH_4$ reduction of both **1f** and **1l**, followed by destruction of the excess hydride with D_2O, gave no noticeable incorporation of deuterium at carbon 5 (^1H NMR analysis). It is noteworthy that both hydantoins examined contained a phenyl substituent at carbon 5, and the product obtained from **1f** was the cis diastereomer. Moreover, we have separated the diastereomers *cis*-**3k** and *trans*-**3k** and have independently resubjected both compounds to the reductive conditions. The reactions were quenched with D_2O and NaOD. The product mixture from both experiments contained the two diastereomers (*cis*-**3k** and *trans*-**3k**) in an approximate 1:4 ratio, and no deuterium incorporation was again observed at carbon 5. These results suggest that for hydantoins containing an alkyl group at nitrogen 3, the stereochemical outcome of the reduction product is dictated by the steric constraints imposed both by the hydride reagent and the carbon 5 substituent of the hydantoin (perferential cis formation). Hydantoins, however, that have an electron-withdrawing group at nitrogen 3 (i.e., phenyl) may epimerize[13] after reduction to give the thermodynamically most stable 4-hydroxy-2-imidazolidinone (**3**).

Successful reduction of **1** to **3** under the present conditions is dependent upon a substituent being present at nitrogen 3. Treatment of the N-3 unsubstituted hydantoins **1b**,**c** at both room and elevated temperatures gave only the corresponding 2-imidazolidinones **4**. This result is in agreement with the findings of Marshall.[5]

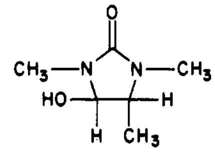


4b, $R_5 = CH_3$; $R_{5'} = H$[14]
c, $R_5 = Ph$; $R_{5'} = H$[15]

Conversely, reduction of the fully nitrogen-substituted hydantoin **1m** at room temperature gave as expected the *cis*-**3m** and *trans*-**3m** adducts in an 1:1 ratio (36% overall yield). The binary mixture was not separated. Treatment of **3m** with trifluoroacetic acid gave **2m**[16] in 52% yield. The cis isomer underwent dehydration more rapidly to **2m** than the trans derivative.



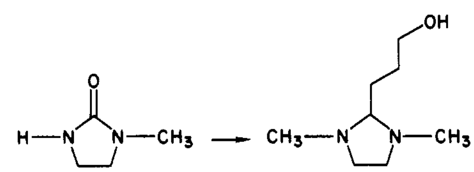
cis-3m



trans-3m

High-Temperature Reductions. Repetition of the reduction of the 3-substituted hydantoins **1d–l** under more vigorous conditions (THF reflux) gave principally ring opened *N*-methylethylenediamines[17] **7d–l** (Table III). The products **7** were all distillable liquids. Ring cleavage of **1** occurred selectively, leading to a vicinal diamine in which the initial N-3 substituent and the newly formed methyl group are attached to different nitrogen atoms. A comparable reductive cleavage of cyclic amidines has recently been reported.[18]

Additional information concerning the generality of this process stemmed from the reduction of **8** and **1m**. Treatment of **8** with $LiAlH_4$ in THF at reflux (4 days), followed by base workup, led to the isolation of a clear oil. The structure of this compound has been tentatively assigned as **9** on the basis of the ^1H and ^{13}C NMR and mass spectral properties.



8 9

The ^1H NMR spectrum exhibited a multiplet at δ 3.37–3.63 and a triplet at δ 3.75. These signals have been assigned to the methylene protons adjacent to the hydroxyl group and thd carbon-2 methine hydrogen of the ring, respectively. The *N*-methyl protons appeared as a singlet at δ 2.32. The proton-decoupled ^{13}C NMR spectrum for **9** gave a six-line pattern in agreement with the symmetry of this molecule. Key features in the mass spectrum of imidazoline **9** were the appearance of signals at m/e 157 and 99. These ions have been attributed to the P − H and P − C_3H_7O fragments. The elemental composition of these peaks have been verified by high-resolution mass spectrometry. Additional support for the proposed structure of **9** stemmed from the reactivity of this compound with dilute acid. Addition of $DCl-D_2O$ to a $CDCl_3$ solution of **9** led to the rapid formation of the dihydrochloride salt of **7d** (^1H and ^{13}C NMR analysis). The apparent reason for the involvement of the solvent, THF, in this reaction has not been fully ascertained.

Reduction of 1,3,5-trimethylhydantoin (**1m**) in refluxing THF (3 days) gave a complex mixture. Use of more moderate conditions (ether reflux, 3 days) afforded a clear oil. NMR analysis of the reaction product directly after the workup indicated the presence of essentially one compound. Attempted purification of this adduct by distil-

(13) One potential pathway is through a ring opening-ring closure process involving the N_3–C_4 bond. No definitive evidence in support of this mechanism has been obtained.

(14) McKennis, H., Jr.; du Vigneaud, V. *J. Am. Chem. Soc.* **1946**, *68*, 832–835.

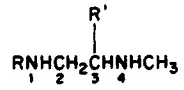
(15) Auterhoff, H.; Stierle, I. *Arch. Pharm. (Weinheim, Ger.)* **1970**, *303*, 237–242.

(16) Petersen, H. *Justus Liebigs Ann. Chem.* **1969**, *726*, 89–99.

(17) (a) Chambers, V. C., Jr.; Oberth, A. E. U.S. Patent 3026203 1962; *Chem., Abstr.* **1962**, *57*, P1791a. (b) Jukar, E.; Rissi, E. *Helv. Chim. Acta* **1962**, *45*, 2383–2402. (c) Kliegel, W.; Franckenstein, G. H. *Justus Liebigs Ann. Chem.* **1977**, 956–969. (d) Portoghese, P. L.; Larson, D. L. *J. Pharm. Sci.* **1962**, *51*, 1115–1116.

(18) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186–4194.

