via syringe. After 0.5 h, the liquid was chilled to −78 °C, and prechilled **34** (Table III) (0.0846 g, 0.42 mmol) was added as an etheral solution via syringe. After 1.0 h, the temperature was allowed to rise to −60 °C at which time the reaction was quenched with saturated aqueous NH_4Cl. Standard workup gave 0.0742 g of clear yellow oil. TLC purification (1000 μm SiO_2 plate, 2% ethyl acetate/petroleum ether, v/v) with two elutions gave two fractions. Fraction 1 afforded starting material (0.020 g). Fraction 2 (R_f 0.16) afforded the *E* isomer in 76% yield (0.0542 g): IR 2960 (s), 2860 (m), 1680 (m), 1600 (m), 1460 (m), 1378 (m), 1365 (m), 1255 (m) 1067 (m), 1020 (m) 904 (m) cm^{-1}; ^1H NMR δ 1.12 (d, *J* = 7.1 Hz, 6 H), 1.09 (s, 9 H), 2.12 (s, 3 H), 2.63 (hept, *J* = 7 Hz, 1 H), 6.18 (s, 1 H); ^{13}C NMR δ 205.7, 165.7, 118.9, 41.8, 37.8, 28.6 (3C), 18.3 (2C), 15.6.

2,6-Dimethyl-5-(1,1-dimethylethyl)-4-octen-3-one (35b). To 0.1628 g of CuSCN was added 10 mL of diethyl ether and the mixture was chilled to −20 to −10 °C. *sec*-Butyllithium, 1.4 mL (1.75 M, 2.45 mmol), was added; the solution was stirred for 0.5 h, cooled to −78 °C, and then treated with an ethereal solution of **34**. Standard workup and TLC purification (1000 μm, SiO_2, petroleum ether/2% ethyl acetate, v/v) afforded 0.0750 g of **35b**: ^1H NMR δ 0.86 (t, *J* = 7 Hz, 3 H), 1.07 (d, *J* = 7 Hz, 6 H), 1.13 (s, 9 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 1.26–2.42 (br m, 3 H), 2.65 (hept, *J* = 7 Hz, 1 H), 6.08 (s, 1 H); *Z* isomer, 5.82 (s, 1 H, 11%).

Ethyl 3-Methyl-2-hexenoate (40).[54] Procedure A was followed employing ester **39** except CuSCN was used. The reaction was quenched at −78 °C. Purification by MPLC (*E* isomer, R_f 0.16; *Z* isomer, R_f 0.27; petroleum ether/2% ethyl acetate, v/v) afforded a 99% yield.

E isomer: IR 2980 (s), 2920 (s), 1708 (s), 1590 (m), 1450 (m), 1370 (m), 1180 (s) cm^{-1}; ^1H NMR δ 0.92 (t, *J* = 7 Hz, 3 H), 1.05 (t, *J* = 8 Hz, 3 H), 1.05–1.79 (m, 2 H), 2.01–2.28 (m, 2 H), 2.14 (s, 3 H), 4.17 (q, *J* = 8 Hz, 2 H), 5.70 (s, 1 H); ^{13}C NMR δ 166.6, 159.6, 115.5, 59.1, 42.8, 20.4, 18.3, 14.1, 13.4.

In a separate experiment, (*E*)-ethyl 3-(ethylthio)-2-hexenoate (**38**) was employed in THF and the *Z* isomer was obtained by MPLC in which the crude product consisted of a 10:90 *E*/*Z* mixture in 72% yield.

Z isomer: IR 2980 (s), 2920 (s), 2880 (s), 1710 (s), 1450 (m), 1380 (m), 1260 (s), 1115 (s), 1020 (m) cm^{-1}; ^1H NMR δ 0.94 (t, *J* = 7 Hz, 3 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.25–1.47 (m, 2 H), 1.87 (d, *J* = 1 Hz, 3 H), 2.41 (t, *J* = 8 Hz, 2 H), 4.15 (q, *J* = 7 Hz, 2 H), 5.67 (s, 1 H); ^{13}C NMR δ 166.8, 159.7, 116.6, 59.7, 35.2, 22.0, 21.4, 14.3, 14.0.

