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Novel Imidazoles and Hydantoins Moderately Strained by Incorporation with 2-Azabicyclo[2.2.1]heptene Skeleton

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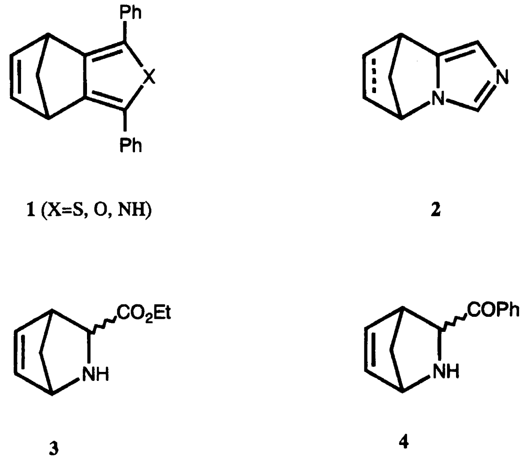
The reactions of 3-acyl-2-azabicyclo[2.2.1]hept-5-enes with phenyl isocyanate, phenyl isothiocyanate, and ethoxycarbonyl isothiocyanate followed by cyclization reactions under basic conditions respectively provided a hydantoin, a thiohydantoin, and a 1,3-dihydro-2*H*-imidazole-2-thione incorporated with the azabicyclic skeleton. Treatment of the imidazolethione with Raney nickel gave a phenyl-substituted imidazole fused with 2-azabicyclo[2.2.1]hept-2-ene. The effect of annulation on the ^{13}C NMR of the imidazole ring is discussed.

Fusion of a strained ring to an aromatic ring is one of the most useful methods to investigate the relationship between π-delocalization and deformation of aromatic rings.[1,2] As for the five-membered heteroaromatics, the chemistry of thiophenes, furans, and pyrroles incorporated with cyclobutene, cyclopropene, or benzvalene has been extensively studied.[3—9] However, no example of imidazoles with a fused, strained ring has been known to the best of our knowledge, although a strained [6](2,4)-imidazolophane was prepared very recently.[10] We have described the syntheses of the diphenyl-substituted thiophene, pyrrole, and furan (**1**) fused at the 3- and 4-positions with a norbornadiene skeleton, and found that the ^{13}C NMR spectra of these compounds show a large downfield shift of the ring-juncture carbon compared with those of cyclohexene-fused analogues, possibly due to angle strain derived from the fusion of the norbornadiene skeleton.[11] As an extension to this study, we considered it worthwhile to prepare imidazole derivatives such as **2** which are incorporated with 2-azabicyclo[2.2.1]hepta-2,5-diene or 2-azabicyclo[2.2.1]hept-2-ene skeleton (Chart 1). We now report the syntheses and properties of novel imidazoles and hydantoins fused at the N-1 and C-5 positions with the azabicyclic skeletons. We supposed that the hydantoin derivatives would be potential precursors for partially unsaturated imidazoles and useful as reference compounds to fully unsaturated derivatives.



1 (X=S, O, NH)

2

3

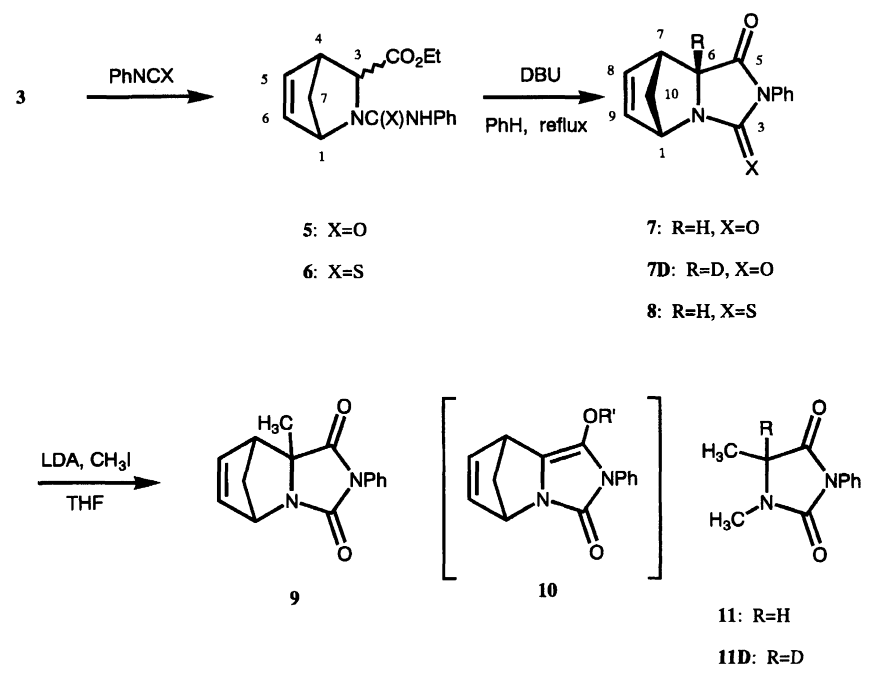
4

Chart 1.

