(2 H, q, J = 6 Hz, CH_2), 1.41 (6 H, br s, CH_3's).

A solution of crude (*S*)-**3b** (7.83 g) in 70 mL of THF cooled to 0 °C under nitrogen was treated sequentially with acetic anhydride (132 mmol, 12.46 mL, 13.46 g, 3.0 equiv), pyridine (154 mmol, 12.43 mL, 12.16 g, 3.5 equiv), and 4-(dimethylamino)-pyridine[5] (5 mg). The reaction mixture was allowed to warm to 25 °C (ca. 3 h) where it was stirred for 20 h before being poured onto crushed ice. The crude product was extracted into CH_2Cl_2 (4 × 25 mL) and the organic phase was washed with 5% aqueous HCl (10 × 25 mL, which effected removal of pyridine and hydrolysis of the ketal-protecting group), saturated aqueous $NaHCO_3$, and water and dried ($MgSO_4$). The acid layer was reextracted with CH_2Cl_2 (5 × 25 mL) to recover additional alcohol. Chromatography (SiO_2, 80% ether–hexane eluant) gave 3.85 g [46% from (*S*)-**2b**] of pure (*S*)-**6b** as a colorless oil: $[\alpha]^{24}_D$ −16.79° (neat); ^1H NMR ($CDCl_3$) δ 4.20 (1 H, m, CHO), 4.15 (2 H, t, J = 6 Hz, CH_2OAc), 4.00 (2 H, d, J = 6 Hz, CH_2OAc), 2.08 and 2.00 (6 H, 2 s, CH_3CO_2), 1.78 (2 H, q, J = 6 Hz, CH_2); IR (film) ν_{max} 3435 (OH), 2950, 1720 (C=O), 1350, 1220, 1120 cm^{-1}; mass spectrum, m/e (relative intensity) 172 (0.03, loss of H_2O), 117 (2), 104 (0.8), 100 (3), 86 (0.2), 70 (3), 57 (11), 43 (51), 31 (base). Anal. Calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.14; H, 7.50.

(*S*)-1,2,4-Butanetriol 1,4-Diacetate 2-Methanesulfonate [(*S*)-6c]. A solution of (*S*)-**6b** (7.0 g, 36.8 mmol) in 70 mL of CH_2Cl_2 cooled to −15 °C under argon was treated sequentially with Et_3N (9.23 mL, 6.70 g, 66 mmol, 1.8 equiv) and methanesulfonyl chloride[3] (4.27 mL, 6.32 g, 55 mmol, 1.5 equiv) and the resulting mixture was stirred for 1 h at −15 °C before being poured onto crushed ice. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, ether eluant) afforded 9.86 g (100%) of pure (*S*)-**6c** as a colorless oil: $[\alpha]^{24}_D$ −8.68° (*c* 5.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.0 (1 H, m, CHOMs), 4.38–4.08 (4 H, m, CH_2OAc), 3.05 (3 H, s, CH_3SO_3), 2.10 and 2.05 (6 H, 2 s, CH_3CO_2), 2.2–1.91 (2 H, m, CH_2); IR (film) ν_{max} 1725 (C=O), 1330, 1215, 1160, 1030, 890 cm^{-1}; mass spectrum m/e (relative intensity) 268 (M^+, 2), 195 (6), 134 (20), 85 (55), 83 (base), 78 (36), 49 (63). Anal. Calcd for $C_9H_{16}O_7S$: C, 40.28; H, 5.96. Found: C, 40.00; H, 5.90.

(*R*)-4-Hydroxy-1,2-epoxybutane [(*R*)-7a, (*R*)-(2-Hydroxyethyl)oxirane]. A solution of (*S*)-**6c** (9.86 g, 36.8 mmol) in 250 mL of 50% MeOH–THF containing anhydrous K_2CO_3 (11.20 g, 80 mmol, 2.2 equiv) was stirred at 25 °C for 10 h. Removal of the solvent in vacuo and chromatography (SiO_2, ether eluant) gave 2.73 g (85%) of pure (*R*)-**7a** as a colorless oil: $[\alpha]^{23}_D$ +16.64° (*c* 5.00, acetone), +23.42° (*c* 5.00, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.72 (2 H, t, J = 6 Hz, CH_2OH), 3.00 (1 H, m, CHO), 2.70 (1 H, t, J = 4 Hz) and 2.52 (2 H, dd, J = 4, 2 Hz) for epoxide CH_2O, 1.78 (3 H, m, CH_2, OH); IR (film) ν_{max} 3350 (OH), 2900, 1460, 1380, 1220, 1010, 850, 785 cm^{-1}; mass spectrum, m/e (relative intensity) 88 (M^+, 0.5%), 87 (5), 70 (3), 58 (16), 57 (45), 31 (base). Anal. Calcd for C_4H_8O: C, 54.53; H, 9.15. Found: C, 54.33; H, 9.18.

