was added, and after 2 h the white Mannich-base precipitate was collected by filtration and washed with water. This solid was dissolved in dimethylformamide to induce decarboxylation and stirred for 1 h. The solvent was then evaporated under reduced pressure, and the resulting oil was dissolved in ethyl acetate and washed with 20% citric acid, water, and saturated sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and evaporated to an oil. Crystallization from diethyl ether/hexane afforded pure 7: 0.032 g (23%); mp 105–108 °C; $[\alpha]^{23}_D$ −34.7° (*c* 1.0, MeOH).

Anal. Calcd for $C_{20}H_{19}NO_6 \cdot {}^1/_2H_2O$: C, 63.49; H, 5.33; N, 3.70. Found: C, 63.42; H, 5.27; N, 3.66.

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Registry No. 1, 3967-21-3; 2, 70706-35-3; 3, 25126-07-2; 3·DCHA, 93255-01-7; 4, 60686-50-2; 5, 93254-98-9; 6, 93254-99-0; 7, 93255-00-6; phenol, 108-95-2; morpholine, 110-91-8; formaldehyde, 50-00-0; *Staphylococcus aureus* V_8 proteinase, 66676-43-5.

Synthesis of 3-*tert*-Alkyl-2,4-imidazolidinediones

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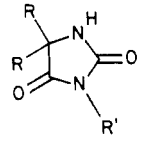
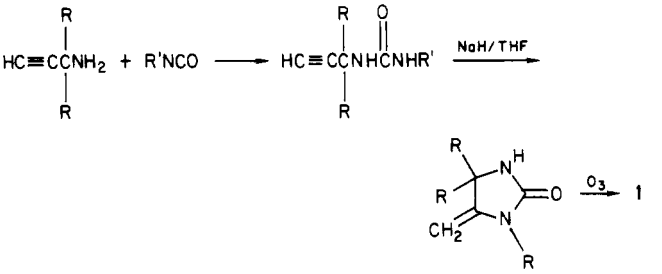
2,4-Imidazolidinediones (hydantoins 1) are widely used as anticonvulsants.[1] Specifically 5,5-diphenyl-2,4-imidazolidinedione (phenytoin or dilantin) is the major drug prescribed for grand mal seizures in epilepsy. However, no hydantoins had been reported to show any efficacy toward petit mal control until we found that 3-*tert*-butyl-5,5-dimethyl-2,4-imidazolidinedione displayed moderate activity in its initial screen.[2] Since it appeared to be a specific function of the 3-*tert*-butyl group we were interested in synthesizing 3-*tert*-butyl-5,5-diphenyl-2,4-imidazolidinedione to see if this compound might carry both grand mal and petit mal activity. In addition, we wished to extend general procedures for preparing other 3-*tert*-alkyl derivatives which are little known. Most alkylations at N-3 are accomplished by using the previously formed hydantoin anion as the nucleophile in an S_N2 displacement of an alkyl halide and thus 3-substitution is usually limited to primary alkyl groups.



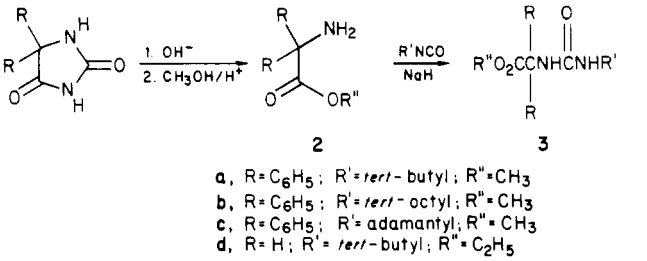
1

A procedure which we previously used, the base-catalyzed cyclization of propargylureas (Scheme I),[3,4] failed because the prerequisite α,α-diphenylpropargylamine[5] could not be prepared.

Scheme I

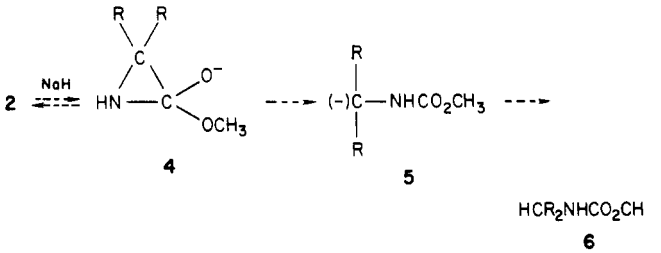


Scheme II



a, R = C_6H_5; R' = *tert*-butyl; R" = CH_3
b, R = C_6H_5; R' = *tert*-octyl; R" = CH_3
c, R = C_6H_5; R' = adamantyl; R" = CH_3
d, R = H; R' = *tert*-butyl; R" = C_2H_5

Scheme III



A method which did prove successful and, in fact, provides an alternative route to 3-substituted hydantoins is outlined in Scheme II. Starting with a 5,5-disubstituted 2,4-imidazolidinedione, hydrolysis to the amino acid and conversion to the ester allows recyclization to take place with the appropriate isocyanate.

