cyclohexyl-2-methyltetrahydrofuran (isomer 1), 96482-14-3; 2-(acetoxymethyl)-5-cyclohexyl-2-methyltetrahydrofuran (isomer 2), 96482-15-4; (2*R**,3*S**,6*S**)-3-acetoxy-2,6-dimethyl-2-(4-methylpent-3-en-1-yl)tetrahydropyran, 96482-17-6.

Supplementary Material Available: Experimental procedures, spectral data, and characterization of compounds not described in the Experimental Section (33 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Bridging with Acetals, Carbonyls, and Thiocarbonyls

George D. Hartman,* Brian T. Phillips,* and Wasyl Halczenko

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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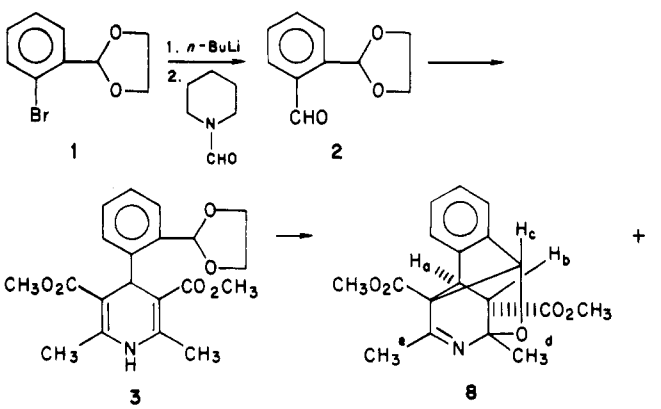
The preparation of new aldehyde and acetal derivatives of 4-aryl-1,4-dihydropyridines has been carried out. Treatment of these compounds under acid conditions affords novel caged molecules derived from sequential intramolecular addition reactions. This process involves initial nucleophilic attack by the dihydropyridine on the acetal function, followed by closure of the resultant hydroxy moiety on an electrophilic iminium species. These molecules represent novel, conformationally restricted analogues of calcium entry blocking agents.

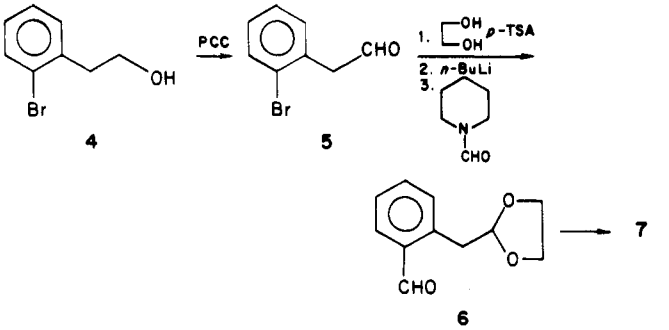
There is an abundant, fruitful literature relating to the chemistry of the dihydropyridines.[1,2] Members of this structural class have served as efficient intermediates in the synthesis of alkaloids such as yohimbine,[3,4] ajmaline,[5] sesbanine,[6] and morphine,[7] as well as in synthetic routes to substituted pyridines.[8,9]

The utility of 4-aryl-1,4-dihydropyridines as therapeutic agents in cardiovascular disorders[10,11] has also fostered interest in the chemistry[12-17] of these compounds. One intriguing question that remains to be answered for this potent class of calcium channel blockers[18] pertains to the geometrical requirements at the dihydropyridine receptor.[19-21] Only recently have compounds[22-24] appeared that, due to conformational restriction, will test these requirements. We wish to report the synthesis of novel, conformationally rigid dihydropyridine analogues prepared via sequential intramolecular acid-catalyzed addition processes.

Scheme I



Scheme II



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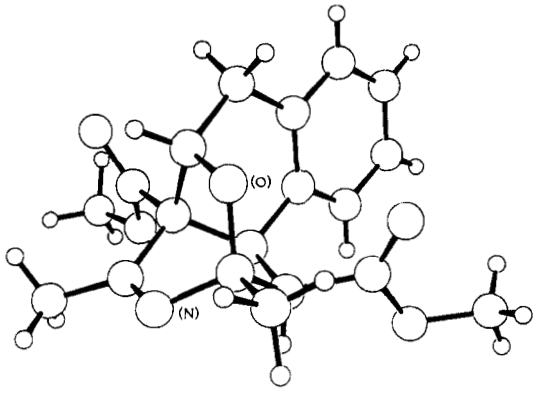


Figure 1. ORTEP representation of **10b**.