(*R*)-(2-Hydroxyethyl)oxirane Methanesulfonate [(*R*)-7b]. A solution of (*R*)-**7a** (2.5 g, 28.0 mmol) in 30 mL of CH_2Cl_2 cooled to −20 °C was treated sequentially with Et_3N (7.02 mL, 5.1 g, 50.0 mmol, 1.8 equiv) and methanesulfonyl chloride[3] (3.25 mL, 4.81 g, 42.0 mmol, 1.5 equiv) and the resulting reaction mixture was stirred for 1 h (−20 °C) before being poured onto crushed ice. The organic layer was washed with 5% aqueous HCl, saturated $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (SiO_2, 75% ether–hexane eluant) afforded 3.61 g (78%) of pure (*R*)-**7b** as a colorless oil: $[\alpha]^{25}_D$ +20.04° (*c* 5.00, acetone); ^1H NMR ($CDCl_3$) δ 4.29 (2 H, t, J = 6 Hz, CH_2OMs), 3.07 (3 H, s, CH_3SO_3), 2.95 (1 H, m, epoxide CHO), 2.78 (1 H, t, J = 4 Hz) and 2.49 (1 H, dd, J = 4, 2 Hz) for epoxide CH_2O, 1.98 (2 H, q, J = 6 Hz, CH_2); IR (film) ν_{max} 2960, 1400, 1325, 1155, 775 cm^{-1}; mass spectrum, m/e (relative intensity) 166 (M^+, 10), 151 (4), 97 (33), 79 (55), 71 (78), 57 (base), 55 (55). Anal. Calcd for $C_5H_{10}O_4S$: C, 36.13; H, 6.02. Found: C, 35.98; H, 5.80.

(*R*)-4-Iodo-1,2-epoxybutane [(*R*)-1, (*R*)-(2-Iodoethyl)oxirane)]. A solution of (*R*)-**7b** (3.61 g, 22 mmol) in 110 mL of acetone cooled to 0–5 °C was treated sequentially with anhydrous K_2CO_3 (304 mg, 0.1 equiv) and NaI (6.59 g, 44.0 mmol, 2.0 equiv) and the resulting mixture was allowed to warm slowly to 25 °C (ca. 3 h) where it was stirred for 48 h. The reaction mixture was partitioned between ether–water (1:1), the organic phase was washed with saturated NaCl and dried ($MgSO_4$), and the solvent was removed at aspirator pressure (<30 °C). Chromatography (SiO_2, 70% ether–hexane eluant) afforded 2.80 g (71%) of pure (*R*)-1: $[\alpha]^{25}_D$ +13.36° (*c* 5.00, CH_2Cl_2);[4] ^1H NMR ($CDCl_3$) δ 3.25 (2 H, t, J = 6 Hz, CH_2I), 3.09–2.84 (1 H, m, epoxide CHO), 2.80 (1 H, t, J = 4 Hz) and 2.56 (1 H, dd, J = 4, 2 Hz) for epoxide CH_2O, 2.22–1.86 (2 H, m, CH_2); IR (film) ν_{max} 2980, 2950, 1400, 1223, 1150, 875, 810 cm^{-1}; mass spectrum, m/e (relative intensity) 198 (M^+, 2), 71 (80), 57 (base). Anal. Calcd for C_4H_4IO: C, 24.24; H, 3.53. Found: C, 24.16; H, 3.46.

Acknowledgment. This work was assisted financially by a grant from the Anna Fuller Fund, a Biomedical Research Grant (RR 5606), and the University of Kansas General Research Allocation no. 3605-xO-0038. We are grateful to the Research Corporation for funds used in the purchase of equipment.

