nor by any linear combination of conformations. Only two shifts may even be assigned with any level of confidence. Since 1,*cis*-2,*trans*-3-trimethylcyclohexane has considerable steric strain energy in the extreme chair forms it is understandable that substantial difficulty might well be encountered in fitting the data with a linear model. It is likely that a skew-boat or other higher energy conformation could also make a considerable contribution to the ring hydrogen shifts in this case. In some respects the failure of the parametric set to fit this obviously distorted molecule dramatizes the success of the parameters in correlating chemical shifts of the "regular" molecules and lends confidence to the structural information which can be obtained from this method.

Conclusion

The application of ^2H natural abundance spectroscopy involves greatly simplified spectra and can aid in simplifying the process of interpretation of very complex ^1H spectra. The simple shift patterns resulting from broad-band proton decoupling due to the absence of ^2H–^2H couplings in all but a very few (0.00024%) of the molecules produce much more readily interpreted spectra. The proton-decoupled, deuterium technique supplements information obtained from the ubiquitous field of ^1H chemical shift data which is known to be rich in structural and conformational information for many compounds. When the ^1H spectral transitions are seriously banded, however, and experience large second order effects, the ^2H information is much easier to interpret. Deuterium shifts contain less error than the shift data obtained from estimating the centers of proton multiplets in highly coupled proton spectra. The structural information obtained for proton-decoupled ^2H spectra is corroborated by ^{13}C chemical shift data.[11]

The use of multiple stepwise regression analysis produced a set of empirical parameters which can be used in predicting and interpreting spectra of compounds which are either rapidly interconverting between multiple conformations or are locked in one chair conformation. Also the results suggest that nonchair conformations contribute to the structural description of certain molecules. The parameters found in this study for methylcyclohexanes which exhibit chair conformations, either rapidly interconverting between chair structures or existing solely in one extremely favored form, should prove useful in the interpretation and prediction of spectra of related compounds. Spectral deviations provide some indication of distortion in the ring system, since compounds with allegedly flattened rings would not be fit as well by the parmeter set. The use of these parameters as a tool in the interpretation of spectra of six-membered paraffin rings with substituted methyls is particularly valuable because of the importance of proximity in the effect of a methyl on a ring proton. The magnitude of these parameters provides a quantitative measure of the steric perturbations in the cyclohexane ring which provides one of the basic moieties for conformational analysis.

Vicinal substituent shifts have been rationalized in terms of the number of gauche steric interactions as modified by vicinal inductive effects. With the availability of improved spectroscopic data refined information on angular deformations could become available from these kinds of data.

Acknowledgment. This work was supported in part by the National Institutes of Health under Grant No. GM08521. Some deuterium spectra were obtained by William R. Croasmun on the Bruker-500 spectrometer at the Southern California Regional NMR facility located at the California Institute of Technology, supported by the National Science Foundation on Grant CHE 79-16324. Their assistance is gratefully acknowledged.

Registry No. Deuterium, 7782-39-0; cyclohexane, 110-82-7; methylcyclohexane, 108-87-2; 1,1-dimethylcyclohexane, 590-66-9; *cis*-1,2-dimethylcyclohexane, 2207-01-4; *trans*-1,3-dimethylcyclohexane, 2207-03-6; *cis*-1,4-dimethylcyclohexane, 624-29-3; *trans*-1,2-dimethylcyclohexane, 6876-23-9; *cis*-1,3-dimethylcyclohexane, 638-04-0; *trans*-1,4-dimethylcyclohexane, 2207-04-7; 1,1,2-trimethylcyclohexane, 7094-26-0; 1,1,3-trimethylcyclohexane, 3073-66-3; 1,1,4-trimethylcyclohexane, 7094-27-1; 1,*trans*-2,*cis*-3-trimethylcyclohexane, 1678-81-5; 1,*cis*-2,*trans*-3-trimethylcyclohexane, 7667-55-2; 1,*trans*-2,*trans*-4-trimethylcyclohexane, 7667-60-9; 1,*trans*-2,*cis*-4-trimethylcyclohexane, 7667-59-6; 1,*cis*-3,*cis*-5-trimethylcyclohexane, 1795-27-3; 1,*cis*-3,*trans*-5-trimethylcyclohexane, 1795-26-2.

Iminium Ion Mediated Cyclizations with 4-Aryl-1,4-dihydropyridines. Bridging with Thiophene and Furan

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Received May 14, 1985

Treatment of [(2-thienyl)phenyl]-, [(3-thienyl)phenyl]-, [((2-thienyl)methyl)phenyl]- and [2-(furylmethyl)-phenyl]-1,4-dihydropyridines with aluminum chloride afforded products derived from intramolecular trapping of the dihydropyridine/iminium ion by the heterocycle. These products were either monocyclized, from heterocyclic attack on the iminium ion followed by rearomatization of the heterocycle, or biscyclized, from trapping of an electrophilic substitution intermediate in a second intramolecular reaction.