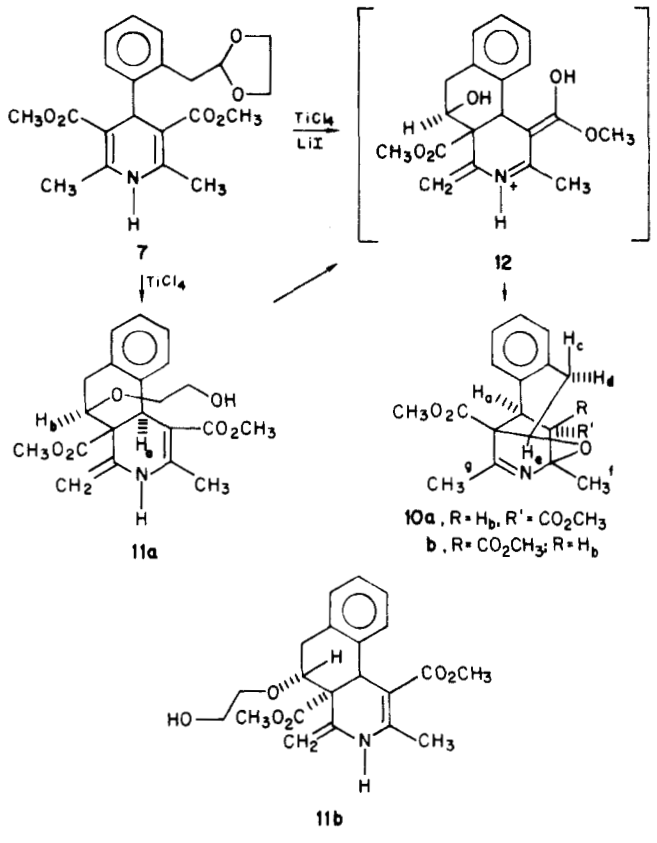
Our observation[24] of the generation of polycyclic products from treatment of styrenic 1,4-dihydropyridines under acid conditions demonstrated the facility of sequential intramolecular processes in this system. On the basis of this finding, we anticipated analogous reactivity in the acid-mediated cleavage of acetals, which were suitably disposed with respect to the dihydropyridine ring. We decided, from a consideration of models, to prepare compounds **3** and **7** in which the incipient electrophilic acetal carbon was respectively five or six atoms distant from C-3 of the dihydropyridine. The synthesis of **3** (Scheme I) involved conversion of acetal **1** to aldehyde **2** via lithiation/formylation,[25] followed by treatment with methyl acetoacetate and methyl 3-aminocrotonate.[26] Preparation of **7** (Scheme II) utilized conversion of 2-(2-bromophenyl)ethanol (**4**)[27] to aldehyde **5**, protection of this as the ethylene glycol acetal, and then lithiation/formylation as before to give **6**. Hantzsch condensation of **6** then provided **7**.

Treatment of dimethyl 2,6-dimethyl-4-[2-(2-(1,3-dioxolanyl))phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**3**) (Scheme I) at room temperature with titanium tetrachloride and lithium iodide in methylene chloride for 18 h provided a 28% isolated yield of dimethyl 2,4a,5,9b-tetrahydro-2,4-dimethyl-2,5-methanoindeno[2,1-*e*]-1,3-oxazine-4a,10α-dicarboxylate (**8**) along with 7% of iodomethyl derivative **9**. The identification of **8** is based on comparison of its 360-MHz ^{1}H NMR spectrum with that of **10b** (vide infra), for which X-ray data are available, and on elemental analysis and mass spectral data.

In similar fashion, treatment of dimethyl 2,6-dimethyl-4-[2-((2-(1,3-dioxolanyl))methyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**7**) with titanium tetrachloride and lithium iodide in methylene chloride gave an 83% yield of a mixture, diastereoisomers **10a** and **10b**, which was predominantly dimethyl 4a,5,10,10a-tetrahydro-2,4-dimethyl-2,5-methano-2*H*-naphth[2,3-*e*]-1,3-oxazine-4a,11α-dicarboxylate (**10a**). In contrast, treatment of **7** with gaseous HCl in chloroform gave mainly the diastereoisomer **10b**. The structure of **10b** (Figure 1) was solved by X-ray analysis,[28] while 360-MHz ^{1}H NMR, elemental analysis, and mass spectrum were confirmatory.

In an effort to study this cyclization process further, **7** (Scheme III) was treated with titanium tetrachloride at room temperture for 2 h in the absence of lithium iodide.

