isolated by concentrating the reaction mixture to yield a solid, dissolving in H_2O, and acidifying, yield 0.1 g.

N. 3-Anilino-3-phenylsuccinamic Acid (16).—A solution of 2.7 g (0.01 mol) of **14** and 40 ml each of EtOH, dioxane, and 1 *N* NaOH was allowed to stand overnight. After neutralizing with 40 ml of 1 *N* HCl, the reaction mixture was concentrated, yield 2 g (70%).

Registry No.—**2**, 5634-62-8; **3**, 25791-42-8; **4**, 25791-43-9; **5**, 13327-23-6; **6**, 25791-45-1; **7**, 25791-46-2; **8** (piperazinium salt), 25791-47-3; **9**, 25791-48-4; **10**, 25791-49-5; **11**, 25791-50-8; **12**, 25791-51-9; **13**, 25791-52-0; **14**, 25791-53-1; **15**, 25791-54-2; **16**, 25791-55-3; **17**, 25834-64-4; **19**, 25791-56-4; **20**, 25791-62-2; **21**, 25791-63-3; *N*-benzyl-2-phenylglycine ethyl ester·HCl, 25791-64-4; *N*-chloroacetyl-*N*-methyl 2-phenylglycine ethyl ester, 25791-65-5; *N*-benzyl-*N*-chloroacetyl-2-phenylglycine ethyl ester, 25791-66-6.

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Synthesis of a Bicyclohydantoin

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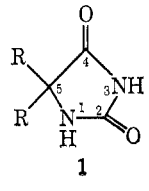
The preparation and intramolecular cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, are described. No products involving the imide nitrogen in the cyclizations could be obtained. Proof of structure of the compounds involving the amide nitrogen in the cyclization is discussed.

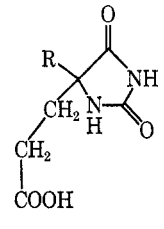
Previous reports have indicated that intermolecular alkylations of 5,5-disubstituted hydantoins, **1**, proceed exclusively at the imide nitrogen (N-3).[2] Amino-



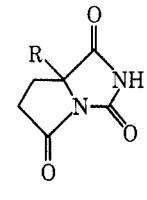
1

methylations utilizing formaldehyde,[3] aminoethylations with ethylenimine,[4] and Michael condensations[5] have also demonstrated a preference for the acidic imide function. Amide nitrogen (N-1) alkylations occur under more rigorous reaction conditions during which both nitrogens are alkylated. Mono N-1-alkylated hydantoins can be obtained by protecting the imide nitrogen with an aminomethyl group followed by alkylation of the amide nitrogen and then the removal of the protecting group by mild aqueous base hydrolysis.[6]

Intermolecular acylations have been reported to occur exclusively at the amide nitrogen and the intramolecular cyclization of the hydantoin propionic acids **2a**[7] and **2b**[8] yield only the amide cyclized products **3a** and **3b**, respectively.

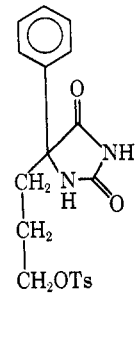


2a, R = H
b, R = CH_3, C_6H_5

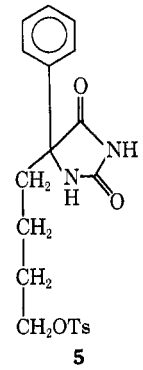


3

In these laboratories the base-catalyzed cyclizations of 5-phenyl-5-(3-hydroxypropyl)hydantoin tosylate, **4**, and 5-phenyl-5-(4-hydroxybutyl)hydantoin tosylate, **5**, produced only amide cyclized monomers. The synthesis of **4** and **5** and the proof of structure of the cyclized products are described below.



4



5

The conversion of 3-benzoylpropionic acid, **6a**, and 4-benzoylbutyric acid, **6b**, to 4-hydroxybutyrophenone, **8a**, and 5-hydroxyvalerophenone, **8b**, was performed by a lithium aluminum hydride reduction of the corresponding ethylene ketal monoethylene glycol esters **7a** and **7b** followed by acid hydrolysis according to the method of Pasto and Serve[9] (Scheme I).