Registry No. (*S*)-**1**, 76282-41-2; (*R*)-**1**, 76282-42-3; (*S*)-**2a**, 97-67-6; (*S*)-**2b**, 617-55-0; (*S*)-**2c**, 76332-79-1; (*S*)-**2d**, 76282-43-4; (*S*)-**3a**, 5055-09-4; (*S*)-**3b**, 66348-33-2; (*S*)-**4a**, 76282-44-5; (*S*)-**4b**, 5055-10-7; (*S*)-**5**, 76282-45-6; (*S*)-**6b**, 76282-46-7; (*S*)-**6c**, 76282-47-8; (*R*)-**7a**, 76282-48-9; (*R*)-**7b**, 76282-49-0; 2-methoxypropene, 116-11-0.

Synthesis and Properties of Two Dioxadioxoparacyclophanes

Clarence W. Schimelpfenig* and Randal R. Ford

Department of Chemistry, Texas Wesleyan College, Fort Worth, Texas 76105

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Considerable current interest centers on macrocycles with lipophilic cavities.[1,2] These molecules may serve as models for enzyme active sites,[2] as ring moieties in rotaxanes and catenanes,[3] or as hosts for inclusion complexes.[4] This report deals with two such macrocycles which have functional groups on opposite sides of the ring.

14,34-Dioxa-4,24-dioxo[7.1.7.1]paracyclophane[5] (**3**) and 12,30-dioxa-3,21-dioxo[5.1.5.1]paracyclophane (**4**) were made from diesters by the Dieckmann condensation. Reactions at high dilution were necessary to preclude complete formation of polymers. Even with dilution, yields of the diphenyl ether derivatives, **3** and **4**, were low. The corresponding monoketones were not formed. The C–O–C bond angle and the bond lengths are evidently sufficient to prevent formation of the smaller rings in this reaction that involves a nucleophilic addition of one end of the chain to the other end of the chain. Lüttringhaus found that a chain of over eight atoms was required to connect the 4 and 4′ positions of diphenyl ether in a nucleophilic substitution reaction,[6] although the 4 and 4′ positions of

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(3) Schill, G. "Catenanes, Rotaxanes, and Knots"; Academic Press: New York, 1971.
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(5) The "paracyclophane" nomenclature has been taken from: Smith, B. W. "Bridged Aromatic Compounds"; Academic Press: New York, 1964. Second names in the Experimental Section are the systematic names provided by personal communication from Dr. K. L. Loening, Chemical Abstracts Service.
(6) Lüttringhaus, A. *Justus Liebigs Ann. Chem.* **1937**, *528*, 223.

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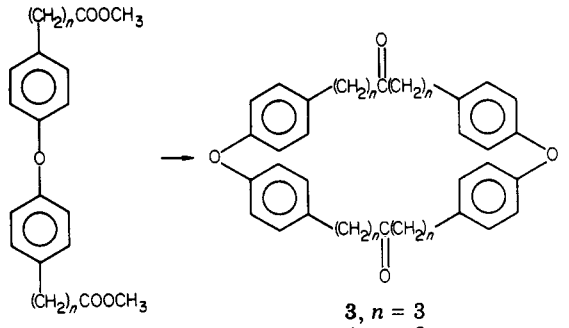

1, $n = 3$
2, $n = 2$

3, $n = 3$
4, $n = 2$

diphenyl sulfone could be bridged by a chain of seven atoms.[7] A precedent for refusal to form the smaller rings is also found in acyloin condensation experience. The acyloin derivative of [7.1]paracyclophane could not be made directly by cyclization of the substituted diphenylmethane.[8]

Infrared spectra of **3**, **4**, 4,17-dioxo[7.7]paracyclophane, 4,17-dioxo[7.7]metacyclophane,[9] and cyclotetradecanone[10] had carbonyl group stretching frequencies of 1713, 1713, 1715, 1717, and 1716 cm^{-1}, respectively. Location of bands of the four cyclophanes at almost the same frequency as that of strain-free cyclotetradecanone indicates that each cyclophane is free from strain and that, in solution, there is no transannular interaction between the carbonyl group and the aromatic ring. The above frequencies may be compared with the carbonyl-stretching frequencies of 4-oxo[8]paracyclophane (1710 cm^{-1}) and 3-oxo[7]paracyclophane (1705 cm^{-1}).[11] Each of these two compounds is a strained molecule with the aliphatic bridge situated above and near the plane of the aromatic ring. In these molecules with short 1,4-bridges, the proximity of aromatic ring and methylene protons near the center of the bridge is also indicated by nuclear magnetic resonance chemical shifts at high field, multiplets at 2.15–0.95 and 1.4–0.8 ppm, respectively.