Scheme III



Under these conditions only trace amounts of **10a** and **10b** were formed and the major product obtained in 85% yield was a dimethyl 2,4a,9,10,10b-pentahydro-10-(hydroxyethoxy)-3-methyl-1-methylidenebenzo[*f*]isoquinoline-4,10b-dicarboxylate, i.e., **11a** or **11b**. The stereochemistry at C-10 could not be determined despite exhaustive NOE analysis. This compound was purified by flash chromatography on silica gel and characterized by its 360-MHz ^{1}H NMR and mass spectra, but it decomposed upon standing at room temperature. Although it proved inert to lithium iodide alone, treatment of a freshly prepared sample with titanium tetrachloride/lithium iodide at room temperature provided a mixture of **10a** and **10b**.

The mechanism for cyclization of **7** most likely involves titanium-assisted nucleophilic attack by C-3 of the dihydropyridine on the acetal carbon to give **11a**.[29] Deprotection, i.e., removal of the hydroxyethyl appendage of **11a**, mediated by lithium iodide/titanium tetrachloride,[30] followed by intramolecular attack of oxygen on iminium ion **12**, would then provide **10a**/**10b**. Since **11b**, wherein the latent hydroxyl function is anti to the dihydropyridine ring, cannot directly undergo further cyclization, the success of the "double cyclization" of **7** to **10a**/**10b** depends crucially upon the selection of diastereoisomer **11a** in the initial attack on the acetal. Alternatively, it should be recognized that **7** or intermediates such as **11a** and **11b** might be converted to the parent aldehyde, which could cyclize to **10a**/**10b** via **12**, in analogy with the conversion of **13** to **8** reported below (vide infra).

Due to success with inducing iminium ion mediated cycloaddition reactions between an olefinic function on the aryl ring and the dihydropyridine,[24] we were encouraged to study similar reactions in the case of aldehyde **13**

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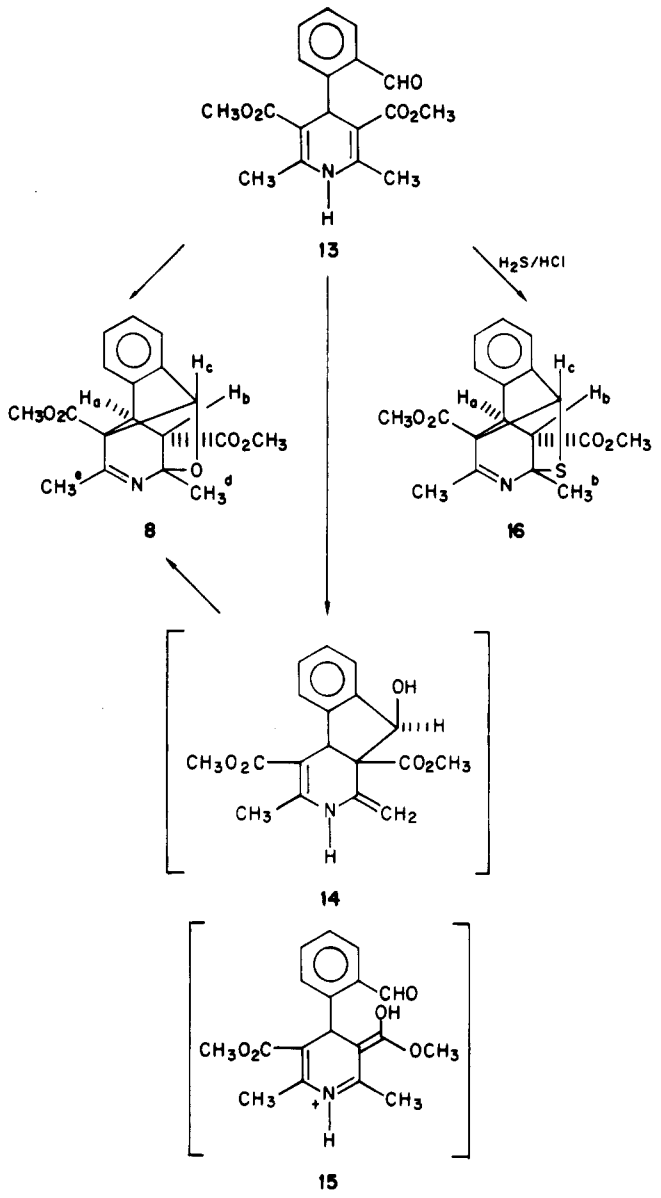
Scheme IV



(Scheme IV). Treatment of **13**, prepared by deprotection of **3** with *p*-toluenesulfonic acid in acetone, with titanium tetrachloride/lithium iodide afforded **8** in 75% yield. Gaseous hydrogen chloride in chloroform also produced **8** (~40% yield); however, treatment with (trimethylsilyl)triflate was not effective. In a similar manner, treatment of **13** with hydrogen sulfide and hydrogen chloride in chloroform provided dimethyl 2,4a,5,9b-tetrahydro-2,4-dimethyl-2,5-methanoindeno[2,1-*e*]-1,3-thiazine-4a,10α-dicarboxylate (**16**) in 65% yield.