The two keto alcohols, **8a** and **8b**, were converted to the 5-phenyl-5-(hydroxyalkyl)hydantoins, **9a** and **9b**,

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(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of The University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

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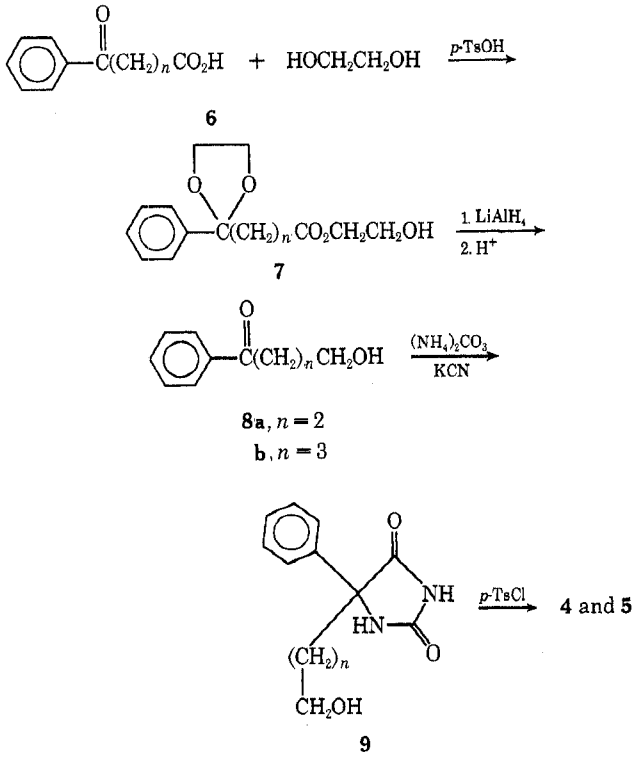
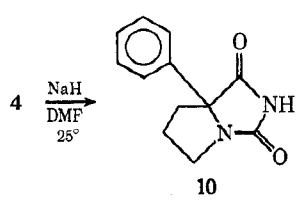
SCHEME I

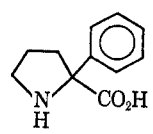


by condensation with ammonium carbonate and potassium cyanide.[10] The resulting hydantoin alcohols were converted to their respective tosylates **4** and **5**. The nmr spectra of **4** and **5** showed absorption at δ 8.5–8.7 and 10.7–10.9, indicating the amide and imide protons[11] to be present, thus excluding the possibility of alkylation having occurred during the formation of the tosylates.

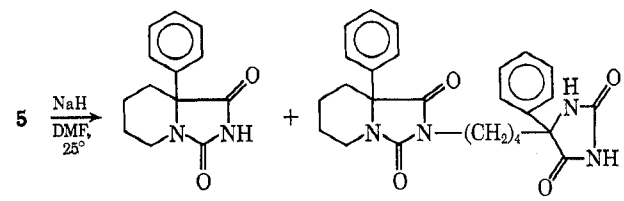
When the tosylate, **4**, was treated with sodium hydride, the products were the amide-alkylated hydantoin, 7(a)-phenylpyrrolidino[1,2-*d*]-1,3-(2*H*)-imidazolidinedione, **10**, and polymeric material.



The infrared spectrum of **10** exhibited strong absorptions at 3250 and 3150 cm^{-1} which are characteristic absorption bands for N-3-substituted hydantoins.[12] The nmr spectrum of **10** showed a broad singlet at δ 10.90 (imide proton)[11] and a molecular ion *m/e* 216. Base hydrolysis of **10** in ammonium hydroxide–hydrogen sulfide[13] or in barium hydroxide solution[14] afforded the amino acid, 2-phenylproline, **11**. Under conditions



analogous to the cyclization of **4**, the hydantoin tosylate **5** afforded 8(a)-phenylpiperidino[1,2-*c*]-1,3-(2*H*)-imidazolidinedione, **12**. The infrared spectrum of **12** showed absorption at 3270 and 3160 cm^{-1} (imide NH stretching frequency).[12] The nmr (broad singlet at δ 10.98)[11] and the mass spectrum (molecular ion *m/e* 230)



confirmed the assigned structure. A crystalline dimer (molecular ion *m/e* 460) was also obtained from the reaction. Its nmr spectrum showed single amide and imide protons. Structure **13** is the most plausible assignment based on the preferred routes of inter- and intramolecular alkylation in the hydantoins.

