also thank Dr. C. Costello for exact mass measurements.

Registry No. 3, 76756-46-2; 4, 76756-41-7; *tert*-butyl phthalimido disulfide, 33704-41-5; *N*-(*tert*-butylthio)phthalimide, 17796-75-7; isopropyl phthalimido disulfide, 33704-40-4; *N*-(isopropylthio)-phthalimide, 17796-72-4; *N*-isopropylphthalimide, 304-17-6; benzyl phthalimido disulfide, 33704-38-0; *N*-benzylphthalimide, 2142-01-0; propyl phthalimido disulfide, 30912-77-7; *N*-propylphthalimide, 5323-50-2; 2-(methoxycarbonyl)ethyl phthalimido disulfide, 81572-60-3; phthalimide, 85-41-6.

N-Amidoyliminium Ion Cyclizations. Synthesis of Annelated Imidazolidinones

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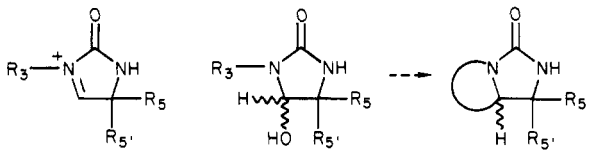
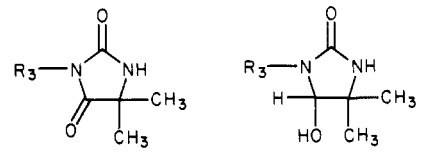
N-Acyliminium ions have proven to be valuable intermediates in the construction of heterocyclic compounds.[2] The corresponding *N*-amidoyl species (**1**) should be accessible from 4-hydroxy-2-imidazolidinones (**2**). In this paper, we describe the use of **2** for the preparation of annelated imidazolidinones **3**. These reactions formally extend the scope of intramolecular amidoalkylation transformations.[3,4]



1 **2** **3**

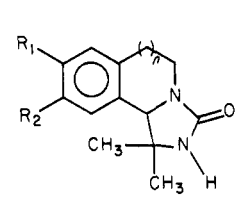
The desired starting materials (**4**) for this study were readily prepared in two steps from 5,5-dimethylhydantoin[5] (**4e**). Alkylation of **4e** with phenethyl bromide,[5] 3,4-dimethoxyphenethyl bromide,[6] *m*-methoxybenzyl chloride,[5] and (*m*-methoxyphenyl)propyl bromide,[7] respectively, under basic conditions (KOH/Me_2SO, 2 days) gave the corresponding 3-substituted hydantoins **4a–d** in moderate yields (55–83%). Reduction of **4a–d** with excess lithium aluminum hydride (THF, room temperature, 2 days) efficiently afforded the 4-hydroxy adducts **5a–d** (75–90% yields).[8] The ^1H NMR spectrum for each of these compounds (**5**) showed two distinct singlets in the upfield region (δ 0.99–1.28) for the *gem*-dimethyl groups.



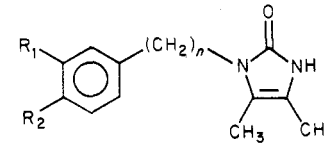
4 **5**

a, $R_3 = C_6H_5(CH_2)_2$; b, $R_3 = 3,4\text{-}(OCH_3)_2C_6H_3(CH_2)_2$; c, $R_3 = 3\text{-}(OCH_3)C_6H_4CH_2$; d, $R_3 = 3\text{-}(OCH_3)C_6H_4(CH_2)_3$; e, $R_3 = H$

Treatment of 4-hydroxy-2-imidazolidinone **5a** with trifluoroacetic acid and trifluoroacetic anhydride (12:1) in methylene chloride (reflux, 2 days) produced the desired tetrahydroisoquinoline **6** (40% yield). A key feature in the decoupled ^{13}C NMR spectrum for **6** was the appearance of six signals in the aromatic region (125.9–135.4 ppm). Moreover, two of these resonances (132.6 and 135.4 ppm) remained singlets in the corresponding coupled spectrum. Conversion of **5a** to **6** was dependent upon the choice of acidic conditions. Use of formic acid or trifluoroacetic acid did not lead to improved yields of **6**. Attempted cyclization of **5a** with a catalytic amount of *p*-toluenesulfonic acid in benzene (reflux, 1 day) gave only the imidazolone **7** (93% yield).