Acknowledgment. We are pleased to acknowledge support of this investigation by NSF (Grant CHE-8219093) and DHHS (Grant GM 31776-01A1). We thank Dr. Catherine E. Costello, Associate Director of the Massachusetts Institute of Technology Mass Spectrometry Laboratory (NIH Division of Research Resources, Grant No. RR00317 to K. Biemann), for the high-resolution mass spectra.

Registry No. **1**, 84308-03-2; **2**, 84308-04-3; **3**, 86310-01-2; **4**, 86310-02-3; **5**, 96899-05-7; **6**, 86310-03-4; **7**, 86310-04-5; **8**, 96899-20-6; **9**, 84308-09-8; **10**, 84308-07-6; **11**, 96899-12-6; **12**, 87615-89-2; **13**, 96899-34-2; (*E*)-**14a**, 86310-07-8; (*Z*)-**14a**, 86310-06-7; (*E*)-**14b**, 104664-45-1; (*Z*)-**14b**, 104664-55-3; (*E*)-**15a**, 23732-25-4; (*Z*)-**15a**, 36219-17-7; (*E*)-**15b**, 104664-46-2; (*Z*)-**15b**, 104664-56-4; (*E*)-**15c**, 23732-21-0; (*Z*)-**15c**, 83810-24-6; (*E*)-**16**, 23732-22-1; (*Z*)-**16**, 23732-23-2; (*E*)-**17a**, 86310-09-0; (*Z*)-**17a**, 86310-08-9; (*E*)-**17b**, 104664-54-2; (*Z*)-**17b**, 104664-57-5; (*E*)-**18**, 56001-51-5; (*Z*)-**18**, 56001-48-0; (*E*)-**19**, 104664-47-3; (*Z*)-**19**, 104664-58-6; (*E*)-**20a**, 104664-48-4; (*Z*)-**20a**, 104664-59-7; (*E*)-**20b**, 104664-49-5; (*Z*)-**20b**, 104664-60-0; (*E*)-**20c**, 104664-50-8; (*Z*)-**20c**, 104664-61-1; (*E*)-**21**, 104664-51-9; (*Z*)-**21**, 104664-62-2; (*E*)-**22**, 96899-09-1; (*Z*)-**22**, 96899-10-4; **23**, 84308-05-4; **24**, 96899-14-8; **25**, 96899-16-0; **26**, 96899-23-9; **27**, 96899-29-5; (*E*)-**28**, 104664-52-0; (*Z*)-**28**, 104664-63-3; (*E*)-**29**, 104664-53-1; (*Z*)-**29**, 104664-64-4; **30**, 62453-10-5; **31**, 96899-24-0; **32**, 96899-26-2; **33**, 86310-05-6; **34**, 96899-32-0; (*E*)-**35a**, 104664-65-5; (*Z*)-**35b**, 104664-66-6; (*E*)-**35b**, 104664-67-7; (*E*)-**36**, 49784-51-2; (*E*)-**37**, 91667-33-3; (*E*)-**38**, 104664-69-9; (*Z*)-**39**, 104664-68-8; (*E*)-**40**, 22210-21-5; (*Z*)-**40**, 22210-22-6; BuLi, 109-72-8; *t*-BuLi, 594-19-4; MeLi, 917-54-4; *sec*-BuLi, 598-30-1.

(54) (a) Matsui, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 426. (b) Tanaka, K.; Yamagishi, N.; Tanikaga, R.; Kaji, A., *Ibid.* **1979**, *52*, 3619.