The use of higher temperatures and different base catalysts, in general, had no effect on the ring closure of **4** except to lower the overall yield of **10**. The use of potassium carbonate in dimethylformamide at elevated temperatures did raise the yield of the cyclic monomer, **12**. No evidence for intramolecular cyclization *via* the imide nitrogen to the [4.2.1]bicyclodiazanonane system could be obtained under any of the various conditions utilized.

Experimental Section[15]

4-Hydroxybutyrophenone (**8a**).—Essentially the method of Pasto and Serve was followed.[9] A mixture of 3-benzoylpropionic acid, **6a** (58.2 g, 0.33 mol), ethylene glycol (40.0 g, 0.65 mol), and TsOH (3.0 g) yielded a yellow oil, **7a** (68.2 g), whose spectra were consistent with the assigned structure.

A solution of the oil, **7a** (68.0 g; 0.30 mol), in Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ (27.7 g; 0.75 mol) in Et_2O at room temperature. The reaction yielded the desired product **8a** (32.3 g; 61% overall from **6a**).

The 2,4-dinitrophenylhydrazone of **8a** was prepared and recrystallized from EtOH–H_2O, mp 128–130° (lit.[16] mp 137°).

5-Hydroxyvalerophenone (**8b**).—A solution of 4-benzoylbutyric acid, **6b** (50.0 g, 0.26 mol), ethylene glycol (48.4 g, 0.68 mol), and TsOH (3.00 g) yielded **7b** (67.1 g) when subjected to the same procedure as above.[9] The ketal ester **7b** was allowed to react with excess $LiAlH_4$ in the manner utilized for **7a** to give the desired product **8b** (35.4 g; 76% from **6b**).

The 2,4-dinitrophenylhydrazone of **8b** was prepared and recrystallized from EtOH–H_2O, mp 136–141° (lit.[17] mp 145°).

5-Phenyl-5-(3-hydroxypropyl)hydantoin (**9a**).—A mixture of **8a** (20.0 g, 0.12 mol), KCN (15.9 g, 0.24 mol), and $(NH_4)_2CO_3$ (47.0 g, 0.49 mol) in EtOH–H_2O (500 ml) was heated at 55–60° with stirring for 22 hr. Part of the solvent was removed *in vacuo* and the reaction mixture cooled, diluted with ice–H_2O (200 ml), and acidified to congo red with 10% HCl. The precipitate was collected, washed repeatedly with water, and dried. Re-

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(15) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data were recorded on Beckman IR-8 and IR-10 spectrophotometers and are reported in cm^{-1}. Nmr data were recorded on Varian Associates Model A-60, A-60A, and HA-100 spectrophotometers (TMS) and are reported as ppm (δ) in the organic solvent specified. If D_2O was used as the solvent, sodium 3-trimethylpropanesulfonate was employed as an internal standard. Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind. and on an F & M Model 185, The University of Kansas. Molecular weights were determined on a Finnigan 1015 mass spectrometer.
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crystallization from EtOH–Me_2CO gave **9a** (14.6 g; 52%): mp 205–206°; nmr (DMSO-d_6) 1.06–1.72 (2 H, multiplet, CH_2), 1.74–2.30 (2 H, multiplet, CH_2), 3.40 (2 H, triplet, CH_2OH), 4.08–4.70 (1 H, multiplet, –OH), 7.20–7.68 (5 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.73 (1 H, broad singlet, imide).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.09; H, 6.04; N, 12.08.