Fisher–Hirschfelder–Taylor molecular models, which define van der Waals radii, show that there are two extreme conformations for **3** and two extreme conformations for **4**. In the first extreme conformation of **3**, that with the negative ends of the carbonyl dipoles pointing in opposite directions away from the center of the macrocyclic ring (as in the structural formula drawn above), **3** contains a rectangular lipophilic cavity or hole of approximate cross section 8 × 5 Å. This hole is large enough to be threaded by a polymethylene or similar chain (diameter of a normal paraffin chain 3.8–4.2 Å). It should also be large enough to encircle a catenane ring moiety or rotaxane rod moiety with small substituents because the hole is almost the size of the channel in the thiourea clathrate.[12] A molecular model of benzene passes easily through the hole. The second extreme conformation, with negative ends of the carbonyl dipoles pointing more toward the center of the macrocyclic ring, has a very small hole. The aliphatic segments are very close to each other. Each carbonyl group is near a benzyl position of the opposite segment.

The first extreme conformation of **4**, that with the carbonyl groups pointing away from the center of the macrocyclic ring, contains a lipophilic cavity or hole of approximate cross section 6 × 5 Å. A polymethylene chain or a rotaxane or catenane moiety could easily pass through the hole. The second extreme conformation has each carbonyl group pointing almost toward the center of the macrocyclic ring. The hole is very small. Each carbonyl group is located near the face of a *p*-phenylene ring of the opposite segment. While molecular models lead to the postulate of flexible cavities with a wide range of sizes, nuclear magnetic resonance spectra **3** and **4** give more support to conformations in solution near the first extremes, rather than the second extremes. Methylene proton resonance at very high field is absent in each spectrum.[13]

Experimental Section[14]

4,4′-Oxybis[benzenebutanoic acid]. To a solution of 4,4′-oxybis[γ-oxobenzenebutanoic acid][15] (7.40 g, 0.02 mol) in 250 mL of boiling acetic acid was added 10% palladium on charcoal (1 g). The mixture was treated with hydrogen (3 atm) in the Parr hydrogenation apparatus. After hydrogenation and hydrogenolysis, the reaction mixture was filtered and the filtrate was poured into 300 mL of water. After digestion and recrystallization from acetic acid, the diacid weighed 5.05 g (74%), mp 166–168 °C (lit.[15] mp 168–169 °C).

Methyl 4,4-Oxybis[benzenebutanoate] (1). 4,4′-Oxybis[benzenebutanoic acid] (0.2 mol) was treated with methanol, sulfuric acid, and methylene chloride according to the method of Clinton and Laskowski.[16] The product was distilled to give 64.3 g (86.5%) of the diester 1: bp 206–208 °C (0.2 torr) [lit.[17] bp 218–219 °C (0.05 torr)]; ^1H NMR ($CDCl_3$) δ 7.17–6.83 (m, 8 H, Ar H), 3.56 (s, 6 H, CH_3O), 2.61 (t, $J = 7$ Hz, 4 H, $ArCH_2$), 2.31 (t, $J = 6$ Hz, 4 H, CH_2CO), 1.90 (quintet, $J = 7$ Hz, 4 H, $CH_2CH_2CH_2$); IR (CCl_4) 1736 cm^{-1} (C=O).