Notes

Total Synthesis of (±)-Isocyclocelabenzine

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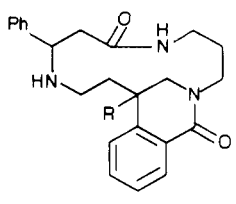
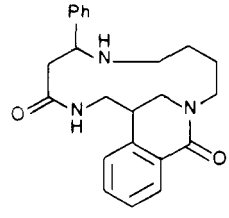
A new family of spermidine alkaloids typified by isocyclocelabenzine (**1**), 13-hydroxyisocyclocelabenzine (**2**), and cyclocelabenzine (**3**) were isolated from *Maytenus mossmbicensis* by Wagner and his co-workers.[1] All three



1; R=H
2; R=OH



3

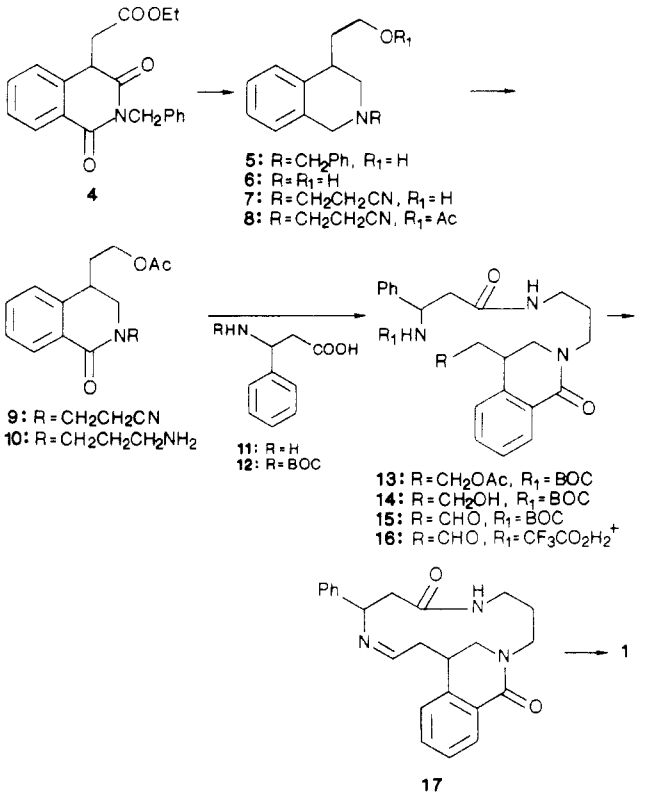
of these alkaloids each show the 13-membered lactam ring of celabenzine being linked to the benzoyl residue within the spermidine unit. These compounds have yet to be synthesized. We recently synthesized (±)-celabenzine and (−)-dihydrocelacinnine by the intramolecular reductive amination of an aldehyde to bring about the closure of the macrocyclic ring.[2] The present paper describes a total synthesis of isocyclocelabenzine in which the macrocyclic ring is formed by the successive intramolecular reductive amination of aldehyde.

The first step in the synthesis was the construction of lactam **9**, which was synthesized from homophthalimide derivative **4** as a key fragment.

Treatment of 2-benzylhomophthalimide with sodium *tert*-butoxide followed by ethyl bromoacetate in *tert*-butyl alcohol at room temperature gave **4**. The reduction of **4** with $LiAlH_4$ in isopropyl ether under reflux for 24 h yielded the isoquinoline derivative **5**. Debenzylation of **5** with

(1) Wagner, H.; Burghart, J.; Hull, W. E. *Tetrahedron Lett.* **1978**, 3893. Wagner, H.; Burghart, J. *Helv. Chem. Acta* **1982**, *65*, 739.
(2) Iida, H.; Fukuhara, K.; Machiba, M.; Kikuchi, T. *Tetrahedron Lett.* **1986**, 207.

0022-3263/86/1951-4701$01.50/0



20% Pd–C gave the amino alcohol **6**; treatment of **6** with acrylonitrile in methanol under reflux gave nitrile **7**, whose acetylation with acetic anhydride yielded **8**. Oxidation of **8** with $KMnO_4$ was carried out in aqueous acetone under a neutral condition gave the isoquinolone derivative **9**. The nitrile function of **9** was reduced by hydrogenation over platinum oxide in ethanol to give the amine **10**.

Condensation of the 3-amino-3-phenylpropionic acid derivative **12**, synthesized from 3-amino-3-phenylpropionic acid (**11**) by using BOC-S in aqueous dimethylformamide in the presence of triethylamine, was carried out with 2-chloro-1-methylpyridinium iodide and amine **10** to yield **13**. The alkaline hydrolysis of **13** in methanol gave alcohol **14**. Oxidation of **14** with pyridinium chlorochromate in dichloromethane at room temperature for 1 h gave the aldehyde **15** [^1H NMR δ 9.80 (s, 1 H) aldehyde proton].