6, $R_1 = R_2 = H$; $n = 1$
8, $R_1 = R_2 = OCH_3$; $n = 1$
10, $R_1 = OCH_3$; $R_2 = H$; $n = 2$



7, $R_1 = R_2 = H$; $n = 2$
9, $R_1 = OCH_3$; $R_2 = H$; $n = 1$

Activation of the aromatic nucleus by the placement of electron-releasing methoxy substituents led to improved yields for the tetrahydroisoquinoline product. By use of similar cyclization conditions, **5b** gave **8** in 72% yield. The site of annelation was ascertained from the infrared and ^1H and ^{13}C NMR spectral data.

Attempts to extend this procedure for the preparation of the corresponding fused five- and seven-membered-ring systems proved successful only in the latter case. Treatment of **5c** with trifluoroacetic acid–trifluoroacetic anhydride gave the rearranged imidazolone **9** (28% yield) along with the recovered starting material **5c**. On the other hand, the 4-hydroxy-2-imidazolidinone **5d** afforded the benzotetrahydro-2-azepine derivative **10** (68%) under these same conditions. These results compare favorably with those previously observed for the cyclization of 1-substituted 5-bromo*hydantoins*.[9] In the latter study, cyclization was limited to the formation of the fused six-membered-ring systems. Neither the five- nor the seven-membered ring product was detected.

The results of this study demonstrate the utility of **2** for the preparation of annelated imidazolidinones. This methodology coupled with either hydrolytic[10,11] or reductive[8] ring opening of the imidazolidinone should permit the synthesis of a wide variety of vicinal diamines.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer Model 700 and 237B spectrometers. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Varian Associates Model FT-

(1) Fellow of the A. P. Sloan Foundation, 1977–1981. Camille and Henry Dreyfus Teacher-Scholar Grant Recipient, 1977–1982.

(2) For numerous elegant examples, please see: (a) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (b) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163. (c) Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Ibid.* **1976**, *32*, 1571. (d) Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, 3797 and references therein.

(3) Zaugg, H. E. *Synthesis* **1970**, *2*, 49. Zaugg, H. E.; Martin, W. B. in Org. *React.* **1965**, *14*, 60.

(4) The corresponding *inter*molecular amidoalkylation reaction with 5-methoxy*hydantoins* has been previously demonstrated.[2c]

(5) Available from Aldrich Chemical Co.

(6) Prepared by treatment of 3,4-dimethoxyphenethanol[5] with phosphorus tribromide.

(7) Available from ICN Pharmaceuticals, Inc.

(8) Further details on the reduction of 2,4-imidazolidinediones are to be submitted for publication by H. Kohn and S. Cortes.

(9) Zaugg, H. E.; Arendsen, D. L. *J. Heterocycl. Chem.* **1974**, *11*, 803.

(10) Flaster, H. F.; Kohn, H. *J. Heterocycl. Chem.* **1981**, *18*, 1425.

(11) Hofmann, K.; Melville, D. B.; duVigneaud, V. *J. Biol. Chem.* **1941**, *141*, 207 and references therein.

0022-3263/82/1947-2787$01.25/0

80A and T-60 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on a Varian Associates Model FT-80A spectrometer. Chemical shifts are in parts per million relative to Me_4Si, and coupling constants (J values) are in hertz. 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. Exact masses were determined by peak matching. 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. When dry solvents were required, CH_2Cl_2 was distilled from P_2O_5, C_6H_6 was distilled and then stored over Na, and THF was distilled from $LiAlH_4$.