The therapeutic utility of 4-aryl-1,4-dihydropyridines as cardiovascular agents has been widely recognized.[1] Mechanistically, these molecules act to inhibit contractility in cells by antagonizing the movement of calcium ions through the slow calcium channels[2] in the cell membrane. Concomitant with clinical success, a renewed interest in the chemistry of this class of compounds is evident.[3-9]

The suggestion that biological activity within the 4-

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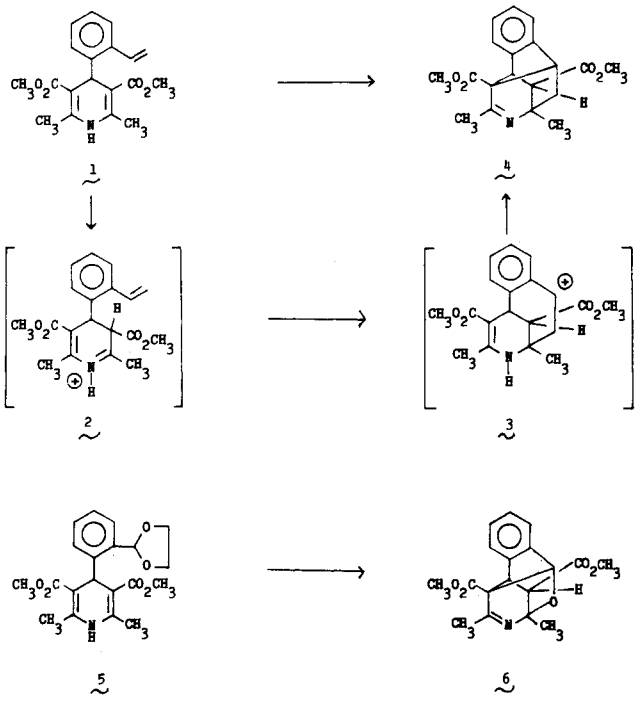
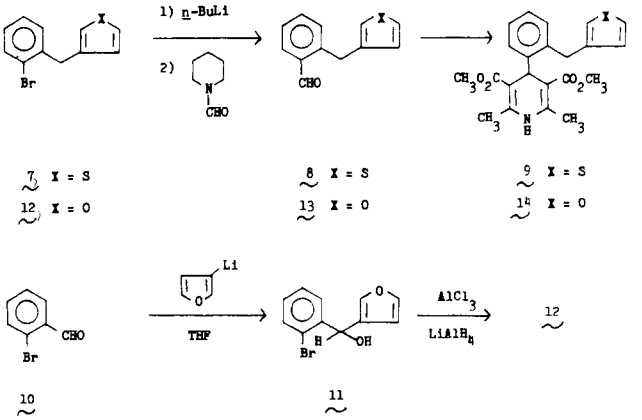
0022-3263/86/1951-0142$01.50/0

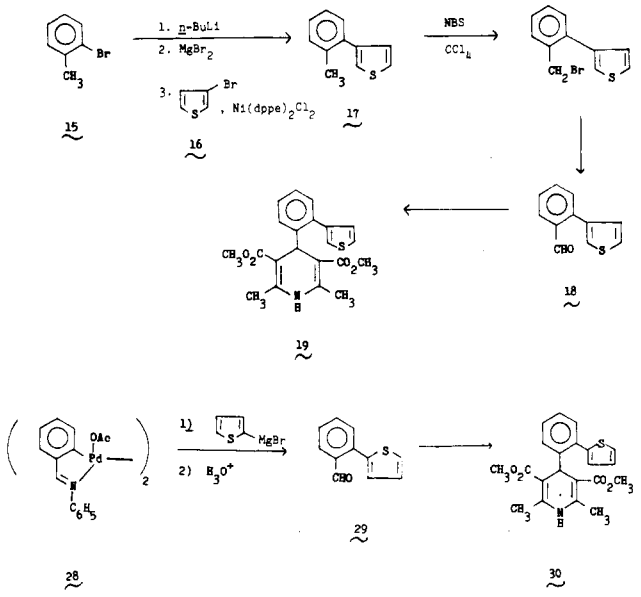
Scheme I



Scheme II



Scheme III



aryl-1,4-dihydropyridine series is related to conformational factors[10,11] has fostered efforts to prepare conformationally constrained derivatives.[12] This research has proven chemically fruitful as a variety of novel cyclization modes for 1,4-dihydropyridines have recently been discovered.[13,14] We have found that dimethyl 2,6-dimethyl-4-(2-ethenylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**1**) gives **4** when treated with hydrogen chloride gas in chloroform.[15] The mechanism of this latter transformation most likely involves capture of iminium ion **2** by the olefinic linkage to give benzyl cation **3** (see Scheme I), followed by nucleophilic attack of the aminocrotonate moiety. We have also been able to prepare heteroatom-bridged compounds such as **6**, via Lewis acid catalyzed attack of the dihydropyridine ring of **5** on the acetal carbon, followed by capture of the resultant iminium ion by oxygen.[16]