Table III. Summary of Selected Physical and Spectral Properties of *N*-Methylethylenediamines (7)[a]

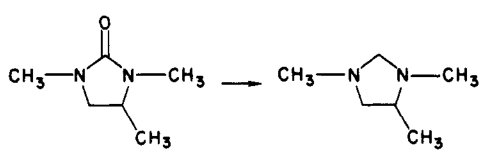


7

no.	R	R[1]	yield,[b] %	bp,[c] °C	[1]H NMR[d]			[13]C NMR[e]		
					C^2-H_aH_b	C^3-H	N^4-CH_3	C^2	C^3	N^4-CH_3
7d	CH_3	H	85	119[f]	2.68 (s)	2.68 (s)	2.42 (s)	51.3	51.3	36.4
7e	CH_3	CH_3	70	130[g]	2.30–2.80 (m)[h]	2.30–2.80 (m)[h]	2.42 (s)	57.6[i]	54.2	33.6
7f	CH_3	Ph	42	78–80 (0.2 torr)[j]	2.74 (d, 6)	3.59 (t, 6)	2.29 (s)	58.7	64.7	34.5
7g	Bn[k]	H	63	108–110 (0.2 torr)[l]	2.70 (s)	2.70 (s)	2.39 (s)	48.6	51.6	36.4
7h	Bn[k]	CH_3	60	102–104 (0.06 torr)[m]	2.54 (m)	2.20–2.90 (m)	2.37 (s)	55.1[n]	54.7	33.9
7i	Bn[k]	Ph	50	95–100 (0.002 torr)[o]	2.60–2.90 (m)	3.58 (m)	2.27 (s)	56.0	65.0	34.5
7j	Ph	H	54	66–70 (0.01 torr)[p]	3.00–3.30 (m)	2.70–2.90 (m)	2.42 (s)	43.2	50.8	36.2
7k	Ph	CH_3	70	76 (10.1 torr)[q]	2.23–3.30 (m)[h]	2.23–3.30 (m)[h]	2.43 (s)	49.0	53.9	33.6
7l	Ph	Ph	41	105–115 (0.05 torr)[r]	3.27 (m)	3.76 (m)	2.30 (s)	50.4	64.1	34.3

[a] All reductions were performed in THF under reflux conditions for 3 days by using 12 equiv of hydride. The $LiAlH_4$–THF solution was filtered and titrated prior to use. [b] Purified yields. [c] Boiling points are uncorrected. [d] [1]H NMR spectrum were run in $CDCl_3$. The number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si, followed by the multiplicity of the signal, followed by the coupling constant in hertz. [e] The number in each entry is the chemical shift value (δ) observed in parts per million relative to Me_4Si in $CDCl_3$. [f] Authentic comparison sample obtained from Aldrich Chemical Co.; bp 119 °C. [g] Lit.[17a] bp 128–129 °C; mol wt 102.1161 (calcd for $C_5H_{14}N_2$, 102.1157). [h] The range reported includes the two sets of protons C^2-H_aH_b and C^3-H. [i] The multiplicities in the proton-coupled spectrum are as follows: δ 57.6 (t, 132), 54.2 (d, 133), 33.6 (q, 136). [j] Anal. Calcd for $C_{10}H_{16}N_2$·2HCl: C, 50.64; H, 7.65; N, 11.81. Found: C, 50.31; H, 7.41; N, 11.54. [k] Bn = benzyl. [l] Lit.[17b] bp 79–80 °C (0.02 torr). Anal. Calcd for $C_{10}H_{16}N_2$·2HCl: C, 50.64; H, 7.65; N, 11.81. Found: C, 50.56; H, 7.52; N, 11.73. [m] Mol wt 178.1468 (calcd for $C_{11}H_{18}N_2$, 178.1470). [n] The multiplicities in the proton-coupled spectrum are as follows: δ 55.1 (t, 130), 54.7 (d, 135), 33.9 (q, 131). [o] Anal. Calcd for $C_{16}H_{20}N_2$·2HCl: C, 61.34; H, 7.03; N, 8.95. Found: C, 61.50; H, 7.06; N, 8.95. [p] Lit.[17c] bp 66 °C (0.01 torr). [q] Lit.[17d] 67–71 °C (0.1 torr); mol wt 164.1311 (calcd for $C_{10}H_{16}N_2$, 164.1313). [r] Mol wt 226.1475 (calcd for $C_{15}H_{18}N_2$, 226.1470).

lation led to extensive decomposition. The oil has been tentatively assigned structure **10**.[19] The [1]H NMR spec-



1m 10

trum revealed a pair of doublets (J = 5.5 Hz) centered at δ 3.17 and 3.65 and two singlets at δ 2.32 and 2.36. These signals have been assigned to the diastereotopic hydrogens at carbon 2 and the two different *N*-methyl groups, respectively, in **10**. The proton-decoupled [13]C NMR spectrum contained six major peaks in accord with the proposed structure. Characteristic signals were observed at 61.1, 62.9, and 80.7 ppm. In the corresponding coupled [13]C NMR spectrum doublet, triplet, and triplet patterns for these peaks, respectively, were centered at these signals. The chemical-ionization mass spectrum of **10** gave the expected P + 1 peak at m/e 114 (P), 113 (P − H), 72 (P − C_2H_4N), and 58 (P − C_3H_6N). The elemental compositions of these ions have been confirmed by high-resolution mass spectrometry. Addition of DCl–D_2O to a $CDCl_3$ solution of **10** led to the disappearance of the starting material. The observed [1]H and [13]C NMR spectra of the acid-promoted-reaction product are in agreement with the formation of the dihydrochloride salt of **7e**.

These results suggest that ring opening does not proceed efficiently to afford *N*-methylethylenediamines if the N-1 site in **1** is substituted and that 2-imidazolidinones **4** are not obligatory intermediates in the overall reduction of **1** to **7**. Finally, the corresponding imidazolidine **6** was not observed in any reduction beginning with an N-1-unsubstituted hydantoin[20] Noteworthily, the elemental analysis reported for compound **6**[4] is equally satisfactory for the corresponding *N*-methyl vicinal diamine **7**.