14,34-Dioxa-4,24-dioxo[7.1.7.1]paracyclophane, 2,18-Dioxapentacyclo[28.2.2.2^{3,6}.2^{14,17}.2^{19,22}]tetraconta-3,5,14,16,19,21,30,32,33,35,37,39-dodecaene-10,26-dione (3). During 31 h, 1 (18.52 g, 0.05 mol) in xylene (250 mL) was added to a stirred and refluxing solution of xylene (1800 mL) and potassium *tert*-butoxide (0.24 mol). After the customary isolation procedure of neutralization with acetic acid, extraction, removal of polymer by filtration, concentration, and acid-catalyzed hydrolysis and decarboxylation, the crude product was triturated with acetone (30 mL). The material that was insoluble in acetone (3.27 g) melted at 185–189 °C. This crude product was recrystallized from 2-butanone to give 3.02 g of diketone, mp 189–191 °C. Final purification was by bulb-to-bulb distillation in the kugelrohr to give pure **3** (2.53 g, 18.0%): mp 191–192 °C; ^1H NMR ($CDCl_3$) δ 7.07–6.78 (m, 16 H, Ar H), 2.56 (t, $J = 6$ Hz, 8 H, $ArCH_2$), 2.24 (t, $J = 6$ Hz, 8 H, CH_2CO), 1.86 (quintet, $J = 6$ Hz, 8 H, $CH_2CH_2CH_2$); IR (CCl_4) 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{38}H_{40}O_4$: C, 81.39; H, 7.19; mol wt, 560.74. Found: C, 81.65; H, 7.29; mol wt (Rast), 576.

Methyl 4,4′-Oxybis[benzenepropanoate] (2). By use of the malonic ester synthesis, 26.2 g of 4,4′-oxydibenzyl chloride was starting material for preparation of 4,4′-oxybis[benzenepropanoic acid]. After decarboxylation of the tetracarboxylic acid, the crude diacid was used to prepare the dimethyl ester by the method outlined above for **1**. The product **2**, 9.00 g (26% after two steps

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from the dichloride), boiled at 200–203 °C (0.2 torr) and melted at 48.5–51 °C (lit.[18] mp 50 °C).

12,30-Dioxa-3,21-dioxo[5.1.5.1]paracyclophane, 2,16-Dioxapentacyclo[24.2.2.2^{3,6}.2^{12,15}.2^{17,20}]tetraconta-3,5,12,14,17,19,26,28,29,31,33,35-dodecaene-9,23-dione (4). As described above for the synthesis of **3**, **2** (17.12 g, 0.05 mol) was used to prepare the crude mixture of ketones. The material that was insoluble in acetone (3.72 g) melted at 194–203 °C. This impure product was recrystallized from 2-butanone to give 2.18 g of diketone, mp 201–205 °C. Final purification by bulb-to-bulb distillation gave pure **4** (2.05 g, 16.2%): mp 205–206.8 °C; ^{1}H NMR ($CDCl_3$) δ 6.97–6.77 (m, 16 H, Ar H), 2.80 (t, J = 6 Hz, 8 H, $ArCH_2$), 2.51 (t, J = 6 Hz, 8 H, CH_2CO); IR (CCl_4) 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{34}H_{32}O_4$: C, 80.93; H, 6.39; mol wt, 504.63. Found: C, 81.16; H, 6.51; mol wt (Rast), 512.

4,17-Dioxo[7.7]paracyclophane. With a retained sample,[19] spectra were recorded: ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 8 H, Ar H), 2.59 (t, J = 6 Hz, 8 H, $ArCH_2$), 2.02 (t, J = 6 Hz, 8 H, CH_2CO), 1.80 (quintet, J = 6 Hz, 8 H, $CH_2CH_2CH_2$); IR (CCl_4) 1715 cm^{-1} (C=O).

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Registry No. 1, 76358-39-9; 2, 32808-31-4; 3, 76358-40-2; 4, 76358-41-3; 4,17-dioxo[7.7]paracyclophane, 76358-42-4; 4,4′-oxybis[benzenebutanoic acid], 36189-36-3; 4,4′-oxybis[γ-oxobenzenebutanoic acid], 4378-33-0; 4,4′-oxydibenzyl chloride, 2362-18-7.

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Intramolecular Anionic Cycloaddition of 1-(3-Phenyl-2-propenyl)-4-piperidinecarbonitrile. Synthesis of the 2,4a-Ethanobenz[*g*]isoquinolin-5(1*H*)-one Ring System[1]

Robert A. Farr,* Joseph E. Dolfini, and Albert A. Carr

Merrell Research Center, Cincinnati, Ohio 45215

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Although the addition of organometallic compounds to 1,3-dienes and styrenes is well documented,[2] very few examples of the addition of stabilized carbanions to such olefins are known which do not require transition-metal catalysis. Takabe et al.[3] reported the addition of the sodium salt of *N*-(3-methylbutylidene)-*tert*-butylamine to isoprene. More recently, Fujita and co-workers[4] reported the addition of carboxylic acid dianions to styrene, isoprene, and myrcene in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA). In this paper we describe the intramolecular addition of an α-lithionitrile to a cinnamyl double bond which leads to substituted quinuclidine derivatives.