In an effort to expand the synthetic utility of this cyclization sequence, as well as to prepare molecules which would enhance our knowledge of structural requirements at the dihydropyridine receptor, we have exploited trapping of the iminium species by aromatic nuclei.

The intramolecular trapping of iminium ions by electron-rich aromatic nuclei has repeatedly proven valuable in alkaloid synthesis. The classic Pictet-Spengler cyclization.[17] the modified Polonovski reaction,[18] and variants have been utilized for the synthesis of yohimbines,[19-21] elwesine,[22] and methanodiazocinoindoles.[23] Herein, we report that (thienylphenyl)- and (furylphenyl)-1,4-dihydropyridines undergo Lewis acid catalyzed reactions involving intramolecular capture of a dihydropyridine/iminium ion by the heterocycle to afford products derived from mono- or biscyclization processes.

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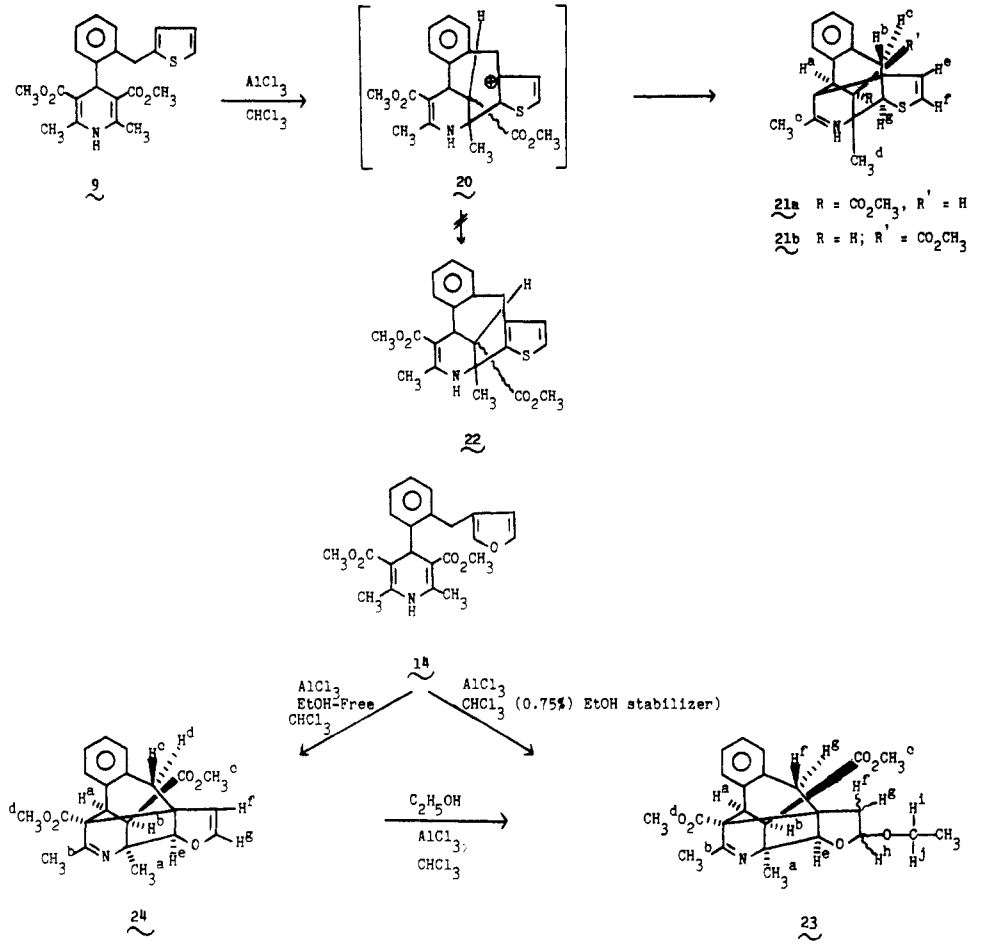
Scheme IV