Spectral Studies

Mass Spectral Data. Each of the hydantoins[22] (**1**) and 4-hydroxy-2-imidazolidinones (**3**) exhibited a discernible parent ion in the mass spectrum (ionization voltage 70 eV; Tables IV and V in the supplementary material). The hydantoins also gave a reliable M − CO fragment. Similar observations have been previously noted and attributed to the loss of carbon monoxide at carbon 4 in **1**.[22] A significant ion corresponding to the expulsion of two carbon monoxide units[22a,c] was detected for the simple N-3-mo-

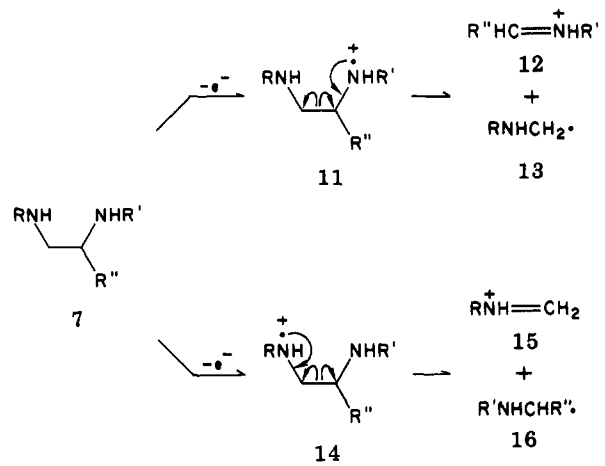
(19) It has not been determined whether **10** is produced directly in the reaction or by subsequent cyclization of the aminomethanol during workup.

(20) Bäckvall and Sharpless and co-workers have recently demonstrated that imidazolidines readily undergo reductive ring-opening with $LiAlH_4$.[21]

(21) Bäckvall, J. E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 1953–1957.

(22) For previous discussions on the mass spectra of hydantoins, see: (a) Corral, R. A.; Orazi, O. O.; Duffield, A. M.; Djerassi, C. *Org. Mass. Spectrom.* **1971**, *5*, 551–563. (b) Rücker, G.; Natarajan, P. N.; Fell, A. F. *Arch. Pharm. (Weinheim, Ger.)* **1971**, *304*, 883–893. (c) Suzuki, T.; Tuzimura, K. *Agric. Biol. Chem.* **1976**, *40*, 225–226. (d) Locock, R. A.; Coutts, R. T. *Org. Mass Spectrom.* **1970**, *3*, 735–745.

Scheme I



nosubstituted derivatives **1d** and **1j** but not for the remaining compounds listed in Table I. Correspondingly, a characteristic fragmentation pattern noted for the 4-hydroxy-2-imidazolidinones (**3**) was the loss of water from the molecular ion. The *N*-methylethylenediamines did not uniformly exhibit a parent ion in the mass spectrum (Table VI in the supplementary material). In some instances (**7f,g,i,j**) the sample was introduced as the dihydrochloride salt. The dominant feature in all the spectra for **7** was the fragments **12** and **15** observed after α-cleavage of ions **11** and **14** respectively,[23] (Scheme I). The appearance of these signals provided strong support for the proposed N,N′-disubstitution pattern in **7** vs. the isomeric N,N-disubstituted derivative.

Infrared Spectral Data. Diagnostic infrared absorptions for both 3-substituted hydantoins (**1**) and 4-hydroxy-2-imidazolidinones (**3**) are incorporated in Tables I and II. A more complete compilation of the infrared spectra for these two classes of compounds appears in Tables VII and VIII of the supplementary material. The hydantoins (**1**) exhibited a pair of carbonyl absorptions at 1770–1790 and 1715–1730 cm^{-1}. Of these two signals, the lower energy absorption was generally more intense.[24] The urea carbonyl band for the 4-hydroxy-2-imidazolidinones (**3**) occurred between 1680 and 1715 cm^{-1}. This frequency range is lower in energy than that previously noted for 2-imidazolidinones.[25] The infrared spectra for the *N*-methyl diamines are as expected. Characteristic values for the N–H stretching and bending vibrations are listed in Table IX of the supplementary material.

Magnetic Resonance Data. **^{1}H NMR.** Key ^{1}H NMR data for the hydantoin derivatives (**1**), 4-hydroxy-2-imidazolidinones (**3**), and the *N*-methylethylenediamines (**7**) are recorded in Tables I–III, respectively. Tables X–XIII in the supplementary material contain a complete description of the ^{1}H NMR spectral data of these compounds.

The chemical shift values observed in the ^{1}H NMR for **1** are in agreement with the proposed structure.[26-28] We note that the N^3-phenyl resonance in **1** appeared as a singlet (ca. δ 7.40) in contast with the multiplet pattern observed for this group in the corresponding 4-hydroxy-2-imidazolidinones (**3**; ca. δ 6.80–7.83) and *N*-methylethylenediamines (**7**; ca. δ 6.40–7.50).

The composite NMR data set for 4-hydroxy-2-imidazolidinones (**3**) provided a series of informative trends which proved helpful in structure determination. First, the proton–proton coupling constants observed for the carbon 4 and carbon 5 hydrogens were larger for the cis compounds (J = 6–7 Hz) than for the trans derivatives (J = 2–3 Hz). These are expected values for a planar ring.[29] Second, introduction of a chiral center at carbon 4 in **3** led to the characteristic appearance of a doublet pattern ($J \approx 15$ Hz) for each of the diastereotopic benzylic protons in compounds **3g**, *cis*-**3h**, and **3i**. Third, the chemical shift values for comparable types of protons at carbons 4 or 5 in the cis adducts always appeared at lower field (0.32–0.55 ppm) than the corresponding resonances for the trans derivatives (i.e., compare *cis*-**3e** and *cis*-**3h** vs. *trans*-**3e**; *cis*-**3k** vs. *trans*-**3k**). We also noted an analogous but smaller downfield shift for the carbon-5 methyl hydrogens in *cis*-**3e** and *cis*-**3k** vs. the same group in *trans*-**3e** and *trans*-**3k**. This trend has been observed in a variety of cyclic systems.[30] Additional information concerning the origin of these patterns may possibly be gleaned from the analysis of the carbon-13 NMR data.

The ^{1}H NMR peak positions for the *N*-methyl vicinal diamines agree well with previous values.[28] Introduction of a phenyl group on the ethylene chain (carbon 3) adjacent to a *N*-methyl group led to a small upfield shift (ca. 0.10 ppm) in the value for this resonance. In those cases where the substituents at the nitrogen atom differed appreciably (i.e., **7j–l**), two distinct N–H absorptions were observed.[31]

^{13}C NMR. Carbon-13 NMR data proved to be of particular value in the assignment of structure for the 4-hydroxy-2-imidazolidinones (**3**) and *N*-methylethylenediamines (**7**). Tables I–III contain the chemical shift values for the key signals observed for compounds **1**, **3**, and **7**, respectively. A complete listing of these spectra is found in Tables XIII–XV of the supplementary material. A majority of the carbon atoms could be identified from correlation charts.[32-34] In many cases, the corresponding proton-coupled ^{13}C NMR spectrum was also taken.