The mechanism for formation of **8** and **16** from **13** could conceivably involve a concerted[31] $\pi_{4s} + \pi_{2s}$ cycloaddition process utilizing the carbonyl or thiocarbonyl π-bond and an electron-deficient iminium species (**15**) generated from the dihydropyridine nucleus. However, on the basis of the results with acetal **7**, we feel a better explanation is that protonation or Lewis acid complexation of the aldehyde oxygen is closely followed by attack of C-3 of the dihydropyridine to give **14**, and this is followed by acid-catalyzed closure to final products. Similar arguments would pertain to formation of **16** from **13** via a hemithioaldehyde formed in situ.

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We are continuing to study the mechanism and synthetic utility of these protic and Lewis acid catalyzed cyclizations.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR specra were recorded on a Varian T-60, an EM-390, or a Nicolet NT-360 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a LKB-9000S mass spectrometer at 70 eV. *N*-Formylpiperidine, methyl acetoacetate, methyl 3-aminocrotonate, and 2-bromobenzaldehyde were obtained from Aldrich and all were used without purification.

2-[2-(1,3-Dioxolanyl)]benzaldehyde (2). To a solution of 43.5 g (0.19 mol) of 2-bromobenzaldehyde ethylene glycol acetal (**1**) in 275 mL of dry tetrahydrofuran cooled to −78 °C under nitrogen was added 0.19 mol of *n*-butyllithium in hexane dropwise with the temperature kept below −70 °C. After addition was complete the reaction mixture was stirred at −78 °C for 0.5 h, and a solution of 23.76 g (0.21 mol) of *N*-formylpiperidine in 25 mL of tetrahydrofuran was added dropwise with the temperature kept below −65 °C. The resulting solution was allowed to gradually warm to room temperature with stirring over the course of 6 h.

The reaction was quenched with the addition of 3 N hydrochloric acid, and then this was diluted with 250 mL of ether. The phases were separated, and the aqueous phase was extracted with 3 × 40 mL of ether. The combined organic extracts were washed with 2 × 30 mL of saturated ammonium chloride solution and brine and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give a dark oil, which was fractionated to provide 25.2 g (75%) of pure **2**: bp 95–100 °C; single spot (R_f 0.4) on silica gel eluting with 4:1 hexane/ether; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.13 (4 H, s), 6.44 (1 H, s), 7.65 (4 H, m), 10.51 (1 H, s, CHO).

Dimethyl 2,6-Dimethyl-4-[2-(2-(1,3-dioxolanyl))phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (3). To 3.0 g (0.0168 mol) of **2** in 20 mL of methanol were added 1.94 g (0.0168 mol) of methyl 3-aminocrotonate, 1.95 g (0.0168 mol) of methyl acetoacetate, and 1 drop of concentrated aqueous ammonium hydroxide. This solution was heated at reflux under nitrogen for 24 h. The solvent was then removed on the rotary evaporator and the residue triturated with a small amount of cold ether to afford a yellow solid. This was collected by filtration and washed with cold ether to give 3.55 g (57%) of pure **3**, mp 235–237 °C dec, as a white solid: 1H NMR ($CDCl_3$, 60 MHz) δ 2.28 (6 H, s), 3.60 (6 H, s), 4.08 (4 H, m), 5.26 (1 H, s), 5.80 (1 H, br s, NH), 6.38 (1 H, s), 7.21 (4 H, m); mass spectrum, *m/e* 373 (M^+). Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 63.94; H, 6.34; N, 4.03.