Results and Discussion

In analogy with previous results,[15,16] we anticipated that dihydropyridines **9**, **14**, and **19** in which the 2-position of the heterocycle was positioned either 7 or 8 atoms away from C-2 of the dihydropyridine, i.e., the iminium ion carbon, would be appropriate choices for cyclization attempts. We also prepared **30** in order to test the ability of the less reactive C-3 of thiophene to participate in this cyclization mode. The synthesis of dimethyl 2,6-dimethyl-4-[2-(3-thienylmethyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**9**) (Scheme II) involved lithiation and formylation[24] of 1-bromo-2-(3-thienylmethyl)benzene (**7**)[25] to aldehyde **8**, followed by condensation under standard Hantzsch[26] conditions with methyl acetoacetate and methyl 3-aminocrotonate. The preparation of dimethyl 2,6-dimethyl-4-[2-(3-furylmethyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**14**) (Scheme II) involved the conversion of 2-bromobenzaldehyde (**10**) to alcohol **11**, followed by reduction with lithium aluminum hydride/aluminum chloride to **12**. Compound **12** was converted to **14** by the same sequence used in the preparation of **9**.

The preparation of dimethyl 2,6-dimethyl-4-[2-(3-thienyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**19**) (Scheme III) utilized the nickel-catalyzed coupling[27] of 3-bromothiophene with the Grignard reagent of *o*-bromotoluene to give 2-(3-thienyl)toluene (**17**). This material was brominated with *N*-bromosuccinimide, and converted under Krohnke conditions to the aldehyde **18**, which provided **19** via the Hantzsch reaction. Dimethyl 2,6-dimethyl-4-[2-(2-thienyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**30**) was prepared (Scheme III) by treatment of bis(μ-acetato)bis[2-(*N*-phenylformimidoyl)-phenyl]dipalladium (**28**)[28] with the Grignard reagent of 2-bromothiophene to give, after hydrolysis, aldehyde **29**. Formation of **30** from **29** under Hantzsch conditions was uneventful. Interestingly, the coupling reacion to give **29** did not occur when the bis(μ-dichloro) derivative[29] of **28** was used.

Treatment of dihydropyridine **9** with gaseous hydrogen chloride or trimethylsilyl trifluoromethanesulfonate, i.e., reagents which successfully cyclized **1**, in a variety of solvents effected either no reaction or, after extended periods, oxidation to the pyridine. However, treatment of **9** with aluminum chloride in chloroform for 48 h at room temperature afforded a mixture of diastereomeric esters **21a** and **21b** (Scheme IV). No significant amount of monocycled **22** was detected. The structures shown for these reaction products are consistent with elemental analysis, mass spectral, and 360-MHz ^{1}H NMR data. In addition, the structure of **21a** was confirmed by single-crystal X-ray analysis.[30] Surprisingly, no cyclization occurred when methylene chloride, rather than chloroform, was used as solvent.

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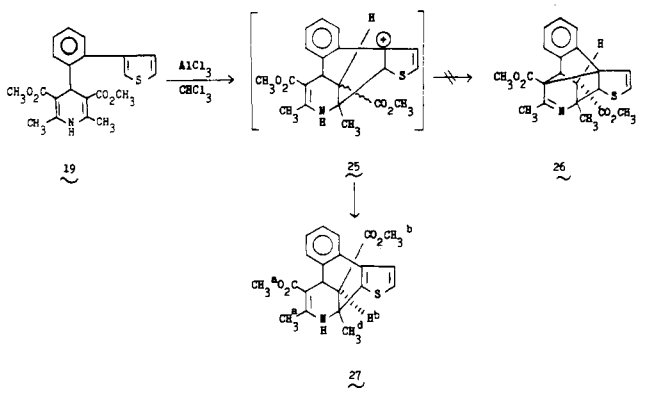
Scheme V



Similarly, treatment of dihydropyridine **14** with aluminum chloride in chloroform afforded a single cyclized product (Scheme IV) which, to our surprise, gave an NMR spectrum lacking both furan protons (indicative of monocyclization) and vinyl ether protons of the biscyclized **24**. Mass spectral and 360-MHz ^{1}H NMR data showed this compound to be **23**, derived from addition of ethanol (present in chloroform as a stabilizer, 0.75%) to the vinyl ether linkage of **24**. When **14** was cyclized in ethanol-free chloroform, **24** was formed in 59% yield as the sole product.

We were gratified that our expectation regarding the ability of reactive heterocycles to trap the dihydropyridine/iminium ion was correct and that cyclized products formed in good yields. However, we had anticipated that, unlike the biscyclization process involving benzyl cation **3**, intermediate **20** should have a greater tendency for proton elimination with formation of the monocyclized **22**, due to rearomatization of the thiophene ring. That monocyclized adduct **22** was not formed in any appreciable amount is testimony to the fact that the cationic center of **20** can approach the nucleophilic crotonate C-3 carbon in a fashion which allows for a favorable stereoelectronic-controlled[31] cyclization process.