The most distinguishing feature in the proton-decoupled ^{13}C NMR spectrum for **1** (Table I) was the regular appearance of two downfield signals between 155.2–159.0 and 171.0–075.9 ppm which have been attributed to the carbon 2 and carbon 4 signals, respectively.[34] Variation of the substituents on the hydantoin ring led to only small changes in the chemical shift values for these two resonances. We also noted in this data set a consistent downfield shift in the carbon 5 signal upon introduction

(23) For a discussion of the α-cleavage fragmentation of amines, see: McLafferty, F. W. "Interpretation of Mass Spectra", 2nd ed.; W. A. Benjamin: New York, 1973; pp 156–163.
(24) Various compilations and interpretations of the absorption bands in the infrared spectra of hydantoins have appeared. See: (a) Fayat, C.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1971**, 987–989. (b) Elliott, T. H.; Natarajan, P. N. *J. Pharm. Phamacol.* **1967**, *19*, 209–216. (c) Paul, W. A. S.; Demoen, P. J. A. *Bull. Soc. Chim. Belg.* **1966**, *75*, 524–538. (d) Horák, M.; Gut, J. *Collect. Czech. Chem. Commun.* **1961**, *26*, 1680–1693. (e) Derkosch, J. *Monatsh. Chem.* **1961**, *92*, 361–364.
(25) Kohn, H.; Cravey, M. J.; Arceneaux, J. H.; Cravey, R. L.; Willcott, M. R. III; *J. Org. Chem.* **1977**, *42*, 941–948.
(26) Corral, R. A.; Orazi, O. O. *Spectrochim. Acta* **1965**, *21*, 2119–2123.
(27) Suzuki, T.; Tomioka, T.; Tuzimura, K. *Can. J. Biochem.* **1977**, *55*, 521–527.
(28) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopyi in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1969; see in particular Part 3, p 159.
(29) Reference 28, p 286 and references therein.
(30) Reference 28, p 224, 228, 232, 235–236 and references therein.
(31) Fernandez, B.; Perillo, I.; Lamdan, S. *J. Chem. Soc., Perkin Trans. 2*, **1978**, *6*, 545–550.
(32) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972, and references cited therein.
(33) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972, and references therein.
(34) (a) Fujiwara, H.; Bose, A. K.; Manhas, M. S.; van der Veen, J. M. *J. Chem. Soc., Perkin Trans. 2*, **1980**, *11*, 1573–1577. (b) Poupaert, J. H.; Claesen, M.; Degelaen, J.; Dumont, P.; Toppet, S. *Bull. Soc. Chim. Belg.* **1977**, *86*, 465–472.

of either a methyl group ($\Delta \approx 5.8$ ppm) or a phenyl group ($\Delta \approx 13.4$ ppm) at this site.

Examination of the ^{13}C NMR spectra for the 4-hydroxy-2-imidazolidinones (**3**) revealed three prominent trends. First, the carbon 2 signal appeared between 157.0 and 160.8 ppm. This value lies between the chemical shift peak positions observed for the carbon 2 atom in hydantoins (**1**; 155.2–159.0 ppm) and simple 2-imidazolidinones (**4**; 163.8–165.0 ppm).[25,35] Second, the proton-coupled ^{13}C NMR spectrum for the carbon 5 methyl-substituted *trans*-4-hydroxy-2-imidazolidinones (*trans*-**3e**, *trans*-**3h**, and *trans*-**3k** exhibited a characteristic long-range coupling between the carbon 4 hydrogen and the carbon 5 methyl carbon atoms ($^3J_{CH} \approx 4.7$ Hz). We could not detect the corresponding coupling in the cis isomers (*cis*-**3e**, *cis*-**3h**, and *cis*-**3k**). This geometrical dependence on the magnitude of the three-bond C–H coupling constant is in accord with previous findings.[36] We have found this parameter to be a helpful structural aid. Third, introduction of a hydroxy moiety at carbon 4 led to the appearance of a diagnostic signal between 78.0 and 87.5 ppm for this carbon atom.

An additional feature present in this data set that proved useful in the assignment of stereochemistry became apparent upon comparison of the carbon-13 chemical shift values obtained for the isomeric *cis*- and *trans*-4-hydroxy adducts **3e**,**h**,**k**. The resonances for carbon 4 and 5 and the carbon 5 methyl substituent in the cis adducts always appeared at *higher* field than those in the trans compounds. The magnitude of this upfield shift was approximately 5.1, 4.0, and 5.8 ppm, respectively, for these three carbon atoms. The direction of these shifts is *opposite* to that previously discussed for the protons bound to these carbons. This inverse relationship as well as the magnitude of the effects suggest that the patterns observed for the cis adducts stem from electron density changes caused by sterically induced polarization. The juxtaposition of both the carbon 4 hydroxy group and the carbon 5 methyl substituent on the same side of the ring should lead to a steric interaction. Similar effects (i.e, gauche γ interactions) have been previously noted in sterically compressed systems.[37,38] Moreover, Faure has reported a comparable trend in the ^{13}C NMR chemical shift values for carbons 2 and 5 in substituted 1,3-diazole derivatives upon the introduction of successively larger alkyl groups at *nitrogen 1*.[39] Finally, we note that the chemical shift values for carbons 4 and 5 for the 4-hydroxy-2-imidazolidinones (**3**) in which only one isomer was observed are in accord with either the presence (i.e., **3f**,**1**) or absence (i.e., **3l**) of this effect.