5-Phenyl-5-(4-hydroxybutyl)hydantoin (9b).—A solution of **8b** (15.0 g, 0.084 mol), KCN (10.9 g, 0.17 mol), and $(NH_4)_2CO_3$ (32.3 g, 0.34 mol) in 50% EtOH–H_2O was allowed to react according to the above procedure. The desired product **9b** (19.2 g, 83%) was isolated: mp 168–170° (EtOH–Me_2CO); nmr (DMSO-d_6) 1.05–1.70 (4 H, multiplet, CH_2), 1.80–2.20 (2 H, multiplet, CH_2,) 3.20–3.60 (2 H, multiplet, CH_2OH), 4.20–4.50 (1 H, multiplet, –OH), 7.20–7.68 (5 H, multiplet, aromatic), 8.60 (1 H, broad singlet, amide), 10.70 (1 H, broad singlet, imide).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.88; H, 6.50; N, 11.29. Found: C, 62.92; H, 6.61; N, 11.35.

5-Phenyl-5-(3-hydroxypropyl)hydantoin *p*-Toluenesulfonate (4).—A solution of **8a** (2.34 g, 0.01 mol) in pyridine (30 ml) was cooled to 0°, treated with TsCl (5.70 g, 0.03 mol), and allowed to stand at 0° for 18 hr. The reaction mixture was poured into ice–H_2O and extracted with Et_2O. The Et_2O extracts were washed repeatedly with cold 10% HCl, H_2O, and dried ($MgSO_4$). Evaporation of the Et_2O afforded **4** (3.40 g, 88%): mp 153–154° (MeCO); nmr (DMSO-d_6) 1.15–2.65 (7 H, multiplet), 4.10 (2 H, multiplet, CH_2–OTs), 7.20–7.92 (9 H, multiplet, aromatic), 8.70 (1 H, broad singlet, amide), 10.80 (1 H, broad singlet, imide).

Anal. Calcd for $C_{19}H_{20}N_2O_5S$: C, 58.75; H, 5.19; N, 7.21; S, 8.26. Found: C, 58.67; H, 5.02; N, 7.40; S, 8.34.

5-Phenyl-5-(4-hydroxybutyl)-hydantoin *p*-Toluenesulfonate (5).—Compound **9b** (10.0 g, 0.40 mol) was allowed to react with TsCl (23.0 g, 0.120 mol) according to the procedure described for **9a**. The tosylate, **5** (14.2 g; 86%), crystallized from $CHCl_3$–Me_2CO: mp 187–188°; nmr (DMSO-d_6) 1.10–2.70 (9 H, multiplet), 4.01 (2 H, multiplet, CH_2OTs), 7.20–7.90 (9 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.75 (1 H, broad singlet, imide).

Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.68; H, 5.51; N, 6.96; S, 7.97. Found: C, 59.39; H, 5.41; N, 7.06; S, 8.09.

Cyclization of 5-Phenyl-5-(3-hydroxypropyl)hydantoin *p*-Toluenesulfonate.—To a stirred solution (under N_2) of **4** (0.500 g, 1.29 mmol) in DMF (75 ml) was added NaH (0.056 g, 1.29 mmol) (50% in mineral oil). The reaction mixture was stirred at room temperature for 24 hr, poured into ice–H_2O, and acidified to congo red with 10% HCl. The acidic mixture was extracted with $CHCl_3$ and the $CHCl_3$ extracts were washed with 5% $NaHCO_3$ and H_2O and dried ($MgSO_4$). The solvent ($CHCl_3$ and DMF) was removed *in vacuo* to give an amorphous gum which partially dissolved in $CHCl_3$. The mixture was filtered to give 0.091 g of a solid (mp 260° dec) which was insoluble in common organic solvents and in 10% NaOH. The substance was assumed to be a polymer.