Based on the above result with **9** and in recognition that cation **3** had as its sole pathway intramolecular capture by the crotonate double bond, we anticipated that **19** also would provide the biscyclization product **26**. This analysis did not of course address the inherent reactivity differences between cations **20** and **25** due to their different stabilities and geometries. However, a consideration of Dreiding models of **20** and **25** showed that the relationship of the cationic center to the nucleophilic C-3 carbon, with respect to both distance and orientation, was quite similar in both cations. To our surprise, however, treatment of dihydropyridine **19** with aluminum chloride in chloroform at room temperature gave dimethyl 5,8-dihydro-4,6-dimethyl-4,8-methano-4*H*-thieno[3,2-*a*]benzazonine-1,13β-dicarboxylate (**27**), the product derived from elimination in cation **25**, as the sole product (see Scheme V). Compound **27** was identified on the basis of elemental analysis, 360-MHz ^{1}H NMR, and mass spectral data. One explanation for the fact that proton elimination has in this case successfully competed with internal attack is that the transition state for the former process is lowered due to conjugative stabilization by the phenyl ring.

One further attempt to effect cyclization utilizatin heterocycles as the iminium-trapping moiety involved **30** (Scheme VI), wherein C-3 of thiophene is recruited as the attacking center. Despite the reported[32] 10^2 to 5×10^2 lower reactivity of C-3 vs. C-2 of thiophene in electrophilic aromatic substitution reactions, **30** underwent facile cyclization. This result most likely indicates that in this intramolecular case, specific geometric features of cation stabilization by sulfur in **25** and **31** are overriding the cited preferences for α- and β-reactivity from intermolecular electrophilic aromatic substitution. Treatment of **30** with aluminum chloride in chloroform at room temperature provided dimethyl 5,8-dihydro-4,6-dimethyl-4,8-methano-4*H*-thieno[2,3-*a*][4]benzazonine-7,13β-dicarboxylate (**32**) along with dimethyl 3a,4,6a,7-tetrahydro-4,6-dimethyl-4,8-methanoindeno[2,1-*c*]thieno-[2,3-*d*]pyridine-6a,12-dicarboxylate as a mixture of the α-(**33b**) and β-(**33a**) isomers. The ratio of cyclization products **32**/**33a**, **33b** was ca. 1/2.5. These compounds were identified on the basis of elemental analysis, 360-MHz ^{1}H NMR, mass spectral data, and in the case of **32**, single-crystal X-ray analysis.[30] An ORTEP plot of compound **32** is displayed in Figure 1. Competitive partitioning of cation **31** toward both mono- (**32**) and biscyclized (**33a**/**33b**) products, represents a situation intermediate between those of **9**/**14** and **19**, where one of these cyclization modes predominantly occurs.

Attempts to extend these cyclization reactions to the phenoxy- (**34**), phenyl- (**35**), benzyl- (**36**), and (3-methoxyphenyl)- (**37**) dihydropyridines (Chart I) were unsuccessful. At reaction periods suitable for thiophenes and furans and with aluminum chloride as catalyst, no reaction was observed, while at longer times, aromatization to the pyridine occurred. The lack of reaction of **37** was particularly surprising in light of the similar reactivity of thiophene and anisole in electrophilic aromatic substitution.[33]

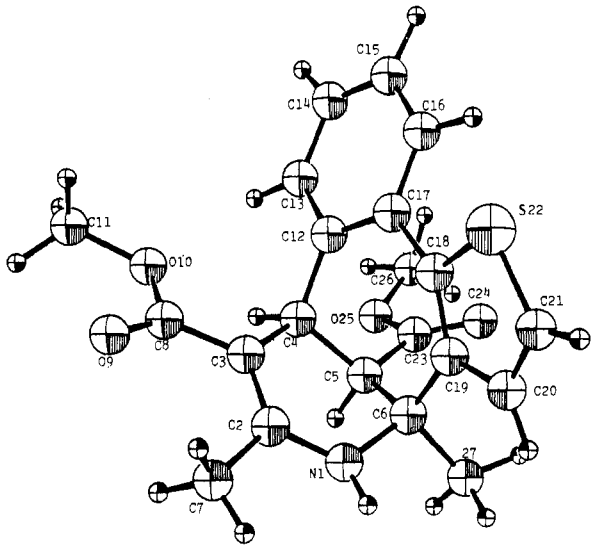
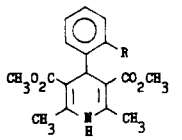


Figure 1. ORTEP plot of compound **32**.