Results and Discussion

Our synthetic approach began with ethyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate[12] (**3**) and 3-benzoyl-2-azabicyclo[2.2.1]hept-5-ene[13] (**4**) which were obtained as previously described. The amino ketone **4** has been reported to be isolated as its hydrochloride,[13] but we found that the salt is hygroscopic. Thus, we purified the amino ketone **4** as the oxalate. The azanorbornenes **3** and **4** were obtained as mixtures of stereoisomers and the *exo*/*endo* ratios were 1 : 3 for both compounds. The stereochemical assignments are based on the vicinal coupling constants between the 3-H and 4-H in the ^{1}H NMR spectra,[12—15] and the *exo*/*endo* ratios were determined by the integration of the proton signals at the 3-position. The reaction of the amino ester **3** with phenyl isocyanate and phenyl isothiocyanate respectively provided the urea **5** (59%) and the thiourea **6** (69%) as mixtures of *exo*-3 and *endo*-3 isomers. The *exo*/*endo* ratio remained 1 : 3 for **6** but the *endo* product was enriched for **5** (*exo*/*endo*=1/9) after isolation of the precipitate which separated out during the reaction. The urea **5** and the thiourea **6** were respectively converted into the hydantoin **7** (84%) and the thiohydantoin **8** (85%) on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene. Each compound **7** and **8** was found to have *endo*-configuration on the basis of the vicinal proton coupling constants ($J_{6,7}$=3.3 Hz for **7** and $J_{6,7}$=3.3 Hz for **8**). The *N*-methyl derivative corresponding to **7** has been prepared in low yield by a different route, but the authors state that the reproducibility of this reaction is poor (Scheme 1).[16]

Hoping to obtain a imidazole derivative **10**, the hydantoin **7** was treated with lithium diisopropylamide (LDA) and chlorotrimethylsilane, but this treatment gave a mixture of complex products. Treatment of **7** with LDA followed by quenching with methyl iodide resulted in the formation of the C(6)-methylated hydantoin **9** (48%). The hydantoin **9** was obtained as a single stereoisomer but the stereochemistry

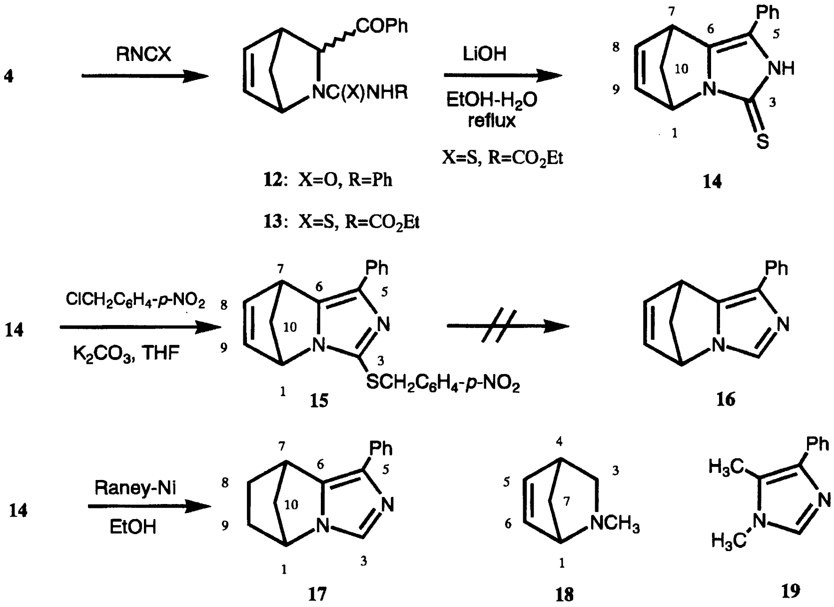


Scheme 1.

could not be determined. The ^{1}H NMR spectrum of the hydantoin **7** in CD_3COCD_3–D_2O under neutral conditions or in the presence of pyridine showed no substantial change of the spectrum. When a small amount of NaOD was added to the solution, the exchange reaction of the hydrogen atom at the 6-position of **7** with deuterium took place, and the exchange was 65% complete after 6 h. The ^{1}H NMR spectrum of this solution indicated the exclusive formation of the *exo*-6-deuterated hydantoin **7D** and no signals assignable to the *endo*-deuterated isomer appeared. Therefore, the deuteration should take place stereoselectively from the more open *exo* face of the enolate intermediate. Under exactly the same conditions as the deuterium-exchange reaction of the hydantoin **7**, the replacement of the 5-hydrogen atom of 1,5-dimethyl-3-phenyl-2,4-imidazolidinedione$^{17)}$ (**11**) was 90% complete. These results suggest that the 2-azanorbornene framework somewhat suppresses the exchange reaction, possibly due to strain of the enolate intermediate.