Dimethyl 2,4a,5,9b-Tetrahydro-2,4-dimethyl-2,5-methanoindeno[2,1-*e*]-1,3-oxazine-4a,10α-dicarboxylate (8). Method 1. To a stirred solution of 2.24 g (6.0 mmol) of 2,6-dimethyl-4-[2-(2-(1,3-dioxolanyl))phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**3**) in 120 mL of CH_2Cl_2 under N_2 was added 0.57 g (3.0 mmol) of titanium tetrachloride followed by 0.88 g (6.6 mmol) of lithium iodide. After 48 h at room temperature the reaction was quenched by addition of H_2O and neutralized with saturated sodium bicarbonate solution, and the layers were separated. The aqueous layer was extracted with 2 × 100 mL of methylene chloride. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 2.5 g of a gummy solid. This solid was flash chromatographed on a column of E. Merck silica gel eluted with 1% MeOH/$CHCl_3$ to give 1.68 g of a glassy solid containing a mixture of **8** and byproduct **9**. A second chromatography followed by recrystallization from hexane gave 0.55 g (28%) of **8**, mp 107–116 °C, and 0.18 g (7%) of **9**, mp 125–126 °C.

8: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.73 (3 H, s, CH_3^d), 2.29 (3 H, s, CH_3^e), 2.89 (1 H, d, J = 1 Hz, H_b), 3.67 (3 H, s), 3.70 (3 H, s), 3.88 (1 H, br s, H_a), 4.85 (1 H, d, J = 1 Hz, H_c), 7.3 (4 H, m); high-resolution mass spectrum, calcd 329.1263, found 329.1266. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.47; H, 5.99; N, 4.16.

9: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.70 (3 H, s), 2.90 (1 H, d, J = 1 Hz, H_b), 3.60 (3 H, s), 3.70 (3 H, s), 3.90 (1 H, br s, H), 4.20 (2 H, d, J = 1 Hz), 4.80 (1 H, d, J = 1 Hz, H_c), 7.30 (4 H, m); mass spectrum, *m/e* 455 (M^+), 328. Anal. Calcd for $C_{18}H_{18}INO_5$:

C, 47.49; H, 3.99; N, 3.08. Found: C, 47.89; H, 4.12; N, 3.33.

Method 2. To a solution of 0.066 g (0.2 mmol) of **13** in 4 mL of methylene chloride was added at room temperature under nitrogen 0.019 g (0.01 mmol) of titanium tetrachloride followed by 0.029 g (0.22 mmol) of lithium iodide. After the reaction was stirred for 72 h, it was quenched as described above in method 1. NMR analysis of the product mixture showed a mixture of **8** and **13** in a ratio of 2:1.

(2-Bromophenyl)acetaldehyde (5). To 14.62 g (0.063 mmol) of pyridinium chlorochromate suspended in 75 mL of methylene chloride at room temperature was added a solution of 9.11 g (0.045 mol) of **4** in 10 mL of methylene chloride in one portion. The reaction mixture became dark with a black precipitate, and this was stirred for 1.5 h. The reaction mixture was diluted with 225 mL of ether and then decanted. The reaction residue was triturated with 150 mL of ether, and the ether extracts were combined and passed through a silica gel pad on a filter funnel to give a clear, greenish solution. The solvent was removed on the rotary evaporator to give 8.0 g (88%) of crude **5** as an oil with R_f 0.7 on silica gel eluting with 1% methanol/chloroform: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.80 (2 H, s), 7.30 (4 H, m), 9.70 (1 H, s).

2-[(2-(1,3-Dioxolanyl))methyl]benzaldehyde (6). To 8.0 g (0.04 mol) of crude **5** dissolved in 50 mL of benzene were added 2.73 g (0.044 mol) of ethylene glycol and 0.05 g of *p*-toluenesulfonic acid monohydrate, and the resulting solution was refluxed until the theoretical amount of H_2O had been collected in a Dean–Stark trap. The reaction mixture was cooled, washed with 2 × 20 mL of 10% aqueous sodium hydroxide solution and brine, and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to afford an oil, which was distilled to give 8.94 g (92%) of pure acetal, bp 74–76 °C (0.1 mm).

To 7.84 g (0.032 mol) of acetal in 40 mL of dry tetrahydrofuran cooled to −78 °C under nitrogen was added a solution of 0.034 mol of *n*-butyllithium in hexane dropwise with the temperature kept below −70 °C. The resulting brown solution was stirred for 1 h at −78 °C, and then a solution of 3.65 g (0.032 mol) of *N*-formylpiperidine in 10 mL of tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to room temperature gradually over 8 h.

The reaction was cooled, quenched with 30 mL of saturated ammonium chloride, and diluted with 75 mL of ether, and the phases were separated. The organic phase was washed with saturated ammonium chloride and brine and dried over anhydrous sodium sulfate. The solvent was removed to give an oil, which was purified by flash chromatography on silica gel (230–400 mesh), eluting with 1:1 hexane/ether to give 4.79 g (78%) of **6** (R_f 0.4) as a clear oil: ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.35 (2 H, d), 3.75 (4 H, m), 5.05 (1 H, q), 7.40 (4 H, m), 10.25 (1 H, s).