Chart I



34, R = OC_6H_5
35, R = C_6H_5
36, R = $CH_2C_6H_5$
37, R = 3-$CH_3OC_6H_4$

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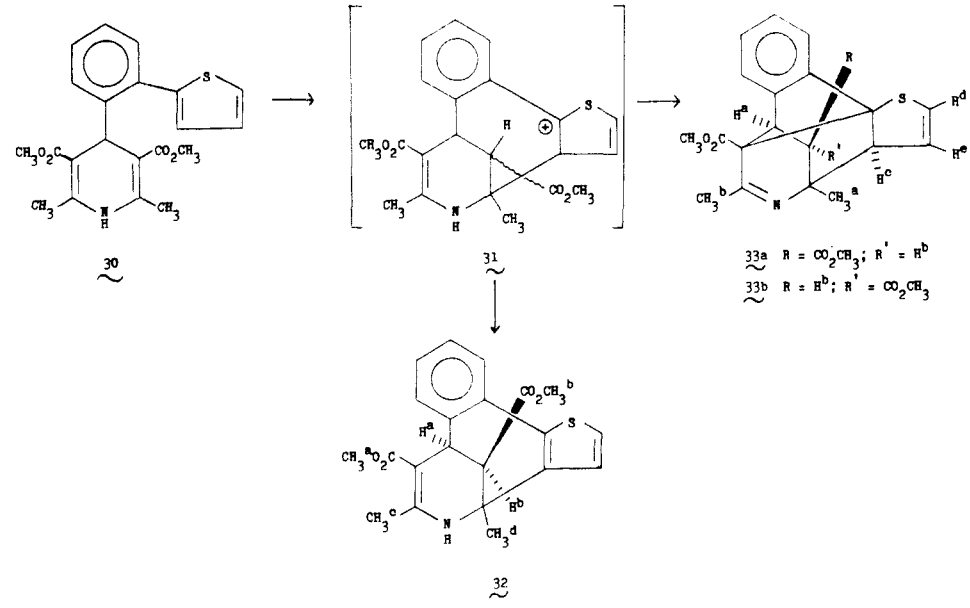
Scheme VI



We are continuing to study the synthetic utility of intramolecular cyclization processes involving the dihydropyridine/iminium species. We are particularly interested in controlling the diastereomeric ratio of the esters that are produced and in generating optically active products via manipulation of the catalysts that are utilized. Details of these efforts will be reported in due course.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. NMR spectra 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 an LKB-9000S mass spectrometer at 70 eV. *N*-Formylpiperidine, methyl acetoacetate, methyl 3-aminocrotonate, 3-bromofuran, and 2-bromobenzaldehyde were obtained from Aldrich and used without purification.

2-(3-Thienylmethyl)benzaldehyde (8). To 10.13 g (0.04 mol) of 1-bromo-2-(3-thienylmethyl)benzene (**7**)[25] dissolved in 125 mL of tetrahydrofuran and cooled to −78 °C under nitrogen was added 0.04 mol of *n*-butyllithium in hexane dropwise at <−70 °C. After the mixture had been stirred for 1 h at −78 °C, a solution of 4.91 g (0.044 mol) of *N*-formylpiperidine in 25 mL of tetrahydrofuran was added dropwise at <−70 °C. The resulting yellow solution was allowed to gradually warm to room temperature with stirring overnight.

The reaction was quenched with 25 mL of saturated ammonium chloride solution and diluted with 150 mL of ether. The organic phase was separated and the aqueous phase reextracted with 100 mL of ether. The combined organic extracts were washed with 2 × 25 mL of saturated ammonium chloride solution and brine and then dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give an oil, which was purified by flash chromatography on silica gel eluting with 95/5 hexane/ether to give 3.5 g (43%) of pure **8** (R_f 0.5) as a clear oil: NMR ($CDCl_3$, 90 MHz) δ 4.42 (2 H, s, CH_2), 6.8–7.9 (7 H, m, aromatic), 10.27 (1 H, s, CHO); mass spectrum, 202 (M^+).

Dimethyl 2,6-Dimethyl-4-[2-(3-thienylmethyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (9). To 0.51 g (0.0025 mol) of **8** dissolved in 10 mL of methanol was added 0.29 g (0.0025 mol) of methyl 3-aminocrotonate, 0.29 g (0.0025 mol) of methyl acetoacetate, and 2 drops of concentrated aqueous ammonium hydroxide solution. This mixture was heated at reflux under nitrogen for 4 days. The solvent was removed on the rotary evaporator and the residue was triturated with 15 mL of 1/1 hexane/ether to afford a solid that was crystallized from cyclohexane to give 0.4 g (40%) of pure **9**, mp 157–158 °C: NMR ($CDCl_3$, 90 MHz) δ 2.3 (6 H, s, CH_3), 3.5 (6 H, s, CO_2CH_3), 4.35 (2 H, s, CH_2), 5.3 (1 H, s, CH), 5.6 (1 H, br s, NH), 6.7–7.4 (7 H, m, aromatic). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.47; H, 5.83; N, 3.52. Found: C, 66.53; H, 6.01; N, 3.32.