The amino ketone **4** reacted with phenyl isocyanate to give the benzoyl urea **12** (87%, *exo*/*endo*=1/4). Attempted cyclization of the benzoyl urea **12** under basic conditions resulted in a recovery of **12**, in contrast to the case with the urea **5**. Treatment of **4** with thiocyanic acid, isothiocyanatotrimethylsilane, or even phenyl isothiocyanate gave a mixture of products and the corresponding thioureas could not be isolated. On the other hand, when the amino ketone **4** was treated with ethyl isothiocynatoformate, the thiourea **13** (*exo*/*endo*=3/7) was obtained in a satisfactory yield (85%). Conversion of the thiourea **13** into the 1,3-dihydro-2*H*-imidazole-2-thione **14** was achieved in 56% yield by treatment with lithium hydroxide in refluxing aqueous ethanol. In the ^{13}C NMR spectrum of **14**, methano bridge carbon ($\delta=62.9$) is significantly deshielded compared with the corresponding carbons observed for the thiohydantoin **8** ($\delta=50.4$) and 2-methyl-2-azabicyclo[2.2.1]hept-5-ene$^{18,19)}$ (**18**) ($\delta=47.9$) (Scheme 2). This downfield shift may have relevance to the observation that introduction of an extra endocyclic double bond in norbornene derivatives exerts a downfield shift of 10—17 ppm on the ^{13}C chemical shift of the methano bridge carbon.$^{20)}$ The C–H coupling constant ($^1J_{C-H}=166$ Hz) at the bridgehead C-1 carbon in **14** is close to that of the thiohydantoin **8** ($^1J_{C-H}=167$ Hz), although these values are much larger than that observed for the C-1 carbon of **18** ($^1J_{C-H}=153$ Hz).

The imidazolethione **14** reacted with *p*-nitrobenzyl chloride in the presence of potassium carbonate to give the (*p*-nitrobenzylthio)imidazole **15** in 73% yield. Similar reactions of **14** with methyl iodide and benzyl chloride gave products, which showed ^{1}H NMR signals expected to the corresponding imidazole derivatives, but they decomposed on attempted purification. The (*p*-nitrobenzylthio)imidazole **15** was also found to decompose during measurement of the ^{13}C NMR spectrum in DMSO-d_6. Attempted conversion of **15** into **16** with Raney nickel (W4) in ethanol resulted in the formation of complex products. On the other hand, when the imidazolethione **14** was treated with Raney nickel (W4) in ethanol, reduction of the olefin moiety as well as desulfurization took place to give the imidazole **17** in a low yield (29%). Comparison of the ^{13}C NMR data of the imidazole **17** with those of 1,5-dimethyl-4-phenyl-1*H*-imidazole (**19**) revealed that the ^{13}C chemical shift of the C-3 carbon ($\delta=128.2$, $^1J_{C-H}=208$ Hz) in **17** is more shielded by 7.9 ppm relative to that of the C-2 carbon of



Scheme 2.

19 (δ=136.1, $^{1}J_{\text{C-H}}$=206 Hz). The chemical shift of the C-3 carbon of **17** is the most shielded one when compared with the corresponding values of monocyclic imidazole and its similarly alkyl- and phenyl-substituted derivatives: imidazole[21] (δ=135.3, $^{1}J_{\text{C-H}}$=205.1 Hz), 1-methyl-1*H*-imidazole[22] (δ=136.6), 1,5-dimethyl-1*H*-imidazole[22] (δ=136.4), 1-methyl-4-phenyl-1*H*-imidazole[22] (δ=138.0), and 4-phenyl-1,5-dipropy-1*H*-imidazole[10] (δ=140.7). On the other hand, the ^{13}C signal of the ring-juncture C-6 carbon (δ=130.1) in **17** shows a downfield shift by 6.8 ppm relative to that of the C-5 carbon **19** (δ=123.3).

The charge distributions on the imidazole ring of **20**—**23** calculated by the MNDO-PM3 method[23] are shown in Table 1 (Chart 2). These data show that the negative charge on the C(2) carbon decreases while that on the C(5) carbon increases as the size of the fused ring decreases. This trend is inconsistent with the outcome observed for the ^{13}C chemical shifts of the imidazoles **17** and **19**. The anisotropic magnetic effect by the phenyl substituent should also be taken into account.

It has been recognized for cycloalkene-fused benzenes and pyridines that the ring-juncture carbon moves downfield while the aromatic carbon *ortho* to the ring-juncture moves upfield with decreasing size of the fused ring.[24,25] Therefore, the feature observed for the ^{13}C NMR of the fused imidazole may be ascribed to the steric effect of the fused azabicyclic skeleton. Further studies on the syntheses of imidazoles fused with a more strained ring or fused at the different positions will be required to probe the effect of strain on the properties of imidazoles.

Table 1. Charges on the Imidazole Ring Calculated by MNDO-PM3 Method

	Charge				
Compounds	N(1)	C(2)	N(3)	C(4)	C(5)
20	.275	−.239	−.118	−.139	−.276
21	.234	−.207	−.132	−.112	−.285
22	.201	−.182	−.147	−.095	−.289
23	.134	−.148	−.156	−.072	−.301

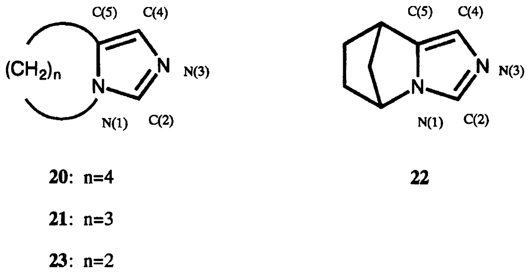


Chart 2.