(1) A preliminary account of this work was presented at the 11th Central Regional Meeting of the American Chemical Society, Columbus, OH, May 7–9, 1979.
(2) For a review of the addition of alkyllithium compounds to conjugated olefins, see: Schöllkopf, U. In "Methoden der Organischen Chemie (Houben-Weyl)"; Georg Thieme Verlag: Stuttgart, 1970; Vol 13/1, p 1.
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Scheme I

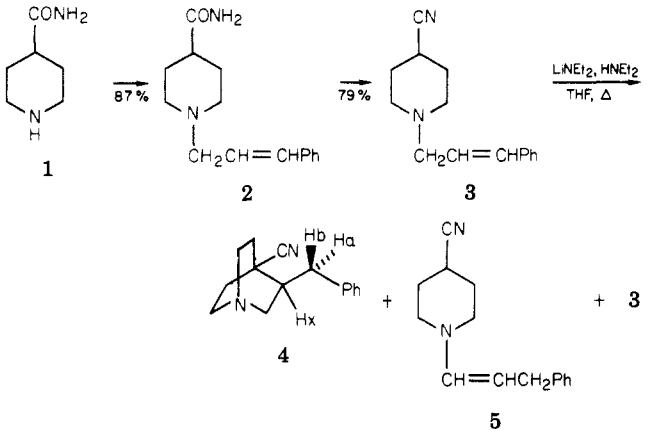
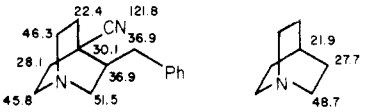


Chart I. Carbon-13 Chemical Shifts[a]



quinuclidine[7]

[a] All shifts are in parts per million downfield from $Si(CH_3)_4$.

Results

In connection with the synthesis of 1-cinnamyl-4,4-disubstituted-piperidine central nervous system agents, cinnamyl nitrile **3** was prepared as a key synthetic intermediate. N-Alkylation of isonipecotamide (**1**) with cinnamyl chloride followed by dehydration of the resulting amide **2** with $POCl_3$ afforded the oily nitrile **3** in excellent overall yield[5] (Scheme I). When cinnamyl nitrile **3** is metalated at 0 °C with 1.03 equiv of lithium diethylamide (LDEA) in the presence of a 1–3 molar excess of diethylamine in tetrahydrofuran (THF) and the resulting solution rapidly warmed[6] to 51–54 °C for 20 min, a 56–60% yield of crystalline 3-(phenylmethyl)-1-azabicyclo[2.2.2]-octane-4-carbonitrile (**4**), a 13% yield of enamine **5**, and a 9–15% yield of recovered cinnamyl nitrile **3** are obtained after quenching with water. Prolonged heating results in the further transformation of products to nonvolatile, intractable materials. The structures of **4** and **5** were assigned on the basis of spectral data and subsequent chemical modifications.

The mass spectrum of **4** showed characteristic peaks at *m/e* 135 and 91 resulting from benzylic cleavage. The UV spectrum [λ_{max} 258 nm (ϵ 190)] indicated the absence of a chromophoric substituted benzene. The 80-MHz ^{1}H NMR spectrum showed no olefinic protons and a doublet of doublets at δ 3.25 assigned to H_a (geminal coupling of 13 Hz and vicinal coupling of 3 Hz), which collapsed to a doublet (J = 13 Hz) upon irradiation at 159 Hz. The ^{13}C NMR spectrum of **4** was in complete accord with the quinuclidine structure. The assignments were made on the basis of chemical shifts and the single-frequency, off-resonance, proton-decoupled spectrum. The ^{13}C chemical shifts for quinuclidine are given in Chart I for comparison.[7] Most notably, there is a characteristic upfield shift for C-5 (δ 22.4) which arises from a γ-gauche interaction with the benzylic carbon atom.[8] A downfield

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