In most cases the order of addition of amino ester **2b–d**, base, and isocyanate was not critical. However, with the diphenyl derivative **2a**, if isocyanate was not present upon the addition of sodium hydride, isomerization resulted with the formation of **6** (Scheme III). Presumably, stabilization of the anion intermediate **5** by the two phenyl groups provides the driving force for ring opening (**4**) in the forward direction as neither derivative when R = CH_3 or H behaves similarly.

Experimental Section

Diphenylglycine. In a Monel metal autoclave was placed 15 g (0.059 mol) of 5,5-diphenylhydantoin and 315 mL of 20% sodium hydroxide, and the mixture was heated at 180–185 °C for 27 h. Water was added and the mixture filtered. The filtrate was cooled in an ice bath and acidified with glacial acetic acid. The precipitate was collected, washed with water and ether, and recrystallized from ethanol–water to give 16.22 g (72%): mp 248–249 °C (lit. mp 244–245 °C).[6]

α,α-Diphenylglycine Methyl Ester. To a stirred mixture of 12.5 g (0.55 mol) of diphenylglycine in 125 mL of anhydrous methanol was bubbled anhydrous HCl gas. The addition took 1 h, during which time the mixture was kept at reflux. The excess methanol and HCl were removed in vacuo. After washing the solid with 3 × 50 mL portions of ether and 200 mL of 1 N Na_2CO_3, 200 mL of ether was added, and the mixture was stirred for 20 min. The water layer was extracted with 200 mL of ether, and the combined organics were dried ($MgSO_4$) and concentrated. The

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resulting oil was recrystallized from low-boiling petroleum ether, yielding 4.64 g (35%): mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (br s, 2 H), 3.72 (s, 3 H), 7.30 (s, 10 H); IR ($CHCl_3$) 3390, 3310, 3080, 3060, 2990, 2950, 1730, 1600 cm^{-1}.

A small sample was converted to the hydrochloride salt: mp 216–218 °C (lit. mp 216–218 °C).[7]

3-*tert*-Butyl-5,5-diphenyl-2,4-imidazolidinedione. To a stirred mixture of 1.6 g (0.33 mol) of NaH in 30 mL of THF was added 5.47 mL (0.048 mol) of *tert*-butyl isocyanate and 3.85 g (0.016 mol) of α,α-diphenylglycine methyl ester. The mixture was heated at reflux for 16 h. Toluene (20 mL) was added and the excess *tert*-butyl isocyanate, THF, and most of the toluene were distilled. The remaining material was dissolved in ether, and water was added to quench the excess NaH. The water layer was extracted with ether, and the combined organics were washed with water, dried ($MgSO_4$), and concentrated. Recrystallization from toluene yielded 2.08 g (42%) of **1a**: mp 193–193.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9 H), 7.34 (s, 10 H); IR ($CHCl_3$) 3440, 3080, 3060, 2995, 2970, 2930, 2900, 1780, 1715 cm^{-1}.[8]

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.05; H, 6.55; N, 8.98.

1-Adamantyl Isocyanate. To a stirred, ice cooled solution of 15.0 g (0.15 mol) of phosgene in 150 mL of toluene was added dropwise 30.0 g (0.38 mol) of pyridine followed by 14.2 g (0.094 mol) of 1-adamantanamine in 200 mL of ether, and the mixture was stirred for 30 min. An additional 50 mL of toluene was added and the mixture was stirred overnight. The reaction mixture was filtered and the filtrate was poured into ice–water. The aqueous layer was washed several times with ether and dried ($MgSO_4$), and the solvent was removed in vacuo. The remaining solid was recrystallized from pentane to yield 7.36 g (44%); mp 145–147 °C (lit. mp 144–145 °C).[9]

***tert*-Octyl Isocyanate.** Following the procedure for the preparation of 1-adamantyl isocyanate, the desired product was obtained in 24% yield as a colorless liquid: bp 137–143 °C; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H), 1.40 (s, 6 H), 1.50 (s, 2 H); IR (film) 2260 cm^{-1} (N=C=O). A small sample was converted into the urea with gaseous ammonia: mp 86–87 °C.

Anal. Calcd for $C_9H_{20}N_2O$: C, 62.79; H, 11.70; N, 16.26. Found: C, 62.83; H, 11.80; N, 16.20.

3-*tert*-Octyl-5,5-diphenyl-2,4-imidazolidinedione (1b). Following the procedure for the preparation of **1a**, 1.25 g (0.03 mol) of NaH, 3.50 g (0.02 mol) of *tert*-octyl isocyanate, and 3.00 g (0.0125 mol) of diphenylglycine methyl ester gave 1.80 g (39% of **1b** from ethanol): mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 0.8 (s, 9 H), 1.65 (s, 6 H), 1.9 (s, 2 H), 7.3 (s, 10 H).