Experimental

General. All the melting points were recorded with a Yanagimoto hot-stage apparatus and are uncorrected. IR spectra were obtained with a Hitachi 345 spectrometer. ^{1}H (90 MHz) and ^{13}C (22.5 MHz) NMR spectra were recorded with a JEOL-FX-90Q spectrometer with tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000EX spectrometer operating in the electron impact mode (70 eV).

Ethyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**3**),[12] 3-benzoyl-2-azabicyclo[2.2.1]hept-5-ene (**4**),[13] 1,5-dimethyl-3-phenyl-2,4-imidazolidinedione (**11**),[17] and ethyl isothiocyanatoformate[26] were prepared as described in the literature. The amino ketone **4** was freshly liberated from the corresponding oxalate with aq KOH, followed by extraction with CH_2Cl_2 before use.

3-Benzoyl-2-azabicyclo[2.2.1]hept-5-ene (4):[13] Oxalate (62%); colorless needles (from acetone); mp 118 °C (decomp); IR (KBr) 1695 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=1.54—2.17 (2H, m, 7-H), 3.53 (0.25H, m, *exo* 4-H), 3.83

(0.75H, m, *endo* 4-H), 4.66 (1H, m, 1-H), 4.76 (0.25H, br s, *exo* 3-H), 5.59 (0.75H, d, J=3.2 Hz, *endo* 3-H), 6.09—6.90 (2H, m, 5- and 6-H), 7.46—7.91 (3H, m), 8.03—8.29 (2H, m), 10.0 (3H, br, NH_2^+ and COOH). Found: C, 62.05; H, 5.11; N, 4.91%. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84%.

Ethyl 2-(Phenylcarbamoyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (5): Phenyl isocyanate (3.21 g, 27 mmol) was added to a solution of the amino ester **3** (5.00 g, 30 mmol) in benzene (20 cm^3) over 10 min. The mixture was stirred at room temperature for 1 h. The resulting precipitates were collected to give **5** (5.77 g, 59%) containing 1/2 molar equivalent of solvated benzene: Colorless needles (from benzene); mp 141—142 °C; IR (KBr) 3300, 1750 (COOEt), 1640 (CO-N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.27 (2.7H, t, J=7.1 Hz, *endo* CH_3), 1.34 (0.3H, t, J=7.1 Hz, *exo* CH_3), 1.54—2.00 (2H, m, 7-H), 3.48 (0.2H, m, *exo* 3- and 4-H), 3.56 (0.9H, m, *endo* 4-H), 4.19 (0.2H, q, J=7.1 Hz, *exo* OCH_2), 4.12 (1.8H, q, J=7.1 Hz, *endo* OCH_2), 4.35 (0.9H, d, J=3.3 Hz, *endo* 3-H), 4.78 (0.1H, m, *exo* 1-H), 5.08 (0.9H, m, *endo* 1-H), 6.00—6.65 (2H, m, 5- and 6-H), 7.34 (3H, s, PhH), 6.64—7.47 (5H, m, Ph), 7.56 (0.9H, br, *endo* NH), 7.84 (0.1H, br, *exo* NH); ^{13}C NMR ($CDCl_3$) for the *endo* isomer δ=13.8, 47.3, 49.0, 59.4, 61.1, 61.6, 119.5, 122.2, 128.0 (PhH), 128.3, 135.5, 136.3, 155.2, 171.2; MS *m/z* (rel intensity) 286 (16, M$^+$), 240 (8, M−EtOH), 213 (7, M−COOEt), 93 (100, M−COOEt−PhNHCO). Found: C, 69.95; H, 6.71; N, 8.76%. Calcd for $C_{22}H_{24}N_2O_3$: C, 70.14; H, 6.51; N, 8.61%.

Ethyl 2-(Phenylthiocarbamoyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (6): Phenyl isothiocyanate (1.66 g, 12 mmol) was added to a solution of the amino ester **3** (2.50 g, 15 mmol) in benzene (40 cm^3) and the mixture was stirred for 6 h. The solution was concentrated and the residue was crystallized from hexane–ether (3/1) to give **6** (2.51 g, 69%): Light tan needles (from hexane–benzene 3/1); mp 127—129 °C; IR (KBr) 3235, 1720, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30 (2.25H, t, J=7.0 Hz, *endo* CH_3), 1.37 (0.75H, t, J=7.0 Hz, *exo* CH_3), 1.51—2.20 (2H, m, 7-H), 3.44—3.63 (1H, m, *exo* 3-H and *endo* 4-H), 3.90 (0.25H, m, *exo* 4-H), 4.22 (1.5H, q, J=7.0 Hz, *endo* OCH_2), 4.31 (0.5H, q, J=7.0 Hz, *exo* OCH_2), 4.88 (0.75H, d, J=3.3 Hz, *endo* 3-H), 5.23 (1H, m, 1-H), 6.13—6.52 (2H, m, 5- and 6-H), 6.97—7.50 (5H, m, Ph), 7.77 (0.75H, br, *endo* NH), 8.47 (0.25H, br, *exo* NH); ^{13}C NMR ($CDCl_3$) for the *endo* isomer δ=13.0, 47.3, 49.1, 61.2, 63.3, 67.4, 123.7, 124.9, 128.4, 133.5, 136.6, 139.8, 169.7, 181.8; MS *m/z* (rel intensity) 302 (68, M$^+$), 256 (5, M−EtOH), 135 (91, PhNCS), 77 (100, Ph). Found: C, 63.29; H, 6.02; N, 8.99%. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.02; N, 9.26%.