Substitution at carbon-3 in the *N*-methylethylenediamines (**7**) led to predictable shifts in the carbon resonances for these compounds. Replacement of a hydrogen by a methyl group caused downfield shifts of approximately 3.0 and 6.2 ppm for carbons 3 and 2, respectively, and a 2.6-ppm upfield shift of the *N*-methyl group. Correspondingly, introduction of a phenyl group at carbon 3 led to a large downfield shift at carbon 3 ($\Delta \approx 13.4$ ppm), a downfield shift at carbon 2 ($\Delta \approx 7.3$ ppm), and an upfield shift at the *N*-methyl carbon ($\Delta \approx 1.9$ ppm). A similar shielding effect ($\Delta \approx 2.6$ ppm) was noted at carbon 2 upon exchange of a methyl group at nitrogen 1 for a benzyl moiety (i.e., compare **7d** vs. **7g**, **7e** vs. **7h** and **7f** vs. **7i**). The direction of these substituent effects on the value of the chemical shift is comparable to that reported for these groups in linear and branched alkanes.[40]

Conclusions

Simple synthetic routes have been developed for the preparation of both 4-hydroxy-2-imidazolidinones (**3**) and *N*-methylethylenediamaines (**7**). Moreover, the 4-hydroxy adducts **3** have proven to be versatile synthetic intermediates for the preparation of a variety of annelated imidazolidinones.[41] Together these procedures permit the synthesis of a wide range of normally inaccessible diamine-based substrates. This structural unit is of importance in light of the many natural products and medicinal agents which contain this moiety.

In connection with these studies, important spectral properties have been obtained for hydantoins (**1**), 4-hydroxy-2-imidazolidinones (**3**), and *N*-methylethylenediamines (**7**). This data should prove useful in deducing structure in more complex systems. In particular, a series of ^1H and ^{13}C NMR probes have been discerned in the 4-hydroxy-2-imidazolidinone series (**3**) which provided meaningful information concerning stereochemistry.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR-4250 spectrophotometer and calibrated against the 1601-cm^{-1} band of polystyrene. Absorption values are expressed in wave numbers (cm^{-1}), and the intensities are indicated by the symbols s (strong), m (medium), w (weak), br (broad), and sh (shoulder). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Models T-60, FT-80A, and XL-100-15 NMR spectrometers. The XL-100 was equipped with a Nicolet Technology Corp. TT-100 data system. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were run on Varian Associates Models FT-80A and XL-100 instruments. Chemical shifts are in parts per million (δ values) relative to Me_4Si, and coupling constants (J values) are in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), and m (multiplet). Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph-mass spectrometer. High-resolution (EI mode) mass spectra were performed by Dr. James Hudson at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. Tetrahydrofuran (THF) was predried over sodium wire and then distilled from $LiAlH_4$. All reactions requiring an inert gas atmosphere and anhydrous conditions were run under argon. The glassware was dried before use.

General Procedure for Room-Temperature Reductions of Hydantoins (1) to 4-Hydroxy-2-imidazolidinones (3). Completely anhydrous conditions[42] were maintained throughout this procedure due to the high reactivity of $LiAlH_4$ toward H_2O. The THF was distilled from $LiAlH_4$ immediately before use. All

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(39) Faure, R.; Assef, G. M.; Vincent, E. J., de Kimpe, N.; Verhe, R.; de Bruyck, L.; Schamp, N. *Chem. Scr.* **1980**, *15*, 193–195. Kister, J.; Hassanaly, P.; Faure, R.; Dou, H. *Spectrosc. Lett.* **1979**, *12*, 157–163. Faure, R.; Vincent, E.-J.; Assef, G.; Kister, J.; Metzger, J. *Org. Magn. Reson.* **1977**, *9*, 688–694. Assef, G.; Kister, J.; Metzger, J.; Faure, R.; Vincent E.-J. *Tetrahedron Lett.* **1976**, 3313–3316.
(40) Reference 36, p 37.
(41) Kohn, H.; Liao, Z. K. *J. Org. Chem.* **1982**, *47*, 2787–2789.
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liquid transfers were made with the aid of a long stainless steel tube (18 gauge) under Ar pressure.

To a rapidly stirred solution of the hydantoin (1) in THF (approximately 9 mg of 1/mL of THF) a THF solution containing an equimolar amount (4 equiv of hydride ion) of $LiAlH_4$ was slowly added. The $LiAlH_4$ solution[43] was titrated prior to use. Upon addition of the reducing agent the evolution of a gas was noted, followed by the formation of a white solid. The mixture was allowed to stir at room temperature (2 days) and then the excess hydride ion destroyed with $NaOH-H_2O$.[44] The inorganic material was filtered, and the remaining solution was dried (Na_2SO_4) and then concentrated in vacuo. Addition of Et_2O to the concentrated organic solution led to the precipitation of the desired 4-hydroxy adduct 3.

General Procedure for Reductions of Hydantoins (1) to the *N*-Methylethylenediamines (7). The preceding experimental procedure was employed by using a 3:1 molar ratio of $LiAlH_4$ to hydantoin (1). The reaction mixture was maintained at reflux for 3 days, and then the excess hydride ion was destroyed with $NaOH-H_2O$. The inorganic material was filtered, and the remaining solution was dried (Na_2SO_4), gently concentrated, and then distilled to give colorless 7.

Reduction of 3-Methyl-5-phenylhydantoin (1f) to 3-Methyl-4-hydroxy-5-phenyl-2-imidazolidinone (3f). NaOD-D_2O Workup. Compound **1f** (0.57 g, 3 mmol) was reduced according to the previously described room-temperature procedure. The excess $LiAlH_4$ was destroyed by using D_2O (0.25 mL) and a 15% NaOD solution in D_2O (0.1 mL). The inorganic materials were filtered off, and the organic layer was dried (Na_2SO_4) and then concentrated in vacuo. Analysis of the residue (0.56 g) by ^1H and ^{13}C NMR indicated no detectable incorporation of deuterium at carbons 4 and 5.

Reduction of 3,5-Diphenylhydantoin (1l) to 3,5-Diphenyl-4-hydroxy-2-imidazolidinone (3l). NaOD-D_2O Workup. The preceding experiment was repeated by using 2.00 g (8 mmol) of **1l**. After destruction of the excess $LiAlH_4$ with D_2O (1.9 mL) and a 15% NaOD solution in D_2O (0.4 mL) and the workup the crude residue (2.10 g) was examined by ^1H and ^{13}C NMR. No evidence for deuterium incorporation at carbons 4 and 5 were noted.