All reactions were run under N_2, and all glassware was dried before use unless otherwise noted. Preparative column chromatography was run by using Merck silica gel 60 PF-254 (catalog No. 7747).

General Procedure for the Preparation of 3-Substituted Derivatives of 5,5-Dimethyl-2,4-imidazolidinedione (4e). A solution of 5,5-dimethyl-2,4-imidazolidinedione **4e**; 0.10 mol), KOH (0.11 mol), and Me_2SO (100 mL; treated with 4-Å molecular sieves, and then freshly distilled from CaH_2) was heated at 100–110 °C (1 h) and then cooled to room temperature. An Me_2SO (30 mL) solution of the alkylating agent (0.11 mol) was then added to the reaction solution, and the mixture was maintained at room temperature (2 days). (In the preparation of **4b** and **4d** the reaction mixture was heated additionally at 70 °C for 5 h.) H_2O (100 mL) was then added to the reaction solution, and the solution was extracted with Et_2O (3 × 400 mL). The organic layers were combined, washed with H_2O (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude oil obtained was purified by column chromatography (10–15 g of silica gel/g of crude product) under reduced pressure by using C_6H_6–EtOAc (65:35) as the eluant. The desired alkylation product was recrystallized from cyclohexane.

3-Phenethyl-5,5-dimethyl-2,4-imidazolidinedione (4a): 79% yield; mp 100–101 °C; IR (KBr) 3300, 1765, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H), 2.94 (t, J = 7 Hz, 2 H), 3.75 (t, J = 7 Hz, 2 H), 6.63 (br s, 1 H), 7.23 (s, 5 H); ^{13}C NMR ($CDCl_3$) 24.9, 33.8, 39.4, 58.6, 126.6, 128.5, 129.0, 137.8, 156.7, 177.3 ppm; the signals located at 24.9, 128.5 and 129.0 ppm were approximately twice the intensity of neighboring peaks; mass spectrum, m/e (relative intensity) 232 (57), 113 (8), 105 (13), 104 (100), 99 (7), 91 (24).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.34; H, 6.90; N, 12.07. Found: C, 67.32; H, 6.81; N, 12.12.

3-(3′,4′-Dimethoxyphenethyl)-5,5-dimethyl-2,4-imidazolidinedione (4b): 55% yield; mp 102–104 °C; IR (KBr) 3250, 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 6 H), 2.90 (t, J = 7 Hz, 2 H), 3.75 (t, J = 7 Hz, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 6.32 (br s, 1 H), 6.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) 24.9, 33.3, 39.5, 55.9, 58.6, 111.3, 112.2, 121.1, 130.3, 147.8, 148.9, 156.5, 177.3 ppm; the signals at 24.9 and 55.9 ppm were approximately twice the intensity of neighboring peaks; mass spectrum, m/e (relative intensity) 292 (34), 165 (12), 164 (100), 151 (38), 149 (18); mol wt 292.1431 (calcd for $C_{15}H_{20}N_2O_4$ 292.1423).

3-(*m*-Methoxybenzyl)-5,5-dimethyl-2,4-imidazolidinedione (4c): 83% yield; mp 114–116 °C; IR (KBr) 3210, 1785, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 6 H), 3.77 (s, 3 H), 4.62 (s, 2 H), 6.46 (br s, 1 H), 6.86–7.23 (m, 4 H); ^{13}C NMR ($CDCl_3$) 25.0, 42.0, 55.2, 58.9, 113.4, 113.6, 120.3, 129.7, 137.7, 156.4, 159.8, 177.2 ppm; the signal at 25.0 ppm was approximately twice the intensity of nearby peaks; mass spectrum, m/e (relative intensity) 248 (100), 163 (54), 135 (8), 134 (11), 121 (21), 91 (10), 78 (8), 77 (8).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found: C, 62.84; H, 6.47; N, 11.32.