4-Phenyl-2,4-diazatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (7): A solution of the urea **5** (4.77 g, 15 mmol) and DBU (1.27 g, 8 mmol) in benzene (60 cm^3) was refluxed for 3 h. The mixture was successively washed with 5% hydrochloric acid and aq $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated. The residue was crystallized from ether to give **7** (3.01 g, 84%): Colorless needles (from hexane–benzene 1/2); mp 132—133 °C; IR (KBr) 1775, 1725, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.86—2.06 (2H, m, 10-H), 3.65 (1H, m, 7-H), 4.39 (1H, d, J=3.3 Hz, 6-H), 4.80 (1H, m, 1-H), 6.30 (1H, m, 8-H), 6.50 (1H, m, 9-H), 7.13—7.55 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=45.5 (d, C-7), 50.7 (t, C-10), 61.5 (d, C-6), 64.3 (d, C-1), 125.9 (d), 128.0 (d), 128.7 (d), 131.5 (s), 132.1 (d, C-8), 136.3 (d, C-9), 162.4 (s, C-3), 172.2 (s, C-5); MS *m/z* (rel intensity) 240 (16, M$^+$), 119 (10, PhNCO), 93 (17, M−PhNCO−CO), 66 (100, C_5H_6). Found: C, 69.72; H, 4.95; N, 11.45%. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66%.

4-Phenyl-3-thioxo-2,4-diazatricyclo[5.2.1.0^{2,6}]dec-8-en-5-one (8): By a similar procedure as described for **7**, the reaction of the thiourea **6** (8.04 g, 27 mmol) with DBU (2.03 g, 13 mmol) provided **8** (5.79 g, 85%): Light tan rods (from hexane–benzene 1/1); mp 150 °C (decomp); IR (KBr) 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.89—2.20 (2H, m, 10-H), 3.63 (1H, m, 7-H), 4.51 (1H, d, J=3.3 Hz, 6-H), 5.17 (1H, m, 1-H), 6.39 (1H, m, 8-H), 6.68 (1H, m, 9-H), 7.04—7.77 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=45.2 (d, $^1J_{C-H}$=155 Hz, C-7), 50.4 (t, $^1J_{C-H}$=139 Hz, C-10), 64.9 (d, $^1J_{C-H}$=153 Hz, C-6), 67.8 (d, $^1J_{C-H}$=167 Hz, C-1), 128.0 (d), 129.1 (d), 132.2 (d, $^1J_{C-H}$=176 Hz, C-8), 132.5 (d), 133.3 (s), 137.8 (d, $^1J_{C-H}$=176 Hz, C-9), 173.2 (s, C-5), 193.4 (s, C-3); MS *m/z* (rel intensity) 256 (100, M$^+$), 135 (25, PhNCS), 93 (18, M−PhNCS−CO), 66 (93, C_5H_6). Found: C, 65.50; H, 4.50; N, 10.67%. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93%.

6-Methyl-4-phenyl-2,4-diazatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (9): To a solution of LDA, prepared from butyllithium (2.2 mmol) and diisopropylamine (2.2 mmol), in anhydrous THF (5 cm^3) was added a solution of the hydantoin **7** (480 mg, 2 mmol) in anhydrous THF (5 cm^3) over 10 min at −78 °C. The mixture was stirred at the same temperature for 2 h and methyl iodide (312 mg, 2.4 mmol) was added. The mixture was warmed up to room temperature over 1 h. Water (20 cm^3) was added and the product was extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated. The resulting solid was recrystallized from hexane–benzene (1/1) to give **9** (242 mg, 48%): colorless plates; mp 130—131 °C; IR (KBr) 1770, 1730, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.72 (3H, s, CH_3), 1.51—2.31 (2H, m, 10-H), 3.24 (1H, m, 7-H), 4.70 (1H, m, 1-H), 6.37—6.57 (2H, m, 8- and 9-H), 7.06—7.60 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=24.2 (q, CH_3), 48.5 (d, C-7), 49.7 (t, C-10), 65.2 (d, C-1), 66.7 (s, C-6), 125.8 (d), 127.9 (d), 128.7 (d), 131.7 (s), 135.0 (d), 135.6 (d), 162.5 (s, C-3), 175.9 (s, C-5); MS *m/z* (rel intensity) 254 (11, M$^+$), 188 (39, M−C_5H_6), 66 (100, C_5H_6). Found: C, 71.06; H, 5.34; N, 11.00%. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02%.