Epimerization Studies of 3-Phenyl-4-hydroxy-5-methyl-2-imidazolidinones (*cis*-3k and *trans*-3k). An isomeric mixture of *cis*-**3k** and *trans*-**3k** was prepared by using the room-temperature $LiAlH_4$ reductive procedure. The two diastereomers were fractionally recrystallized from $EtOH-Et_2O$. Each of these compounds [*cis*-**3k** (0.13 g, 0.68 mmol), *trans*-**3k** (0.38 g, 2.00 mmol)] was independently resubjected to the room-temperature reduction conditions for 1 day with an equimolar amount of $LiAlH_4$. The excess $LiAlH_4$ was destroyed by using D_2O (*cis*-**3k**, 1.3 mL; *trans*-**3k**, 1.4 mL) and a 15% NaOD solution in D_2O (*cis*-**3k** 0.3 mL; Trans-**3k**, 0.4 mL). The inorganic materials were filtered off, and the organic layer was dried (Na_2SO_4) and then concentrated in vacuo. Analysis of each of the reaction residues (*cis*-**3k**, 0.10 g; *trans*-**3k**, 0.36 g) by ^1H and ^{13}C NMR indicated the presence of both *trans*-**3k** and *cis*-**3k** in an approximate 4:1 ratio, respectively.

Preparation of 1,3,5-Trimethylhydantoin (1m). To an aqueous solution (300 mL) containing KOH (11.00 g, 0.20 mol) and *N*-methylalanine[45] (20.00 g, 0.20 mol), MeNCO (11.10 g, 0.20 mol) was added dropwise with vigorous stirring. After the addition was complete, the mixture was stirred for additional 30 min, acidified to pH ~2 with aqueous 5 N HCl and then concentrated to dryness in vacuo. The residue was dissolved in aqueous 5 N HCl (250 mL) and heated to reflux for 1 h. The solution was neutralized with saturated aqueous $KHCO_3$ and then extracted with CH_2Cl_2 (2 × 200 mL). The organic layers were combined, dried (Na_2SO_4), and then concentrated in vacuo. Distillation of the residue gave 18.75 g (68% yield) of purified **1m**: bp 84–85 °C (1.0 torr); IR (neat, NaCl) 2990, 2940, 1775, 1720, 1475, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 7 Hz, 3 H), 2.95 (s, 3 H), 3.00 (s, 3 H), 3.88 (q, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 15.5 (q, J = 130 Hz), 25.0 (q, J = 140 Hz), 27.8 (q, J = 140 Hz), 57.5 (d, J = 140 Hz), 156.3 (s), 173.5 (s) ppm; mass spectrum, m/e (relative intensity) 142 (100), 127 (96), 99 (3), 85 (33), 83 (47), 70 (6), 57 (15), 56 (17). Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.71; H, 7.19; N, 19.68.

Preparation of 1,3,5-Trimethyl-4-hydroxy-2-imidazolidinone (3m). The general procedure described for the room temperature reductions was employed by using 1,3,5-trimethylhydantoin (**1m**; 2.27 g, 16 mmol) in THF (250 mL) and a solution of $LiAlH_4$ in THF (0.99 M; 8.0 mL, 32 mmol of active hydride). The excess $LiAlH_4$ was destroyed by the successive addtion of H_2O (0.2 mL), 15% aqueous NaOH (0.2 mL), and H_2O (1.0 mL). The workup afforded a light yellow oil, which was purified by bulb-to-bulb distillation at 88–92 °C (0.05 torr) to give 0.94 g (41%) of the product as a 1:1 diastereomeric mixture (^1H NMR analysis). The following spectral data for the binary mixture were obtained: IR (neat, NaCl) 3320, 2980, 2940, 2880, 1690, 1500, 1450, 1410 cm^{-1}; mass spectrum, m/e (relative intensity) 144 (9), 129 (9), 127 (11), 126 (9), 112 (4), 111 (4), 86 (67), 84 (100), 72 (18), 58 (84); mol wt 144.0900 (calcd for $C_6H_{12}N_2O_2$, 144.0899). Selective proton–proton decoupling NMR experiments on 3m, as well as the addition of trifluoroacetic acid to the NMR sample, permitted the following tentative assignments for the cis and trans adducts. *cis*-1,3,5-Trimethyl-4-hydroxy-2-imidazolidinone (*cis*-**3m**): ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 6.1 Hz, 3 H), 2.69 (s, 3 H), 2.83 (s, 3 H), 3.39 (quin, J = 6.5 Hz, 1 H), 4.76 (br s, 1 H), 4.87 (d, J = 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 11.9 (d, J = 127 Hz), 27.5 (q, J = 138 Hz), 28.6 (q, J = 137 Hz), 56.6 (d, J = 137 Hz), 81.6 (d, J = 167 Hz), 160.8 (s) ppm. *trans*-1,3,5-Trimethyl-4-hydroxy-2-imidazolidinone (*trans*-**3m**): ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3 H), 2.74 (s, 3 H), 2.80 (s, 3 H), 3.28 (qd, J = 6.4, 2.9 Hz, 1 H), 4.53 (d, J = 2.9 Hz, 1 H), 4.76 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 16.7 (dd, J = 127, 4.8 Hz), 27.6 (q, J = 138 Hz), 28.1 (q, J = 138 Hz), 60.3 (d, J = 142 Hz), 86.5 (d, J = 160 Hz), 159.0 (s) ppm.

Preparation of 1,3,5-Trimethyl-2-imidazolone (2m). Compound **3m** was prepared as previously described and used without further purification. To a solution of **3m** (0.71 g, 4.93 mmol) in CH_2Cl_2 (60 mL) were added four drops of trifluoroacetic acid, and the solution was stirred (30 min) at room temperature. Evaporation of the solvent in vacuo afforded a yellow oil. Further purification by bulb-to-bulb distillation at 60–62 °C (0.03 torr) [lit.[16] bp 75–78 °C (0.2 torr)] gave 0.32 g (52%) of **2m** as a light yellow liquid: IR (neat, NaCl) 3140, 2960, 1690, 1640, 1470, 1450, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (d, J = 1.3 Hz, 3 H), 3.17 (s, 3 H), 3.19 (s, 3 H), 5.75–5.87 (m, 1 H); ^{13}C NMR ($CDCl_3$) 10.1, 27.3, 30.1, 107.3, 118.8, 153.8 ppm; mass spectrum, m/e (relative intensity) 126 (100), 111 (22), 97 (25), 85 (12), 56 (71).