Trifluoroacetic acid cleavage of the BOC group generated the amine salt **16**, and this was followed by solvent removal at room temperature. The residue was dissolved in water. The aqueous solution was neutralized to give a cyclic compound **17**, subsequently reduced with $NaBH_4$ in methanol to afford (±)-isocyclocelabenzine (**1**). This compound was identical (400-MHz ^1H NMR, IR, MS, and TLC) with the authentic sample of natural isocyclocelabenzine (**1**).

Experimental Section

Instrumentation. ^1H NMR spectra were recorded on a Varian EM 390 or Bruker AM-400 (400-MHz) NMR spectrometer, using tetramethylsilane as the internal standard. Infrared spectra were recorded on a Hitachi 260 spectrometer. Melting points were measured on a Yanagimoto micro hot stage and reported uncorrected. Mass spectra were obtained on a Hitachi RMV-7L instrument.

2-Benzyl-4-[(ethoxycarbonyl)methyl]homophthalimide (4). Ethyl bromoacetate (7.35 g, 44 mmol) was added dropwise to a stirred solution of 2-benzylhomophthalimide (10 g, 40 mmol) in *tert*-butyl alcohol in the presence of sodium *tert*-butoxide (4.8 g, 50 mmol) at room temperature. Following this addition, stirring was continued for 6 h. The reaction mixture was acidified with acetic acid. Following the removal of the solvent, the residue was extracted with benzene. The extract was washed with water, dried ($MgSO_4$), and evaporated to give **4** (9.5 g, 70%) as colorless needles: mp 88–90 °C (EtOH); IR (Nujol) 1720, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.4 (1 H, dd, J = 8, 2 Hz), 7.2–7.3 (9 H, m), 5.3 (2 H, d, J = 3 Hz), 3.8–4.3 (3 H, m), 3.2 (1 H, dd, J = 18, 6 Hz), 1.00 (3 H, t, J = 7 Hz); mass spectrum, m/z 337 (M^+). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.02; H, 5.72; N, 4.24.

2-Benzyl-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (5). To a stirred solution of $LiAlH_4$ (10.0 g, 260 mmol) in isopropyl ether (150 mL) was added a solution of **4** (20 g, 60 mmol) in THF (150 mL) under ice cooling. Stirring was continued for an additional 24h following this. The mixture was decomposed with 10% KOH. The inorganic precipitate was removed the organic layer was evaporated to give **5** (13.5 g, 85%) as an oil: IR ($CHCl_3$) 3150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.8–7.5 (9 H, m), 3.68 (2 H, d, J = 12 Hz), 2.9–4.0 (5 H, m), 2.70 (1 H, dd, J = 12, 5 Hz), 1.9–2.1 (2 H, m); mass spectrum, m/z 267 (M^+).

2-(2-Cyanoethyl)-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (7). Isoquinoline derivative **5** (10.7 g, 40 mmol) in methanol (200 mL) was treated with concentrated hydrochloric acid (4.5 mL, 52 mmol), and the resulting mixture was hydrogenated over 20% palladium on carbon (3.0 g) under hydrogen at 20 °C and 1 atm for 24 h. Filtration of the mixture, washing of the residue with methanol, and concentration of the combined filtrates left the ammonium salt of **6**, which was used for the following reaction without further purification. A mixture of **6**, acrylonitrile (2.32 g, 40 mmol) and anhydrous sodium acetate (4.1 g, 50 mmol) in ethanol (200 mL) was heated under reflux for 2 h. The solvent was then evaporated, and the residue was diluted with 5% ammonium hydroxide (50 mL) and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated to give an oil, which was then purified by column chromatography on a silica gel (100 g). Elution with $CHCl_3$ gave **7** (6.9 g, 75%) as an oil: IR ($CHCl_3$) 3150, 2200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.3 (4 H, m), 3.9–4.2 (4 H, m), 3.1–3.6 (5 H, m), 2.5–3.1 (3 H, m), 1.9–2.2 (2 H, m); mass spectrum, m/z 230 (M^+).