3-[3-(3-Methoxyphenyl)propyl]-5,5-dimethyl-2,4-imidazolidinedione (4d): 68% yield; mp 61–63 °C, IR (KBr) 3300, 1770, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 6 H), 1.69–2.13 (m, 2 H), 2.63 (t, J = 7 Hz, 2 H), 3.55 (t, J = 7 Hz, 2 H), 3.79 (s, 3 H), 6.44 (br s, 1 H), 6.56–7.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) 25.0, 29.5, 33.0, 39.4, 55.1, 58.6, 111.5, 114.0, 120.7, 129.4, 142.7, 156.8, 159.7, 177.5 ppm; mass spectrum, m/e (relative intensity) 276 (66), 148 (35), 135 (48), 122 (100), 121 (21), 117 (14), 91 (21).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.19; H, 7.31; N, 10.16.

General Procedure for the Reduction of 3-Alkyl-5,5-dimethyl-2,4-imidazolidinedione (5). An equimolar amount of $LiAlH_4$ was added in increments to a THF (100 mL of THF/0.1 g of $LiAlH_4$) solution of the 3-alkyl-5,5-dimethylhydantoin (**4**). The reaction mixture was allowed to stir at room temperature (2 days) and then the excess $LiAlH_4$ destroyed with H_2O and aqueous NaOH.[12] The reaction mixture was filtered, and the organic layer was collected, dried ($MgSO_4$), and concentrated to dryness. The desired 4-hydroxy-2-imidazolidinones (**5**) were recrystallized from $CHCl_3$.

3-Phenethyl-4-hydroxy-5,5-dimethyl-2-imidazolidinone (5a): 83% yield; mp 160–161 °C; IR (KBr) 3300, 1690 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.99 (s, 3 H), 1.08 (s, 3 H), 3.34–3.43 (m, 4 H), 4.44 (d, J = 7 Hz, 1 H), 5.82 (d, J = 7 Hz, 1 H), 6.44 (s, 1 H), 7.23 (s, 5 H); ^{13}C NMR (Me_2SO-d_6) 21.2, 27.6, 33.9, 40.2, 55.2, 85.7, 125.9, 128.2, 128.6, 139.6, 158.7 ppm; the signals at 128.2 and 128.6 ppm were approximately twice the intensity of neighboring peaks; mass spectrum, m/e (relative intensity) 234 (38), 143 (100), 105 (24), 104 (11), 91 (31).

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.68; H, 7.68; N, 11.98.

3-(3′,4′-Dimethoxyphenethyl)-4-hydroxy-5,5-dimethyl-2-imidazolidinone (5b): 81% yield; mp 150–152 °C; IR (KBr) 3390, 3250, 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.00 (s, 3 H), 1.06 (s, 3 H), 2.69–3.49 (m, 4 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 4.45 (d, J = 7 Hz, 1 H), 5.80 (d, J = 7 Hz, 1 H), 6.42 (br s, 1 H), 6.42–6.81 (m, 3H); ^{13}C NMR (Me_2SO-d_6) 21.9, 27.6, 33.4, 40.3, 55.2, 55.3, 55.4, 85.6, 111.8, 112.5, 120.5, 132.0, 147.1, 148.5, 158.6 ppm; mass spectrum, m/e (relative intensity) 294 (14), 165 (18), 164 (100), 151 (24), 149 (12), 143 (9); mol wt 294.1577 (calcd for $C_{15}H_{22}N_2O_4$ 294.1579).

3-(*m*-Methoxybenzyl)-4-hydroxy-5,5-dimethyl-2-imidazolidinone (5c): 72% yield; mp 143.5–144.5 °C; IR (KBr) 3300, 1695 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.10 (s, 6 H), 3.73 (s, 3 H), 3.96 (d, J = 16 Hz, 1 H), 4.34 (d, J = 7 Hz, 1 H), 4.53 (d, J = 16 Hz, 1 H), 5.92 (d, J = 7 Hz, 1 H), 6.64 (s, 1 H), 6.78–7.25 (m, 4 H); ^{13}C NMR (Me_2SO-d_6) 21.9, 27.7, 41.5, 54.8, 55.3, 85.2, 112.1, 112.8, 119.4, 129.3, 140.2, 158.7, 159.3 ppm; mass spectrum, m/e (relative intensity) 250 (41), 179 (27), 165 (16), 136 (100), 129 (26), 122 (43), 121 (64), 105 (16), 91 (17).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.40; H, 7.20; N 11.20. Found: C, 62.42; H, 7.16; N, 11.13.