1,5-Dimethyl-3-phenyl-2,4-imidazolidinedione (11):[17] Colorless needles (from ethanol); mp 151—152 °C (lit,[17] mp 145—146 °C); IR (KBr) 1785, 1725, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.51 (3H, d, J=7.0 Hz), 3.00 (3H, s), 4.00 (1H, q, J=7.0 Hz), 7.17—7.75 (5H, m); ^{13}C NMR ($CDCl_3$) δ=14.8 (q), 27.3 (q), 56.6 (d), 125.7 (d), 127.6 (d), 128.6 (d), 131.9 (s), 154.7 (s), 172.1 (s); MS *m/z* (rel intensity) 204 (66, M$^+$), 119 (100, PhNCO).

Exchange Reactions with D_2O for the Hydantoins 7 and 11. A mixture of the substrate (0.12 mmol), a 40% solution of NaOD in D_2O (0.05 cm^3), and CH_2Cl_2 as a reference standard in acetone-d_6 (0.30 cm^3) was placed in an NMR tube, and the exchange reaction was monitored by ^{1}H NMR. Comparisons of the integrated signals *vis-à-vis* that of the internal standard gave the results described in the test.

3-Benzoyl-2-(phenylcarbamoyl)-2-azabicyclo[2.2.1]hept-5-ene (12): Phenyl isocyanate (357 mg, 3 mmol) was added to a solution of the amino ketone **4**, freshly liberated from the oxalate (867 mg, 3 mmol), in CH_2Cl_2 (15 cm^3) and the mixture was stirred at room temperature for 2 h. The solution was concentrated and the resulting crystals were collected to give **12** (827 mg, 87%): Colorless needles (from benzene); mp 92—95 °C; IR (KBr) 3310, 1705, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.40—2.11 (2H, m, 7-H), 3.34 (0.2H, m, *exo* 4-H), 3.64 (0.8H, m, *endo* 4-H), 4.63 (0.2H, br s, *exo* 3-H), 4.76 (0.2H, *exo* 1-H), 4.99 (0.8H, m, *endo* 1-H), 5.41 (0.8H, d, J=3.1 Hz, *endo* 3-H), 5.88—6.70 (2H, m, 5- and 6-H), 6.86—7.71 (9H, Ph, COPh, and NH); ^{13}C NMR ($CDCl_3$) for the *endo* isomer δ=48.9, 49.4, 62.0, 62.5, 120.1—139.4, 154.5, 195.8; MS m/z (rel intensity) 318 (4, M$^+$), 252 (13, M$-C_5H_6$), 213 (13, M$-$COPh), 105 (78, COPh), 94 (63, M$-$PhNCO$-$PhCO), 7 (100, Ph). Found: C, 75.68; H, 5.67; N, 8.81%. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80%.

3-Benzoyl-2-[(ethoxycarbonyl)thiocarbamoyl]-2-azabicyclo[2.2.1]hept-5-ene (13): A solution of ethyl isothiocyanatoformate[26] (3.14 g, 24 mmol) in CH_2Cl_2 (5 cm^3) was added to a solution of the amino ketone **4**, freshly liberated from the oxalate (6.92 g, 24 mmol), in CH_2Cl_2 (50 cm^3) at 0 °C. The solution was stirred at room temperature for 2 h and concentrated. The residue was crystallized from ether to give **13** (6.71 g, 85%): Colorless needles (from ethanol); mp 136—138 °C (decomp); IR (KBr) 3185, 1750, 1700 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=0.90 (0.75H, t, J=7.0 Hz, *exo* CH_3), 1.25 (2.25 Hz, t, J=7.0 Hz, *endo* CH_3), 1.76—2.06 (2H, m, 7-H), 3.44—3.76 (1H, m, 4-H), 3.83 (0.5H, q, J=7.0 Hz, *exo* OCH_2), 4.11 (1.5H, q, J=7.0 Hz, *endo* OCH_2), 4.99 (0.75H, br s, *endo* 1-H), 5.48 (0.25H, br s, *exo* 1-H), 5.80—6.53 (3H, m, 1-, 3-, and 5-H), 7.38—8.20 (5H, m, Ph), 9.97 (0.25H, br), 10.10 (0.75H, br, NH); ^{13}C NMR (DMSO-d_6) for the *endo* isomer δ=14.2, 47.1, 49.1, 60.8, 66.4, 68.9, 127.8—135.8, 151.6 (NCO), 175.2 (CS); MS m/z (rel intensity) 330 (3, M$^+$), 284 (4, M$-$EtOH), 179 (14, M$-$EtOH$-$PhCO), 105 (100, PhCO). Found: C, 61.96; H, 5.68; N, 8.68%. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.50; N, 8.48%.