4,6a,7,12-Tetrahydro-4,6-dimethyl-4,7-methano-3a*H*-benzo[*g*]thieno[2,3-*d*]isoquinoline-6a,13-dicarboxylate (21a, 21b). To 1.0 g (2.5 mmol) of dimethyl 2,6-dimethyl-4-[2-(3-thienylmethyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (**9**) in 50 mL of chloroform at room temperature under nitrogen was added 0.5 g (3.75 mmol) of aluminum chloride and the reaction mixture stirred for 48 h.

The solvent was removed on the rotary evaporator, and the residue was taken up in 25 mL of H_2O, neutralized with saturated sodium bicarbonate solution, and extracted with 4 × 50 mL portions of methylene chloride. The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed on the rotary evaporator to give an oil. This oil was purified by flash chromatography on silica gel (230–400 mesh) eluted with 1/3 hexane/ether to afford the β-isomer **21b** (R_f 0.4) as a white solid, 0.108 g (10.8%), mp 180.5–181.5 °C and the α-isomer **21a** (R_f 0.3) as a white solid, 0.09 g (9%), mp 155–156 °C.

21b: NMR ($CDCl_3$, 360 MHz) δ 1.58 (3 H, s, CH_3^d), 2.05 (3 H, s H^c), 2.72 (1 H, d, H^d), 3.04 (1 H, d, H^c), 3.21 (1 H, d, H^b), 3.30 (3 H, s, CH_3^b), 3.66 (3 H, s, CH_3^a), 3.81 (1 H, d, H^a), 4.60 (1 H, s, H^g), 6.01 (1 H, d, H^e), 6.09 (1 H, d, H^f), 6.9–7.24 (4 H, m, aromatic); mass spectrum, 397 (M^+). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.47; H, 5.83; N, 3.52. Found: C, 66.45; H, 5.86; N, 3.53.

21a: NMR ($CDCl_3$, 360 MHz) δ 1.60 (3 H, s, CH_3^d), 2.08 (3 H, s, CH_3^c), 2.40 (1 H, d, H^b), 2.94 (1 H, d, H^c), 3.27 (1 H, d, H^d), 3.41 (1 H, s, H^g), 3.68 (3 H, s, CH_3^b), 3.74 (3 H, s, CH_3^a), 3.88 (1 H, d, H^a), 6.04 (2 H, s, H^e and H^f), 6.99–7.23 (4 H, m, aromatic); mass spectrum, 397 (M^+). Anal. Calcd for $C_{22}H_{23}NO_4S$: C, 66.47; H, 5.83; N, 3.52. Found: C, 66.41; H, 5.76; N, 3.38.

1-Bromo-2-[1-(3-furyl)hydroxymethyl]benzene (11). A solution of 0.44 g (3.0 mmol) of 3-bromofuran in 1 mL of ether was added dropwise to a solution of 2.7 mmol of *n*-butyllithium in hexane in 2.5 mL of ether cooled to −78 °C under nitrogen. This was stirred for 45 min at −78 °C and then a solution of 0.5 g (2.7 mmol) of 2-bromobenzaldehyde in 2 mL of ether was added dropwise over 5 min. The reaction mixture was stirred overnight while slowly warming to room temperature.

The reaction was quenched with 1 mL of saturated ammonium chloride solution, diluted with 2 mL of H_2O, and extracted with 3 × 10 mL of ether. The combined organic phase was washed with H_2O and brine and then dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give 0.68 g of an orange oil which was crude **11**. This was purified by flash chromatography on silica gel (230–400 mesh) eluting with 10% ethyl acetate/hexane to give pure **11** (R_f 0.4), 0.40 g (59%) as an oil: NMR ($CDCl_3$, 60 MHz) δ 2.8 (1 H, d, exchanged by D_2O, J = 4 Hz), 6.0 (1 H, d, J = 4 Hz), 6.3 (1 H, m), 7.0–7.6 (6 H, m).