4-(2-Acetoxyethyl)-2-(2-cyanoethyl)-1,2,3,4-tetrahydroisoquinoline (8). A mixture of **7** (6.9 g, 30 mmol) and acetic anhydride was heated at 100 °C for 2 h. The excess acetic anhydride was then decomposed with water, and the mixture was basified with concentrated ammonium hydroxide and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated. The residue thus obtained was purified by column chromatography on a silica gel (100 g). Elution with $CHCl_3$ gave **8** (7.3 g, 90%) as an oil: IR ($CHCl_3$) 2250, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.0–7.4 (4 H, m), 4.1–4.4 (2 H, m), 3.65 (2 H, dd, J = 12, 7 Hz), 2.5–2.9 (3 H, m), 2.0–2.3 (2 H, m), 2.1 (3 H, s); mass spectrum, m/z 272 (M^+).

4-(2-Acetoxyethyl)-2-(2-cyanoethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (9). To a stirred solution of **8** (8.16 g, 30 mmol) and $MgSO_4$ (7.5 g, 50 mmol) in aqueous acetone (acetone/H_2O = 2:1) (300 mL) was added $KMnO_4$ (7.9 g, 50 mmol) at room temperature, at which stirring was continued for additional 1 h. Following removal of the precipitate, the solvent was removed by evaporation. The residual oil was extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue thus obtained was chromatographed on a silica gel (50 g). Elution with $CHCl_3$ gave **9** (8.4 g 95%): IR ($CHCl_3$) 3450, 2250, 1720 cm^{-1}; ^1H NMR δ 8.20 (1 H, dd, J = 7, 2 Hz), 7.2–7.6 (3 H, m), 2.1 (3 H, s) ; mass spectrum, m/z 286 (M^+).

4-(2-Acetoxyethyl)-2-(3-aminopropyl)-1,2,3,4-tetrahydroisoquinolin-1-one (10). The cyano ester (5.72 g, 20 mmol) in $CHCl_3$–ethanol (1:50) (200 mL) was hydrogenated over platinum oxide (0.6 g) under hydrogen at 20 °C and 1 atm for 8 h. Filtration of the mixture, washing of the residue with ethanol, and concentration of the combined filtrates left an oil (5.5 g, 95%). This oil was used for the following reaction without further purification: IR ($CHCl_3$) 3330, 1710 cm^{-1}; mass spectrum, m/z 290 (M^+).

3-[*N*-(*tert*-Butoxycarbonyl)amino]-3-phenylpropionic Acid (12). A solution of BOC-S (7.2 g, 30 mmol) in DMF (50 mL) was added dropwise at room temperature to a stirred solution of **3-amino-3-phenylpropionic acid (11)** (4.95 g, 30 mmol) and triethylamine (4.04 g, 40 mmol) in aqueous DMF (H_2O/DMF = 1:1) (50 mL). Stirring was continued at room temperature for an additional 8 h. The reaction mixture was poured into water

(50 mL) and then extracted with ethyl acetate. The aqueous solution acidified with concentrated HCl and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated to give **12** (7 g, 88%): mp 143–144 °C (benzene); IR (Nujol) 3400, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, m), 5.10 (1 H, m), 2.86 (2 H, d, J = 7 Hz), 1.42 (9 H, s); mass spectrum, m/z 209 (M^+). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.30; H, 7.21; N, 5.26.