Dimethyl 2,6-Dimethyl-4-[2-((2-(1,3-dioxolanyl))methyl)-phenyl]-1,4-dihydropyridine-2,6-dicarboxylate (7). To 3.4 g (0.0177 mol) of **6** in 20 mL of dry methanol were added 2.06 g (0.0177 mol) of methyl acetoacetate and 2.64 g (0.0177 mol) of methyl 3-aminocrotonate followed by 1 drop of concentrated ammonium hydroxide, and the resulting solution was heated at reflux under nitrogen for 4 days. The solvent was removed on the rotary evaportor and the residue purified by flash chromatography on silica gel, eluting with 2% methanol/chloroform to give a yellow oil (R_f 0.4). This was triturated with 1:1 ether/hexane to give 4.80 g (71%), of pure **7**: mp 162–166 °C; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.25 (6 H, s), 3.26 (2 H, d, CH_2), 3.57 (6 H, s, CO_2CH_3), 3.93 (4 H, m), 5.03 (1 H, t), 5.19 (1 H, s), 5.75 (1 H, s, NH), 7.14 (4 H, m, Ar); mass spectrum, *m/e* 386 (M^+). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.12; H, 6.62; N, 3.31.

Dimethyl 4a,5,10,10a-Tetrahydro-2,4-dimethyl-2,5-methano-2*H*-naphth[2,3-*e*]-1,3-oxazine-4a,11α-dicarboxylate (10a). To a stirred solution of 0.58 g (1.5 mmol) of dimethyl 2,6-dimethyl-4-[2-((2-(1,3-dioxolanyl))methyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**7**) in 15 mL of ether and 30 mL of CH_2Cl_2 under N_2 was added 0.14 g (0.75 mmol) of titanium tetrachloride followed by 0.22 g (1.6 mmol) of lithium iodide. After 4 days at room temperature the reaction was quenched by addition of H_2O and neutralized with brine, and the layers were separated. The aqueous layer was extracted with 2 × 30 mL of methylene chloride. The combined organic extract was washed with brine and dried over sodium sulfate and the solvent removed to give 0.66 g of a gummy orange solid. The solid was flash chromatographed on a column of E. Merck silica gel, eluted with 1% methanol/chloroform to give 0.34 g (66%) of **10a** and 0.09 g (17%) of **10b**. Recrystallization of **10a** from *n*-butyl chloride/hexane and then from hexane gave 0.057 g (11%) of analytically pure **10a**: mp 124–127.5 °C; IR (KBr pellet) 3450, 2350, 1730, 1620, 1240, 1010, 780, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.69 (3 H, s), 2.23 (3 H, s), 2.77 (1 H, d, J = 3 Hz, H_b), 3.03 (1 H, d of d, J = 18, 3 Hz, H_d), 3.10 (1 H, d of d, J = 18, 3 Hz, H_c), 3.70 (3 H, s), 3.75 (3 H, s), 3.82 (1 H, d of d, J = 3, 2 Hz, H_a) 4.23 (1 H, m, H_e), 7.10 (4 H, m); high-resolution mass spectrum, calcd 343.149, found 417. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.38; H, 6.15; N, 4.10.

Dimethyl 4a,5,10,10a-Tetrahydro-2,4-dimethyl-2,5-methano-2*H*-naphth[2,3-*e*]-1,3-oxazine-4a,11β-dicarboxylate (10b). Into a solution of 0.58 g (1.5 mmol) of **7** in 15 mL of $CHCl_3$ was bubbled HCl for 15 min. The solution was stirred 3 days and neutralized with saturated sodium carbonate solution. The mixture was diluted with H_2O and 75 mL of chloroform, the layers were separated, and the aqueous layer was extracted with 2 × 75 mL of chloroform. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.61 g of a glassy solid. The solid was flash chromatographed on a column of E. Merck silica gel, eluting with 1% methanol/chloroform to give 0.16 g (31%) of **10b**. **10b** was recrystallized from *n*-butyl chloride/hexane and finally from hexane to give 0.093 g (18%) of yellow crystals: mp 121–123 °C; IR (KBr pellet) 3450, 2330, 1740, 1720, 1630, 1430, 1260, 1160, 810, 770, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.63 (3 H, s), 2.20 (3 H, s), 2.74 (1 H, d, J = 12 Hz, H_b), 3.10 (1 H, d of d, J = 18, 4 Hz, H_c), 3.16 (3 H, s), 3.21 (1 H, d, J = 18 Hz, H_d), 3.64 (1 H, d of d, J = 12, 2 Hz, H_a), 3.67 (3 H, s), 4.34 (1 H, m, H_e), 7.10 (4 H, m); high-resolution mass spectrum, calcd 343.1419, found: 343.1410. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.25; H, 6.24; N, 4.19.