3-[3-(3-Methoxyphenyl)propyl]-4-hydroxy-5,5-dimethyl-2-imidazolidinone (5d): 76% yield; mp 98–100 °C; IR (KBr) 3360, (100), 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3 H), 1.26 (s, 3 H), 1.75–2.06 (m, 2 H), 2.63 (t, J = 7 Hz, 2 H), 3.13–3.56 (m, 2 H), 3.78 (s, 3 H), 4.59 (m, 2 H), 6.43 (br s, 1 H), 6.63–7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$) 21.8, 28.1, 29.8, 33.3, 39.5, 55.1, 56.4, 87.4, 111.2, 114.2, 120.8, 129.4, 143.3, 159.7 ppm; the signal at 159.7 ppm was approximately twice the intensity of nearby peaks; mass spectrum, m/e (relative intensity) 278 (80), 176 (51), 157(73), 148 (65), 147 (51), 144 (46), 126 (42), 124 (92), 122 (100), 121 (99), 109 (38).

Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.07. Found: C, 64.85; H, 8.02; N, 10.16.

General Procedure for Intramolecular Cyclization of 3-Alkyl-4-hydroxy-5,5-dimethyl-2-imidazolidinone (5). The 3-alkyl-4-hydroxy-5,5-dimethyl-2-imidazolidinone (**5**; 0.015 mol) was added to a solution of trifluoroacetic anhydride (0.02 mol), trifluoroacetic acid (20 mL), and CH_2Cl_2 (150 mL) and was heated to reflux (2 days). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and then neutralized with an aqueous 15% NaOH solution. The organic layer was separated, washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo. Recrystallization of the residue afforded the observed products.

Imidazolidinone 6: 40% yield (from benzene–chloroform, 1:1); mp 171–173 °C; IR (KBr) 3200, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3 H), 1.60 (s, 3 H), 2.56–3.10 (m, 3 H), 4.06–4.25 (m, 1 H), 4.63 (s, 1 H), 4.96 (br s, 1 H), 7.16 (s, 4 H); ^{13}C NMR ($CDCl_3$) 24.1, 28.5, 29.9, 36.9, 59.2, 64.3, 125.9, 126.4, 127.0, 129.8, 132.6, 135.4, 159.8 ppm; mass spectrum, m/e (relative intensity) 216 (87), 215

(12) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 584 and references therein.

(12), 132 (40), 131 (100), 130 (69); mol wt 216.1269 (calcd for $C_{13}H_{16}N_2O$ 216.1262).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.40; N, 12.96. Found: C, 72.16; H, 7.36; N, 12.87.

Imidazolidinone 8: 72% yield (from $CHCl_3$); mp 160–162 °C; IR (KBr) 3200, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 1.59 (s, 3 H), 2.78–2.95 (m, 3 H), 3.97 (s, 6 H), 4.13 (d, J = 7 Hz, 1 H), 4.61 (s, 1 H), 4.75 (br s, 1 H), 6.64 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) 24.0, 28.5, 29.5, 37.0, 55.8, 56.1, 59.3, 64.1, 108.8, 112,2, 124.1, 127.9, 147.7, 148.1, 159.8 ppm; mass spectrum, m/e (relative intensity) 276 (19), 192 (19), 191 (100), 190 (20), 176 (30); mol wt 276.1468 (calcd for $C_{15}H_{20}N_2O_3$ 276.1474).