4-(2-Acetoxyethyl)-2-[8-(*tert*-butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-1,2,3,4-tetrahydroisoquinolin-1-one (13). A solution of amine **10** (8.7 g, 30 mmol) in CH_2Cl_2 (50 mL) was added to a stirred solution of acid **12** (7.95 g, 30 mmol), 1-methyl-2-chloropyridinum iodide (7.65 g, 30 mmol), and triethylamine (3.03 g, 30 mmol) in CH_2Cl_2 (100 mL) at room temperature for 2 h. This was followed by evaporation of the solvent and purification of the residue by column chromatography on a silica gel (150 g). Elution with ethyl acetate gave **13** (13.85 g, 86%) as colorless crystals: mp 94–95 °C (ether); IR (Nujol) 3350, 1730, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (1 H, dd, J = 7, 2 Hz), 7.0–7.6 (8 H, m), 5.1 (1 H, m), 2.1 (3 H, s), 1.4 (9 H, s); mass spectrum, m/z 537 (M^+). Anal. Calcd for $C_{30}H_{39}N_3O_6$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.90; H, 7.35; N, 7.86.

2-[8-(*tert*-Butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (14). A mixture of **13** (10.74 g, 20 mmol) and K_2CO_3 (13.8 g, 100 mmol) in methanol (100 mL) was stirred at room temperature for 2 h. The solvent was evaporated and the residue poured into iced water and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated. The remaining residue was purified by column chromatography on a silica gel (100 g). Elution with ethyl acetate gave **14** (8.9 g, 90%) as an oil: IR ($CHCl_3$) 3370, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (1 H, dd, J = 7, 2 Hz), 7.2–7.6 (8 H, m), 5.1 (1 H, m), 1.4 (9 H, s); mass spectrum, m/z 422 [(M − 73)$^+$].

2-[8-(*tert*-Butoxycarbonyl)-5-oxo-7-phenyl-4,8-diazaoctyl]-4-(formylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-one (15). A solution of pyridinum chlorochromate (4.3 g, 20 mmol) in CH_2Cl_2 (50 mL) was added dropwise to one of alcohol **14** (4.95 g, 10 mmol) in CH_2Cl_2 (50 mL) at room temperature for 2 h. The reaction mixture was washed with water, dried ($MgSO_4$), and evaporated. The remaining residue was purified by column chromatographed on a silica gel (50 g). Elution was carried out with $CHCl_3$ and then ethyl acetate to give **15** (3.7 g, 75%) as an oil: IR ($CHCl_3$) 3370, 1720, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.9 (1 H, s), 8.1 (1 H, dd, J = 7, 2 Hz), 5.1 (1 H, m), 1.4 (9 H, s); mass spectrum, m/z 493 (M^+).

Isocyclocelabenzine (1). A mixture of aldehyde **15** (2 g, 4 mmol) and trifluoroacetic acid (20 mL) was stirred at room temperature for 0.5 h. The excess trifluoroacetic acid was removed, and the residue was extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water, followed by drying ($MgSO_4$). TLC ($CHCl_3$/MeOH = 10:1 on silica gel plates) analysis of the reaction product indicated the conversion of **15** to **17**, which was used for the following reaction without purification. The product (1 g, 2.6 mmol) in MeOH (30 mL) was reduced with $NaBH_4$ (0.37 g, 10 mmol) at room temperature for 1 h. Following removal of the solvent, the residue was decomposed with aqueous NH_4Cl and extracted with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated. The residue was purified by column chromatography on a silica gel (30 g). Elution with ethyl acetate gave isocyclocelabenzene (**1**) (450 mg, 46%) as colorless prisms: mp 224–225 °C (ethyl acetate) [lit.[1] mp 227–228 °C (ethyl acetate)]; IR ($CHCl_3$) 3300, 1630, 1600, 1580 cm^{-1}; ^1H NMR (400 Mz, $CDCl_3$) δ 8.11 (1 H, dd, J = 7.5, 1.5 Hz), 7.43 (1 H, td, J = 7.5, 1.5 Hz), 7.37 (1 H, td, J = 7.5, 1.5 Hz), 7.10–7.18 (4 H, m), 6.82 (2 H, m), 7.70 (1 H, dd, J = 8.0, 4.0 Hz), 3.98 (1 H, dd, J = 11.4, 3.1 Hz), 3.90–4.02 (3 H, m), 3.82 (1 H, dd, J = 13, 2.6 Hz), 3.78 (1 H, dd, J = 13, 4.9 Hz), 3.71 (1 H, m), 3.02 (1 H, m), 2.84 (1 H, m), 2.58 (2 H, ddd, J = 12.2, 6.2 and 3.0 Hz), 2.35 (1 H, dd, J = 13.4, 3.1 Hz), 2.22 (2 H, m), 2.18 (2 H, dd, J = 13.4, 11.4 Hz), 1.58–1.82 (3 H, m), 1.25 (1 H, s); mass spectrum, m/z 377 (M^+). Anal. Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7,21; N, 11.13. Found: C, 73.17; H, 7.20; N, 11.10.