Treatment of 1,3,5-Trimethylhydantoin (1m) with $LiAlH_4$ in Refluxing Et_2O. A THF solution of $LiAlH_4$ (0.99 M, 42.0 mL, 168 mmol of active hydride) was added dropwise to a stirred Et_2O solution (250 mL) of hydantoin **1m** (2.00 g, 14 mmol) under Ar. Upon addition of the $LiAlH_4$ solution, a white solid formed immediately and persisted through the reduction. Moreover, no significant amount of gas was evolved during the procedure. The mixture was allowed to stir at reflux for 3 days. The excess $LiAlH_4$ was destroyed by the successive addition of H_2O (0.8 mL), 15% aqueous NaOH (0.8 mL), and H_2O (2.5 mL). The inorganic precipitate was filtered off, the filtrate dried (Na_2SO_4), and the solvent gently evaporated. Further drying for a short period of time in vacuo afforded 1.75 g (87% recovery) of proposed **10**. Attempted distillation of this product at 35 °C (115 torr) led to decomposition of this material. The following properties were obtained on the crude reaction product: IR (neat, NaCl) 3300, 2980, 2950, 2850, 2790, 1460, 1380, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 5.9 Hz, 3 H), 2.32 (s, 3 H), 2.36 (s, 3 H), 2.43–3.10 (m, 3 H), 3.17 (d, J = 5.5 Hz, 1 H), 3.65 (d, J = 5.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 18.0 (q, J = 126 Hz), 39.4 (q, J = 133 Hz), 42.0 (q, J = 133 Hz), 61.1 (d, J = 137 Hz), 62.9 (t, J = 141 Hz), 80.7 (t, J = 143 Hz) ppm; mass spectrum, m/e (relative intensity) 113 (39), 111 (24), 97 (12), 86 (7), 72 (100), 58 (20), 56 (28); mol wt 114.1157 (calcd for $C_6H_{14}N_2$, 114.1157); mol wt of fragments 113.1082 (calcd for $C_6H_{13}N_2$, 113.1079), 72.0815 (calcd for $C_4H_{10}N$, 72.0813), 58.0659 (calcd for C_3H_8N, 58.0657).

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Compound **10** was dissolved in $CDCl_3$ (2 mL) and an equal volume of D_2O added. A 20% solution of DCl in D_2O was then added dropwise with shaking to acidify the mixture (pH ~2). The layers were separated, and the D_2O layer was concentrated to dryness. The following spectral properties were observed for a D_2O solution of the residue: ^1H NMR (D_2O, reference DSS) δ 1.47 (d J = 6.5 Hz, 3 H), 2.78 (s, 3 H), 2.82 (s, 3 H), 2.93–3.87 (m, 3 H); ^{13}C NMR (D_2O, reference DSS) 14.4 (q, J = 129 Hz), 30.9 (q, J = 144 Hz), 34.4 (q, J = 144 Hz), 50.4 (t, J = 143 Hz), 52.1 (d, J = 146 Hz) ppm; no significant signals were detected in the $CDCl_3$ layer; mass spectrum, m/e (relative intensity) 72 (26), 58 (100), 44 (25).

General Procedure for Reduction of 3-Unsubstituted Hydantoins (1) to 2-Imidazolidinones (4). An experimental procedure similar to that described for the preparation of **3** was utilized in these cases. A 2:1 molar ratio of $LiAlH_4$ to **1** was employed. After destruction of the excess $LiAlH_4$ and concentration of the organic layer to dryness, the residue was recrystallized from MeOH–Et_2O.

4-Methyl-2-imidazolidinone (4b): yield 20% [the reaction performed in THF at reflux temperatures (3 days) gave a 72% yield of **4b**]; mp 119–121 °C (lit.[14] mp 121–122 °C); IR (KBr) 3200, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, J = 6 Hz, 3 H), 3.05 (t, J = 7 Hz, 1 H), 3.60 (t, J = 8 Hz, 1 H), 3.86 (quin, J = 7 Hz, 1 H), 5.72 (br s, 2 H); ^{13}C NMR ($CDCl_3$) 21.3, 48.2, 48.6, 164.7 ppm; mass spectrum, m/e (relative intensity) 100 (34), 85 (100), 57 (3), 56 (4).

4-Phenyl-2-imidazolidinone (4c): yield 15% [the reaction run in THF at reflux temperatures (3 days) gave a 69% yield of **4c**]; mp 160–162 °C (lit.[15] mp 162 °C); IR (KBr) 3140, 1690 cm^{-1}; ^1H NMR (Me_2-SO-d_6) δ 3.01 (t, J = 8 Hz, 1 H) 3.69 (t, J = 9 Hz, 1 H), 4.73 (t, J = 8 Hz, 1 H), 6.26 (br s, 1 H), 6.80 (br s, 1 H), 7.34 (s, 5 H); ^{13}C NMR (Me_2DMSO-d_6) 49.6, 56.7, 126.1, 128.2, 128.9, 141.5, 164.1 ppm; mass spectrum, m/e (relative intensity) 162 (100), 161 (22), 118 (6), 104 (20), 91 (4).

Preparation of 1-Benzyl-2-imidazolone (2g). Trifluoroacetic Acid Method. The 4-hydroxy adduct **3g** was prepared according to the previously described $LiAlH_4$ room-temperature procedure by using 2.30 g (12 mmol) of **1g**. Crude **3g** (1.95 g, 10 mmol) was suspended in CH_2Cl_2, and 2 drops of trifluoroacetic acid were added to the constantly stirred mixture. Methanol (2 mL) was then added until partial dissolution of **1g** was noted, and the mixture was stirred at room temperature until all the solid had entered into solution. The solution was then concentrated in vacuo, and the residue was recrystallized from methylene chloride–hexanes to give **2g**: yield 0.91 g (43% overall yield); mp 134–136 °C (lit.[12] mp 133–135 °C); IR (KBr) 3140, 1680, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (s, 2 H), 6.09 (dd, J = 2.9, 2.4 Hz, 1 H), 6.27 (dd, J = 2.9, 2.4 Hz, 1 H), 7.26 (s, 5 H), 11.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 46.7 (t, J = 139 Hz), 108.8 (d, J = 190 Hz); 111.2 (d, J = 190 Hz), 127.6, 127.7, 128.8, 136.9, 155.0 (s); mass spectrum, m/e (relative intensity) 174 (19), 91 (100), 65 (18).