Imidazolidinone 10: 68% yield (from benzene–chloroform, 1:1); mp 216–219 °C; IR (KBr) 3250, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 1.44 (s, 3 H), 2.00–3.44 (m, 6 H), 3.80 (s, 3 H), 4.38–4.94 (br s, 1 H), 4.61 (s, 1 H), 6.50–7.13 (m, 3 H); ^{13}C NMR ($CDCl_3$) 25.3, 26.4, 29.6, 31.1, 37.6, 55.2, 57.8, 73.4, 111.7, 116.7, 127.2, 129.3, 141.0, 159.1, 160.2 ppm; mass spectrum, m/e (relative intensity) 260 (23), 176 (18), 175 (100), 160 (15), 147 (29); mol wt 260.1529 (calcd for $C_{15}H_{20}N_2O_2$ 260.1525).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.23; H, 7.78; N, 10.78.

3-(3-Methoxybenzyl)-5,5-dimethyl-2-imidazolone (9): 27% yield (from EtOH); mp 186.5–189.5 °C; IR (KBr) 3200, 1700 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.79 (s, 3 H), 1.85 (s, 3 H), 3.71 (s, 3 H), 4.64 (s, 2 H), 6.56–7.50 (m, 4 H), 9.63 (br s, 1 H); ^{13}C NMR (Me_2SO-d_6) 8.1, 8.9, 41.6, 54.8, 111.0, 112.0, 112.3, 112.9, 118.6, 129.5, 140.4, 153.4, 159.3 ppm; mass spectrum, m/e (relative intensity) 232 (100), 121 (72), 111 (24), 91 (21), 78 (20), 77 (14).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.15; H, 6.92; N, 11.91.

3-Phenethyl-5,5-dimethyl-2-imidazolone (7). A benzene (80 mL) solution of **5a** (1.43 g, 0.005 mol) and *p*-toluenesulfonic acid monohydrate (1.43 g, 0.0075 mol) was heated to reflux (24 h) during which time the H_2O was azeotropically removed. The benzene solution was then washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated to dryness. The crude product was recrystallized from EtOH to give 1.00 g (93%) of **7**: mp 164–167 °C; IR (KBr) 3200, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3 H), 1.94 (s, 3 H), 2.89 (t, J = 8 Hz, 2 H), 3.75 (t, J = 8 Hz, 2 H), 7.19 (s, 5 H), 10.25 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 8.9, 9.4, 36.0, 42.6, 112.1, 113.7, 126.4, 128.5, 129.0, 138.9, 154.4 ppm; the signals at 128.5 and 129.0 ppm were approximately twice the intensity of neighboring peaks; mass spectrum, m/e (relative intensity) 216 (43), 125 (81), 112 (100), 111 (18), 105 (22), 97 (80), 91 (19).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.40; N, 12.96. Found: C, 71.96; H, 7.44; N, 12.88.

Acknowledgment. We thank Mr. Sergio Cortes for many helpful discussions. Support of this work by the National Institutes of Health (Grant No. NS15604) is gratefully acknowledged.

Registry No. 4a, 81572-12-5; **4b**, 81572-13-6; **4c**, 81572-14-7; **4d**, 81572-15-8; **4e**, 77-71-4; **5a**, 81572-16-9; **5b**, 81572-17-0; **5c**, 81572-18-1; **5d**, 81572-19-2; **6**, 81572-20-5; **7**, 65383-36-0; **8**, 81583-49-5; **9**, 81572-21-6; **10**, 81572-22-7; phenethyl bromide, 103-63-9; 3,4-dimethoxyphenethyl bromide, 40173-90-8; *m*-methoxybenzyl chloride, 824-98-6; (*m*-methoxyphenyl)propyl bromide, 6943-97-1.

Synthesis of Tetrakis(perfluorocyclohexyl)methane and Bis(perfluorocyclohexyl)difluoromethane by Direct Fluorination

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Carefully controlled low-temperature direct fluorination has become perhaps the most facile chemical technique for rapid preparation of unknown fluorocarbon compounds and particularly structurally unknown[1] classes of compounds. The synthesis of tetrakis(perfluorocyclohexyl)methane and bis(perfluorocyclohexyl)difluoromethane was undertaken because they possess chemical and stereochemical properties thought to be advantageous for use in fluorocarbon emulsions for oxygen transport (see Figure 1). Such emulsions are currently used as artificial blood in humans[2] and were studied in earlier pioneering experiments[3] establishing the utility of this novel concept.