Chromatography of the $CHCl_3$ layer on silica gel (80% $CHCl_3$, 20% EtAc) gave the bicyclo[3.3.0] derivative, 7(a)-phenylpyrrolidino[1,2-*d*]-1,3-(2*H*)-imidazolidinedione, **10** (0.120 g; 56%): mp 187–188° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3250, 3150, 2710, 1670–1760; nmr (DMSO-d_6) 1.55–2.45 (4 H, multiplet, CH_2), 3.00–3.86 (2 H, multiplet, CH_2), 7.25–7.66 (5 H, multiplet, aromatic), 10.88 (1 H, broad singlet, imide).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.35; H, 5.46; N, 13.30.

2-Phenyproline (11).—Compound **10** (1.00 g, 0.426 mmol) in H_2O (90 ml) and 35% NH_4OH (10 ml) was saturated with H_2S, placed in a steel autoclave, and heated at 100–105°. After 72 hr the reaction was cooled, and the contents were removed. The aqueous solution was heated to boiling and decolorized with charcoal. The water was removed *in vacuo* and the crude residue recrystallized from 95% EtOH to give **11** (0.540 g; 61%): mp 260–265° (dec); ir (KBr) 3390, 1600, 1433; nmr (D_2O) 2.00–3.80 (6 H, multiplet, $-CH_2-$) 7.50 (5 H, singlet, aromatic).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.59; N, 7.33. Found: C, 68.92; H, 6.63; N, 7.01.

Compound **11** was also prepared in 34% yield by refluxing **10** in 8% aqueous $Ba(OH)_2$.

Cyclization of 5-Phenyl-5-(4-hydroxybutyl)hydantoin *p*-Toluenesulfonate.—To a solution of 5-phenyl-5-(4-hydroxybutyl)hydantoin *p*-toluenesulfonate, **5** (3.00 g, 7.45 mmol), in DMF (500 ml) (under N_2) was added NaH (0.338 g, 7.45 mmol) (50% mineral oil). The reaction mixture was stirred for 24 hr, poured into ice–H_2O, and acidified to congo red with 10% HCl. The acidic mixture was extracted with $CHCl_3$ and the extracts were washed with 5% $NaHCO_3$ and water and dried ($MgSO_4$). Removal of the solvent ($CHCl_3$ and DMF) *in vacuo* gave a residue which partially dissolved in $CHCl_3$. The $CHCl_3$–insoluble material was filtered to give a white solid (1.41 g) (250° dec) which was insoluble in common organic solvents and in 10% NaOH. The $CHCl_3$-soluble fraction was chromatographed on silica gel.

Elution with 90% $CHCl_3$–10% EtAc gave the bicyclo[4.3.0]-hydantoin, 8(a)-phenylpiperidino[1,2-*c*]-1,3-(2*H*)-imidazolidinedione, **12** (0.041 g; 2.5%): mp 199–200°; ir (KBr) 3270, 3160, 1690–1790; nmr (DMSO-d_6), 1.15–2.05 (6 H, multiplet, CH_2), 2.35–3.00 (2 H, multiplet, CH_2), 7.45 (5 H, singlet, aromatic), 10.78 (1 H, broad singlet, imide); *m/e* 230.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.97; H, 6.24; N, 12.42.

Further elution with 50% $CHCl_3$–50% EtAc gave the dimer, **13** (0.341 g; 20%): mp 230–234°; nmr (DMSO-d_6), 0.80–2.40 (12 H, multiplet, CH_2), 2.45–3.70 (4 H, multiplet, CH_2), 7.30–7.70 (10 H, multiplet, aromatic), 8.63 (1 H, broad singlet, amide), 10.73 (1 H, broad singlet, imide).

Anal. Calcd for $C_{26}H_{28}N_4O_4$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.02; H, 6.13; N, 12.05.

The reaction was repeated in the presence of K_2CO_3 (1 equiv) and DMF at 100° for 12 hr. The yields of **12** and **13** were 12% and 7%, respectively.

Registry No.—**4**, 25860-39-3; **5**, 25860-40-6; **9a**, 25860-41-7; **9b**, 25860-42-8; **10**, 25860-43-9; **11**, 25860-44-0; **12**, 25860-45-1; **13**, 25860-46-2.

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