Acknowledgment. We express our appreciation Professor H. Wagner of the University of Munich for kindly providing the sample of natural isocyclocelabenzene.

Registry No. **1**, 104595-98-4; (±)-**4**, 104465-74-9; (±)-**5**, 104465-75-0; (±)-**6**, 104465-76-1; (±)-**7**, 104465-77-2; (±)-**8**, 104465-78-3; (±)-**9**, 104465-79-4; (±)-**10**, 104465-80-7; (±)-**11**, 3646-50-2; (±)-**12**, 104465-81-8; **13**, 104465-82-9; **14**, 104465-83-0; **15**, 104465-84-1; **17**, 104487-52-7; 2-benzylhomophthalimide, 21640-31-3; ethyl bromoacetate, 105-36-2; acrylonitrile, 107-13-1.

Imidate Anions: *E*/*Z* Interconversion by Rotation vs. Nitrogen Inversion?

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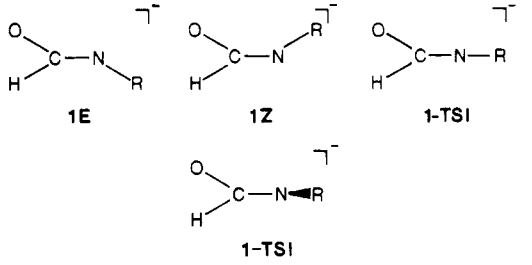
The preparation and characterization of some imidate anions, $HCONR^-$, the conjugate bases of amides, have recently been reported by Perrin, Lollo, and Hahn.[1] This study dealt with, among other things, the stereochemistry and *E*/*Z* isomerization of these new species. On the basis of NMR data, they concluded that in solution, the *E* stereoisomer is more stable than the *Z* and the anions undergo *nitrogen inversion* with a barrier of ca. 20 kcal/mol. With regard to the latter, the following was stated:[1] "The activation barriers for *E*/*Z* interconversion are only 19–23 kcal/mol. These are too low to be due to rotation about the C–N bond. For comparison, the barriers to rotation in the parent amide are 18–20 kcal/mol.... Therefore the mechanism for *E*/*Z* interconversion is not rotation, but nitrogen inversion." In what follows, we intend to show that this argument could be misleading.

Previously, Zielinski and co-workers[2] reported a conformational study of the imidate anion $HCONH^-$ (**1**, R = H) at the ab initio HF/3-21G level with complete geometry optimization. Local minima **1Z** and **1E** and structures **1-TSI** and **1-TSR** which repesent the transition states for the nitrogen inversion and rotation about carbon–nitrogen bond processes, respectively, were also considered. They



concluded that in the gas phase (a) the **1Z** (R = H) isomer is about 7 kcal/mol more stable than the **1E** (b) the inversion transition structure **1-TSI** lies *above* the rotational **1-TSR** by about 7 kcal/mol (**1-TSI** is in fact not a true transition state since it has two negative eigenvalues[2]), and (c) the barrier height of the rotation process is 30.6 kcal/mol; both findings are therefore at variance with the conclusions reached by Perrin et al.[1]

In order to ensure that the calculated relative energies reported[2] are not an artifact of the geometry optimization procedure using a rather small basis set (3-21G), we have first reconsidered the four stationary points of interest at higher level of accuracy. The energy difference between

(1) Perrin, C. L.; Lollo, C. P.; Hahn, C.-S., *J. Org. Chem.* **1985**, *50*, 1405.
(2) Zielinski, T. J.; Poirier, R. A.; Peterson, M. R.; Csizmadia, I. G. *J. Comput. Chem.* **1982**, *3*, 477.

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