Dimethyl 3,4,4a,5,6,10b-Hexahydro-5-(hydroxyethoxy)-2-methyl-4-methylidenebenzo[*f*]isoquinoline-1,4a-dicarboxylate. To a solution of 1.94 g (5.0 mmol) of **7** in 80 mL of $CHCl_3$ was added 1.90 g (10.0 mmol) of titanium tetrachloride under N_2. A gumballl formed, which dissolved over 15 min. After 2 h the reaction was quenched by addition of H_2O and neutralized with saturated bicarbonate solution, and the layers were separated. The aqueous layer was extracted with 2 × 50 mL of chloroform. The combined extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 2.43 g of a glassy solid. The solid was flash chromatographed on a column of E. Merck silica gel, eluting with 1% methanol/chloroform to give 1.45 g (75%) of product as a yellow glassy solid, which decomposed on standing or on attempted recrystallization: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 2.34 (3 H, s), 3.11 (1 H, d of dd, J = 18, 3 Hz), 3.43 (1 H, d of d, J = 18, 5 Hz), 3.70 (4 H, m), 3.78 (3 H, s), 3.84 (3 H, s), 4.40 (1 H, d of d, J = 5, 3 Hz, H_b), 4.40 (1 H, d, J = 24 Hz), 4.41 (1 H, d, J = 24 Hz), 4.82 (1 H, s, H_a), 5.88 (1 H, br s), 7.20 (4 H, m); mass spectrum, *m/e* 387 (M^+).

Dimethyl 2,6-Dimethyl-4-(2-formylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (13). To 9.0 g (0.024 mol) of **3** in 500 mL of acetone was added 175 mg of *p*-toluenesulfonic acid monohydrate, and this was allowed to stand at room temperature for 24 h. The solvent was removed on the rotary evaporator, and the residual yellow solid was taken up in 300 mL of methylene chloride, washed with saturated sodium bicarbonate solution and brine, and dried over sodium sulfate. The solvent was removed, and the residual yellow solid was triturated with 1:1 hexane/ether to give a solid, which was recrystallized from acetonitrile to give 7.63 g (93%) of pure **13**: mp 227–228 °C; single spot (R_f 0.4) on TLC (silica gel), eluting with 2% methanol/methylene chloride; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.3 (6 H, s), 3.5 (6 H, s), 5.8 (1 H, s), 6.4 (1 H, br s, NH), 7.4 (4 H, m), 10.8 (1 H, s). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.49; H, 5.82; N, 4.55.

Dimethyl 2,4a,5,9b-Tetrahydro-2,4-dimethyl-2,5-methanoindeno[2,1-*e*]-1,3-thiazine-4a,10α-dicarboxylate (16). To a stirred solution of 2.0 g (6.1 mmol) of **13** in 40 mL of chloroform at room temperature was added 10 mL of methanol saturated with hydrogen chloride gas. Hydrogen sulfide gas was then passed through this solution for 8 h with cooling in an ice

bath for the first hour. The solvent was then removed on the rotary evaporator and the residue taken up in H_2O and neutralized with saturated sodium bicarbonate solution. This was extracted with 2 × 50 mL portions of methylene chloride. The combined organic phase was dried over anhydrous sodium sulfate and the solvent removed on the rotary evaporator to give a sticky yellow solid. Trituration of this with 1:4 hexane/ether and recrystallization of the resulting solid from 2-propanol provided 1.04 g (50%) of pure **16**; mp 203–209 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.76 (3 H, s, CH_3^b), 2.28 (3 H, s, CH_3^a), 2.99 (1 H, d, J = 1 Hz, H_b), 3.72 (3 H, s, CO_2CH_3), 3.73 (3 H, s, CO_2CH_3), 3.88 (1 H, br s, H_a), 4.71 (1 H, s, H_c), 7.33 (4 H, m, aromatic); mass spectrum, m/e 345 (M^+). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.98; H, 5.65; N, 4.19.