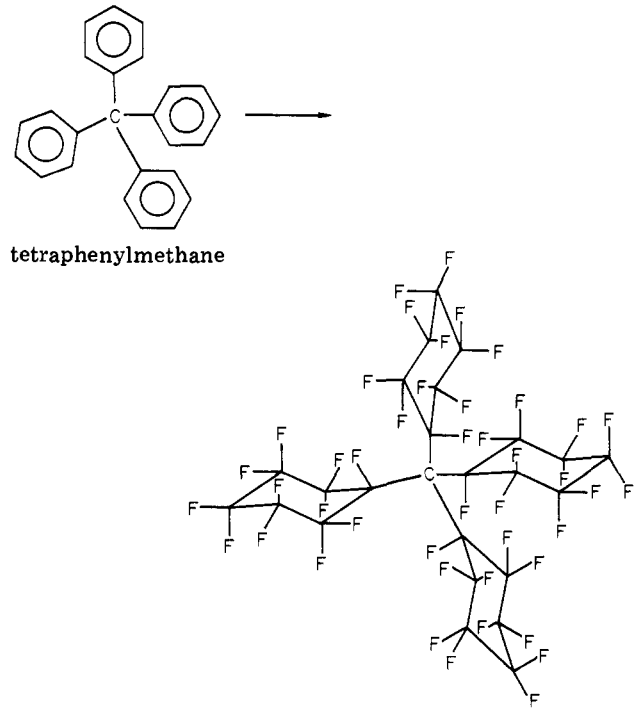

Figure 1.

We have previously shown that polynuclear aromatic systems could be exhaustively fluorinated to produce their saturated fluoroalkane analogues.[1] Thus, it appeared possible that both tetraphenylmethane and diphenylmethane could be converted to their perfluorocyclohexyl analogues.

Experimental Section

Fluorination of Tetraphenylmethane. Tetraphenylmethane (0.26 g) was ground to a fine powder (100 mesh) and placed in a nickel flow reactor described previously for the direct fluorination of solids.[1] After following the reaction conditions described below, 0.89 g of the white solid, tetrakis(perfluorocyclohexyl)methane (96% yield), was recovered from the reactor (mp 91–92 °C). ^{19}F NMR in perfluorobenzene consisted of a broad multiplet centered at +124 ppm from $CFCl_3$ and a second multiplet at +180 from $CFCl_3$ which integrated for 10 and 1, respectively. Infrared analysis of a KBr disk gave absorptions at 1190 (br), 1000 (m), 960 (m), 550 (w), 495 (w), and 470 (w) cm^{-1}. Mass spectral analysis gave a base peak of m/e 281 ($C_6F_{11}^+$) along with peaks at 855, 574, and 293 corresponding to the parent minus one, two, and three perfluorophenyls, respectively.

Anal. Calcd for $C(C_6F_{11})_4$: C, 26.4; F, 73.6. Found: C, 26.1; F, 73.4.

Fluorination of Diphenylmethane. Diphenylmethane (0.24 g) was placed in a fluorine reactor, and the reaction conditions below were followed. Bis(perfluorocyclohexyl)difluoromethane was obtained in 93% yield (0.72 g) by recrystallization in hexafluorobenzene. ^{19}F NMR of the product dissolved in C_6F_6 gave

(1) R. J. Lagow and J. L. Margrave, *Prog. Inorg. Chem.*, **26**, 161 (1979).
(2) T. Kawabata, *Jpn. Times*, 10 (1980).
(3) L. C. Clark, Jr., S. Kaplan, and F. Becattini, *Pediatr. Res.*, **4**, 464 (1970).

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