5-Phenyl-2,4-diazatricyclo[5.2.1.0^{2,6}]deca-5,8-diene-3-thione (14): A solution of the thiourea **13** (990 mg, 3 mmol) and lithium hydroxide monohydrate (1.26 g, 30 mmol) in a mixture of ethanol (25 cm^3) and water (5 cm^3) was refluxed for 30 h. The mixture was concentrated and water (20 cm^3) was added to the residue. The product was extracted with CH_2Cl_2 and the organic phase was washed with water prior to drying over Na_2SO_4. After removal of the solvent, the resulting crystals were collected to give **14** (420 mg, 56%): Colorless needles (from ethanol); mp 189 °C (decomp); IR (KBr) 3080 (NH), 1470, 1355, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.45 (2H, m, 10-H), 4.29 (1H, m, 7-H), 5.23 (1H, m, 1-H), 6.85 (2H, m, 8- and 9-H), 7.28—7.50 (3H, m), 7.56—7.70 (2H, m), 11.49 (1H, br, NH); ^{13}C NMR (DMSO-d_6) δ=45.4 (d, $^1J_{C-H}$=155 Hz, C-7), 61.5 (d, $^1J_{C-H}$=166 Hz, C-1), 62.6 (t, $^1J_{C-H}$=139 Hz, C-10), 120.9 (s, C-6), 124.2 (dd, $^1J_{C-H}$=159 Hz, C-3′), 127.0 (dt, $^1J_{C-H}$=161 Hz, C-4′), 128.5 (s, C-5), 128.9 (dt, $^1J_{C-H}$=161 Hz, C-2′), 131.3 (s, C-1′), 137.3 (d, $^1J_{C-H}$=175 Hz, C-8); 141.2 (d, $^1J_{C-H}$=178 Hz, C-9), 157.8 (s, CS); UV (EtOH, log ε) 227 (4.15), 294 (4.28) nm; MS m/z (rel intensity) 240 (100, M$^+$), 206 (11, M$-$SH$-$H), 77 (27, Ph). Found: C, 69.97; H, 5.03; N, 11.66%. Calcd for $C_{14}H_{12}N_2S$: C, 69.83; H, 4.92; N, 11.59%.

3-(*p*-Nitrobenzylthio)-5-phenyl-2,4-diazatricyclo[5.2.1.0^{2,6}]deca-3,5,8-triene (15): A mixture of the 1,3-dihydro-2*H*-imidazole-2-thione **14** (1.00 g, 4.2 mmol), *p*-nitrobenzyl chloride (0.74 g, 4.3 mmol), and potassium carbonate (5.80 g, 42 mmol) in THF (15 cm^3) was stirred at room temperature for 4 d. Insoluble materials were removed by filtration and the filtrate was treated with activated carbon and concentrated to give **15** (1.15 g, 73%): Yellow needles (from benzene); mp 161—164 °C (decomp); IR (KBr) 1600, 1595, 1520 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.35 (2H, m, 10-H), 4.32 (2H, s, S–CH_2), 4.42 (1H, m, 7-H), 4.99 (1H, dt, J=2.6, 1.3 Hz, 1-H), 6.61 (1H, dd, J=5.3, 2.6 Hz, 9-H), 6.85 (1H, dd, J=5.3, 3.1 Hz, 8-H), 7.15—7.75 (7H, m), 8.03—8.18 (2H, m); UV (CH_2Cl_2, log ε) 228 (4.10), 277 (4.43) nm; MS m/z (rel intensity) 375 (32, M$^+$), 239 (45, M$-O_2NC_6H_4CH_2$), 181 (100, M$-O_2NC_6H_4CH_2SCN$). Found: C, 67.13; H, 4.60; N, 11.10%. Calcd for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19%.

5-Phenyl-2,4-diazatricyclo[5.2.1.0^{2,6}]deca-3,5-diene (17): A mixture of the 1,3-dihydro-2*H*-imidazole-2-thione **14** (300 mg, 1.26 mmol) and Raney nickel (W4, 70 mmol) in ethanol (30 cm^3) was stirred at room temperature for 5 h. Insoluble materials were removed by filtration through Celite and the filtrate was concentrated. The residue was separated by column chromatography (alumina, chloroform) to give **17** (75 mg, 29%): Colorless plates (from benzene); mp 79—80 °C; IR (KBr) 1480, 1455, 1335, 1245, 1210, 1180, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.22—1.56 (2H, m, 10-H), 1.64—2.24 (4H, m, 8- and 9-H), 3.74 (1H, br s, 7-H), 4.62 (1H, br s, 1-H), 7.19—7.52 (3H, m), 7.39 (1H, s, 3-H), 7.72—7.92 (2H, m); ^{13}C NMR ($CDCl_3$) δ=28.2 (d, $^1J_{C-H}$=128 Hz, C-8), 29.8 (t, $^1J_{C-H}$=132 Hz, C-9), 38.4 (d, $^1J_{C-H}$=149 Hz, C-7), 48.0 (t, $^1J_{C-H}$=135 Hz, C-10), 58.8 (d, $^1J_{C-H}$=162 Hz, C-1), 124.4 (dt, $^1J_{C-H}$=158 Hz, $^3J_{C-H}$=6 Hz, C-2′), 125.3 (dt, $^1J_{C-H}$=160 Hz, $^3J_{C-H}$=7 Hz, C-4′), 128.2 (d, $^1J_{C-H}$=208 Hz, C-3); 128.3 (dd, $^1J_{C-H}$=159 Hz, $^3J_{C-H}$=7 Hz, C-3′), 130.1 (dm, J_{C-H}=9 Hz, C-6), 135.0 (t, $^3J_{C-H}$=8 Hz), 135.9 (tm, $^3J_{C-H}$=6 Hz, C-5); UV (EtOH, log ε) 204 (4.23), 266 (4.20) nm; MS m/z (rel intensity) 210 (100, M$^+$), 182 (72, M$-C_2H_4$). Found: C, 80.17; H, 6.71; N, 13.60%. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32%.