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Registry No. **1**, 34824-58-3; **2**, 59259-01-7; **3**, 96557-29-8; **4**, 1074-16-4; **5**, 96557-30-1; **6**, 96557-31-2; **6** (Br derivative), 96557-36-7; **7**, 96557-32-3; **8**, 96575-47-2; **9**, 96575-48-3; **10a**, 96557-33-4; **10b**, 96614-26-5; **11**, 96557-34-5; **13**, 96575-49-4; **16**, 96557-35-6; $MeC(NH_2)$=$CHCO_2Me$, 14205-39-1; $AcCH_2CO_2Me$, 105-45-3; $CH_2(OH)CH_2(OH)$, 107-21-1; H_2S, 7783-06-4.

Supplementary Material Available: Crystallographic data, including tables of the atomic positional and thermal parameters, bond distances, and bond angles for **10b** (6 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Bridging with Olefins

George D. Hartman,* Wasyl Halczenko,* and Brian T. Phillips

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

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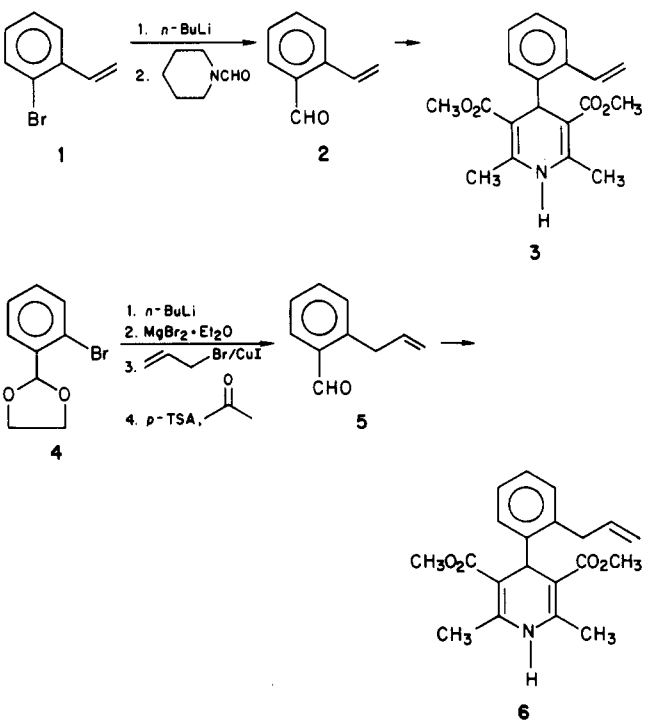
Acid-catalyzed cyclization of 4-(2-alkenylphenyl)-1,4-dihydropyridines affords products derived from formal [4 + 2] cycloaddition processes between the olefinic moiety and a vinyl iminium species. Mechanistically, these products arise by sequential intramolecular capture of cationic intermediates. These molecules constitute novel, conformationally rigid analogues of biologically important 1,4-dihydropyridines.

As described in the accompanying paper, 4-aryl-1,4-dihydropyridines have gained importance as therapeutic agents in cardiovascular disease. Our particular interest has been in the preparation of novel, conformationally constrained dihydropyridine analogues with which to study the dihydropyridine receptor. Herein we report the preparation of the carbocyclic analogues of the compounds described in this earlier paper, via a novel intramolecular iminium ion mediated bis-cyclization process.

The intramolecular capture of iminium ions by various nucleophiles has proven to be a highly effective method in the total synthesis of complex alkaloids.[1] The observation[2] that a vinyl iminium species could be generated from 4-aryl-1,4-dihydropyridines prompted us to explore the capture of this reactive intermediate with simple carbon–carbon double bonds. From a consideration of molecular models we anticipated that intramolecular capture of the dihydropyridine/iminium species would be optimum in molecules **3** and **6**, where the electrophilic iminium carbon is positioned respectively seven or eight atoms from the olefin terminus. Pseudoaxial orientation of the 4-aryl substituent allows for extremely favorable stereoelectronic orientation of the terminal olefin relative to the iminium carbon at C-2.

The preparation (Scheme I) of dimethyl 2,6-dimethyl-4-(2-ethenylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3**) involved metalation of commercially available 2-bromostyrene followed by formylation[3] with *N*-formylpiperidine to give **2**. Treatment of **2** under Hantzsch conditions with methyl 3-aminocrotonate and methyl acetoacetate provided **3** in 26% yield. The generation of dimethyl 2,6-dimethyl-4-[2-(3-propenyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**6**) required metalation of acetal **4** with *n*-butyllithium and cation exchange with magnesium bromide etherate to give the corresponding Grignard reagent. Coupling of this with allyl bromide and deprotection of the aldehyde under standard conditions provided 2-(3-propenyl)benzaldehyde (**5**). Formation of **6** under Hantzsch conditions via treatment with methyl

Scheme I



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