Preparation of 1-Benzyl-2-imidazolone (2g). HCl Method. The same procedure described for the reduction of **1g** with $LiAlH_4$ at room temperature was employed by using 1.90 g (10 mmol) of **1g** except that the excess reducing reagent was destroyed by the dropwise addition of aqueous 5 N HCl at 0 °C. Excess HCl was then added until the pH was ~2, followed by H_2O to dissolve the existing solids, and the solution was allowed to stir at room temperature (45 min). The reaction solution was then neutralized with saturated aqueous K_2CO_3 and filtered, and the filtrate was extracted with CH_2Cl_2 (2 × 200 mL). The organic layers were combined, dried (Na_2SO_4), and evaporated. Recrystallization of the residue from methylene chloride–hexanes gave pure **2g** (0.68 g) in 39% overall yield; mp 134–136 °C (lit.[12] mp 133–135 °C).

Treatment of 1-Methyl-2-imidazolidinone (8) with $LiAlH_4$ in Refluxing THF. 1-Methyl-2-imidazolidinone (**8**; 1.00 g, 10 mmol) was dissolved in dry THF (125 mL) under Ar. A THF solution of $LiAlH_4$ (0.47 M, 40.0 mL, 80 mmol of active hydride) was then added dropwise with stirring. During the process evolution of a gas was noted. After the addition of the reducing agent was complete, a white solid slowly formed. The mixture was allowed to stir at reflux (4 days). The excess $LiAlH_4$ was then destroyed by the successive addition of H_2O (0.4 mL), 15% aqueous NaOH (0.4 mL), and H_2O (1.5 mL). The inorganic precipitate was filtered off, the filtrate dried (Na_2SO_4), and the organic solution gently concentrated, leaving a yellow oil. Further purification by bulb-to-bulb distillation at 64–66 °C (0.06 torr) afforded 0.43 g of proposed **9** as a clear liquid: IR (neat, NaCl) 3340, 2940, 2860, 2790, 1460, 1360, 1250, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63–1.87 (m, 4 H), 2.32 (s, 6 H), 2.37–3.31 (m, 4–6 H), 3.37–3.63 (m, 2 H), 3.75 (t, J = 5 Hz, 1 H), 5.60 (br s, 1 H); selective irradiation of the signal at δ 1.63–1.87 led to the collapse of the triplet at δ 3.75 to a singlet and a sharpening of the multiplet at δ 3.37–3.63; ^{13}C NMR ($CDCl_3$) 25.4 (t, J = 128 Hz), 28.3 (t, J = 124 Hz), 39.7 (q, J = 135 Hz), 52.3 (t, J = 139 Hz), 62.8 (t, J = 140 Hz), 86.6 (d, J = 142 Hz); mass spectrum, m/e (relative intensity) 157 (5), 140 (2), 125 (2), 114 (10), 99 (100), 84 (33), 71 (38), 58 (43), 56 (22); mol wt of fragments 157.1342 (calcd for $C_8H_{17}N_2O$, 157.1341);, 99.0925 (calcd for $C_5H_{11}N_2$, 99.0922).

Compound **9** was dissolved in $CDCl_3$ (2 mL), and an equal volume of D_2O was added. A 20% solution of DCl in D_2O was then added dropwise with shaking to acidify the mixture (pH ~2). The layers were separated, and the D_2O layer was examined: ^1H NMR (D_2O, reference dioxane) δ 2.61 (s, 3 H), 3.26 (s, 2 H); ^{13}C NMR (D_2O, reference dioxane) 33.3, 44.1 ppm. Dissolution of an authentic sample of ethylenediamine in D_2O and then acidifying with 20% DCl in D_2O to pH ~2 gave the following spectral data: ^1H NMR (D_2O, reference dioxane) δ 2.63 (s, 3 H), 3.30 (s, 2 H); ^{13}C NMR (D_2O, reference dioxane) 33.4, 44.2 ppm.

Acknowledgment. Support of this work by the National Institutes of Health (Grant No. NS15604) and the Robert A. Welch Foundation is gratefully acknowledged.

Registry No. **1a**, 461-72-3; **1b**, 616-03-5; **1c**, 89-24-7; **1d**, 6843-45-4; **1e**, 6851-79-2; **1f**, 6846-11-3; **1g**, 2301-40-8; **1h**, 2301-36-2; **1i**, 34658-65-6; **1j**, 2221-13-8; **1k**, 33558-00-8; **1l**, 85369-75-1; **1m**, 80029-12-5; **2g**, 67909-04-0; **2m**, 24138-94-1; **3d**, 85569-76-2; *cis*-**3e**, 85369-77-3; *trans*-**3e**, 85369-78-4; *cis*-**3f**, 85369-79-5; **3g**, 85369-80-8; *cis*-**3h**, 85369-81-9; *trans*-**3h**, 85369-82-0; *cis*-**3i**, 85369-83-1; **3j**, 85369-84-2; *cis*-**3k**, 85369-85-3; *trans*-**3k**, 85369-86-4; *trans*-**3l**, 85369-87-5; *cis*-**3m**, 85369-88-6; *trans*-**3m**, 85369-89-7; **4b**, 6531-31-3; **4c**, 27129-49-3; **7d**, 110-70-3; **7e**, 44595-64-4; **7f**·2HCl, 85369-90-0; **7g**·2HCl, 67245-10-7; **7h**, 85369-91-1; **7i**·2HCl, 85369-92-2; **7j**, 64469-32-5; **7k**, 34051-99-5; **7l**, 42164-58-9; **8**, 694-32-6; **9**, 85369-93-3; **10**, 85369-94-4; MeNCO, 624-83-9; THF, 109-99-9; *N*-methylalanine, 3913-67-5.

Supplementary Material Available: The complete spectral (mass, infrared, and ^1H and ^{13}C NMR) properties observed for compounds **1**, **3**, and **7** are reported (Tables IV–XV) (16 pages). Ordering information is given on any current masthead page.