2-Methyl-2-azabicyclo[2.2.1]hept-5-ene (18):[19,20] ^{1}H NMR ($CDCl_3$) δ=1.20—1.70 (3H, m, 7-H and 3-H$_{endo}$), 2.17 (3H, s, CH_3), 2.91 (1H, br s, 4-H), 3.16 (1H, dd, J=8.6, 2.9 Hz, 3-H$_{exo}$), 3.78 (1H, br s, 1-H), 6.04 (1H, m, 6-H), 6.38 (1H, m, 5-H); ^{13}C NMR ($CDCl_3$) δ=40.3 (q, $^1J_{C-H}$=135 Hz, CH_3), 43.7 (d, $^1J_{C-H}$=120 Hz, C-4), 47.9 (t, $^1J_{C-H}$=135 Hz, C-7), 52.8 (t, $^1J_{C-H}$=140 Hz, C-3), 65.4 (d, $^1J_{C-H}$=153 Hz, C-1), 129.8 (d, $^1J_{C-H}$=168 Hz, C-5), 135.5 (d, $^1J_{C-H}$=171 Hz, C-6).

1,5-Dimethyl-4-phenyl-1*H*-imidazole (19): A solution of 2-methylamino-1-phenyl-1-propanone hydrochloride[28] (1.38 g, 6.9 mmol) and potassium thiocyanate (0.80 g, 8.2 mmol) in water (15 cm^3) was heated at 90 °C for 7 h. The solution was cooled to room temperature, and the resulting solid was collected by filtration to give 1,3-dihydro-1,5-dimethyl-4-phenyl-2*H*-imidazole-2-thione (600 mg, 42%): Light tan needles (from methanol); mp 247—249 °C; IR (KBr) 3080, 1635, 1595, 1490, 1380, 1270, 1120

cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=2.27 (3H, s, 5-CH_3), 3.48 (3H, s, N–CH_3), 7.35—7.42 (5H, m, Ph), 12.40 (1H, br, N–H); ^{13}C NMR (DMSO-d_6) δ=9.60 (CH_3), 30.4 (NCH_3), 122.4, 122.9, 126.5, 126.9, 128.3, 128.7, 161.0 (CS); MS m/z (rel intensity) 204 (100, M^+), 171 (14, M−SH), 103 (16, PhCN). Found: C, 64.37; H, 5.74; N, 13.76%. Calcd for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71%.

A mixture of the 1,3-dihydro-2*H*-imidazole-2-thione (344 mg, 1.7 mmol) and iron(III) chloride (1.64 g, 10.1 mmol) in water (12 cm^3) was heated at 90 °C for 7 h. The pH of the solution was adjusted to 11 by adding aq Na_2CO_3. Insoluble materials were removed by filtration and washed with CH_2Cl_2. The product was extracted with CH_2Cl_2, and the organic phase was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was purified by TLC (silica gel, ethyl acetate) to give 1,5-dimethyl-4-phenyl-1*H*-imidazole **19** (122 mg, 44%) as a colorless liquid: IR (neat) 1600, 1490, 1445, 1380, 1240, 1075, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.31 (3H, s, 5-CH_3), 3.47 (3H, s, N–CH_3), 7.19—7.69 (6H, Ph and 2-H); ^{13}C NMR ($CDCl_3$) δ=9.1 (q, $^1J_{C-H}$=128 Hz, 5-CH_3), 30.8 (q, $^1J_{C-H}$=139 Hz, N–CH_3), 123.3 (m, C-5), 125.7 (dt, $^1J_{C-H}$=160 Hz, $^3J_{C-H}$=8 Hz, C-4′), 126.6 (dt, $^1J_{C-H}$=159 Hz, $^3J_{C-H}$=7 Hz, C-2′), 127.9 (dd, $^1J_{C-H}$=159 Hz, $^3J_{C-H}$=8 Hz, C-3′), 135.5 (t, $^3J_{C-H}$=7 Hz, C-1′), 136.1 (dm, $^1J_{C-H}$=206 Hz, C-2), 137.6 (m, C-4); MS m/z (rel intensity) 172 (100, M^+), 130 (27, M−$HCNCH_3$), 103 (19, PhCN). Picrate: Yellow needles (from ethanol); mp 203—204 °C (lit,[29] mp 205—207 °C). Found: C, 51.18; H, 3.77; N, 17.45%. Calcd for $C_{17}H_{15}N_5O_7$: C, 50.88; H, 3.77; N, 17.45%.

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