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 76.02; H, 7.69; N, 7.81.

3-Adamantyl-5,5-diphenyl-2,4-imidazolidinedione (1c). Following the procedure for the preparation of **1a**, from 1.0 g (0.015 mol) of NaH, 4.00 g (0.023 mol) of adamantyl isocyanate, and 2.00 g (0.008 mol) of diphenylglycine methyl ester was obtained 1.00 g (31% of **1c** from ethanol): mp 217–219 °C; ^{1}H NMR ($CDCl_3$) δ 1.6–2.4 (adamantyl ring, 15 H), 2.75 (s, 10 H).

Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25. Found: C, 77.72; H, 6.75; N, 7.19.

***N*-(*tert*-Butylcarbamoyl)glycine Ethyl Ester (3d).** To a slurry of 1.5 g (0.031 mol) of NaH in 50 mL of ether was added 4.2 g (0.03 mol) of glycine ethyl ester hydrochloride (**2d**), and the mixture was stirred for 1 h at room temperature. *tert*-Butyl isocyanate (3.3 mL, 0.03 mol) was added, and the mixture was heated at reflux for 16 h. Water was added and the aqueous layer was extracted with 10 mL of ether. The combined organics were washed with 2 × 20 mL of water, dried ($MgSO_4$), and concentrated. The solid was recrystallized from ether–hexane to yield 2.94 g of **3d** (48.5%): mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.30 (s, 9 H), 3.81 (d, 2 H), 4.07 (q, 2 H), 5.10 (br s, 1 H), 5.43 (br s, 1 H); IR ($CHCl_3$) 3410, 2940, 2905, 2850, 1740, 1670 cm^{-1}; mass spectrum, *m/e* 202.

Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 53.54; H, 8.97; N, 13.81.

The reaction was repeated with a twofold excess of NaH producing **1d** in 45% yield.

3-*tert*-Butyl-2,4-imidazolidinedione (1d). Following the procedure for the preparation of **1a**, 1.0 g (0.021 mol) of NaH and 2.63 g (0.014 mol) of **3d** yielded 1.1 g (50% of **1d** from ether–hexane): mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 9 H), 3.72 (s, 2 H); IR ($CHCl_3$) 3680, 3600, 3450, 2950, 2920, 2860, 1750, 1700 cm^{-1}.

Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.73; H, 7.70; N, 17.83.

Rearrangement of Diphenylglycine Methyl Ester. Diphenylglycine methyl ester (0.48 g, 2 mmol) was dissolved in 5 mL of THF and added to 0.10 g (2 mmol) of NaH in 5 mL of THF. After heating at reflux for 1 h, cooling to room temperature, and quenching with 3 mL of water, the THF was removed in vacuo. The solid was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated. The solid recrystallized from ethanol yielded 0.35 g (73%) of **6**: mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3 H), 5.40 (br s, 1 H), 5.98 (d, 1 H), 7.21 (s, 10 H); IR 3445, 3080, 3030, 2995, 1730 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.48; H, 6.20; N, 5.65.

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Registry No. **1a**, 93504-25-7; **1b**, 93504-27-9; **1c**, 93504-26-8; **1d**, 93099-59-3; **2d**, 623-33-6; **3d**, 93504-28-0; **6**, 14983-80-3; 5,5-diphenylhydantoin, 57-41-0; diphenylglycine, 3060-50-2; α,α-diphenylglycine methyl ester, 93504-23-5; α,α-diphenylglycine methyl ester hydrochloride, 93504-24-6; *tert*-butyl isocyanate, 1609-86-5; 1-adamantanamine, 768-94-5; phosgene, 75-44-5; 1-adamantyl isocyanate, 4411-25-0; *tert*-octylamine, 107-45-9; *tert*-octyl isocyanate, 1611-57-0.

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Effect of Oxidized States of Heteroatoms and of Orthogonal π Systems on Radical Stabilities

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The rates of thermal decomposition of azo compounds of structure **1** are known to be sensitive to the nature of the substituent.[1] These rates have been used to assess incipient radical stabilities for which absolute thermodynamic stabilities are difficult or impossible to obtain.[2] Several addition compounds have been analyzed here in an attempt to understand the effect of oxidized states of heteroatoms (**1b,d,f**) and secondly to evaluate the influence of orthogonal π systems (**1m**).

We have previously noted that the influence of a π system adjacent to a radical center is the most significant factor in providing an enhanced rate of decomposition.[3] Furthermore, groups like nitriles, esters, and ketones which are carbanion-stabilizing groups also show pronounced radical stabilization. The effects of sulfur substituents are somewhat harder to rationalize, for with the exception of **1g**, the others (**1h–j**) all show negative activation entropies. This is unexpected for a fragmentation process where presumably three fragments are generated in the transition state.[2] Nonetheless, the stabilization of sulfur toward radical centers appears to be the result of better lone pair

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