1-Bromo-2-(3-furylmethyl)benzene (12). A solution of 10.40 g (0.078 mol) of aluminum chloride in 40 mL of ether was carefully added via syringe to a suspension of 3.12 g (0.078 mol) of lithium aluminum hydride in 40 mL of ether cooled in an ice bath and under nitrogen. The ice bath was removed and a solution of **11** in 25 mL of ether was added dropwise at such a rate that reflux was maintained. After addition was complete, the mixture was refluxed another 15 min and then, with ice-bath cooling, dilute (3 M) sulfuric acid was added dropwise until gas evolution stopped. The reaction mixture was poured into a mixture of 100 mL of ice and 25 mL of 3 N hydrochloric acid and this extracted with 2 × 50 mL of ether. The combined organic extract was washed with 3 N HCl, saturated sodium bicarbonate, H_2O, and brine and dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give an oil which was purified by flash chromatography on silica gel (230–400 mesh) eluting with 2% ethyl acetate/hexane to give pure **12** (R_f 0.4), 9.41 g (76%), as an oil: NMR ($CDCl_3$, 60 MHz) δ 3.8 (2 H, s), 6.2 (1 H, m), 6.9–7.6 (6 H, m).

2-(3-Furylmethyl)benzaldehyde (13). To a solution of 9.01 g (0.038 mol) of **12** in 120 mL of tetrahydrofuran cooled to −78 °C under nitrogen was added 0.038 mol of *n*-butyllithium in hexane dropwise with the internal temperature maintained <−74 °C. This solution was stirred for 0.5 h at −78 °C and then a solution of 4.75 g (0.038 mol) of *N*-formylpiperidine in 60 mL of tetrahydrofuran was added dropwise keeping the temperature below −73 °C. The resulting solution was stirred for 5 h while gradually warming to −10 °C. This solution was quenched by addition of 25 mL of saturated ammonium chloride solution and diluted with 150 mL of ether. The aqueous phase was extracted with 2 × 100 mL of ether and the combined organic phase was washed several times with saturated ammonium chloride solution and once with brine and then dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give a dark oil which was purified by flash chromatography on silica gel (230–400 mesh) eluting with 2–5% ethyl acetate/hexane to give pure **13** (R_f 0.4), 4.10 g (58%) as an oil: NMR ($CDCl_3$, 60 MHz) δ 4.2 (2 H, s), 6.2 (1 H, m), 7.0–7.4 (5 H, m), 7.8 (1 H, m), 10.2 (1 H, s).

Dimethyl 2,6-Dimethyl-4-[2-(3-furylmethyl)phenyl]-1,4-dihydropyridine-2,6-dicarboxylate (14). To 2.79 g (15 mmol) of 2-(3-furylmethyl)benzaldehyde (**13**) in 30 mL of pyridine was added 4.18 g (0.36 mmol) of methyl acetoacetate and 4.3 mL (32 mmol) of concentrated ammonium hydroxide. The resulting solution was refluxed for 16 h. The solvent was removed on the rotary evaporator to give an orange oil which was purified by flash chromatography on silica gel eluting with 1% methanol/chloroform followed by recrystallization from ether to provide **14** as a white solid, 0.55 g (10%), mp 140–143 °C: NMR ($CDCl_3$, 360 MHz) δ 2.33 (6 H, s), 3.55 (6 H, s), 4.17 (2 H, s), 5.29 (1 H, s), 5.61 (1 H, br s), 6.27 (1 H, s), 7.0–7.4 (6 H, m). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.20; H, 6.07; N, 3.56.

Dimethyl 4,6a,7,12-Tetrahydro-4,6-dimethyl-4,7-methano-3a*H*-benzo[*g*]furo[2,3-*d*]isoquinoline-6a,13β-dicarboxylate (24). A solution of 0.31 g (0.80 mmol) of **14** in 8 mL of ethanol-free chloroform was added to a suspension of 0.32 g (2.4 mmol) aluminum chloride in 24 mL of ethanol-free chloroform. After being stirred for 4 h at room temperature under nitrogen, the reaction was quenched by the addition of dilute sodium bicarbonate solution. This was extracted with 2 × 20 mL of methylene chloride, and the combined organic phases were washed with saturated sodium bicarbinate and brine, and the resulting solution was dried over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to afford crude residue which was purified by flash chromatography on silica gel eluting with 1% methanol/chloroform followed by recrystallization from ether/hexane to give 0.082 g (27%) of pure **24**, mp 128–131 °C: NMR ($CDCl_3$, 360 MHz) δ 1.57 (3 H, s, CH_3^a), 2.02 (3 H, s, CH_3^b), 2.72 (1 H, d, H^b, J = 12 Hz), 2.94 (1 H, d, H^c, J = 18 Hz), 3.22 (3 H, s, CH_3^c), 3.32 (1 H, d H^d, J = 18 Hz), 3.61 (3 H, s, CH_3^d), 3.73 (1 H, d, H^e, J = 12 Hz), 5.12 (1 H, s, H^e), 5.26 (1 H, d, H^f, J = 3 Hz), 6.28 (1 H, d, H^g, J = 3 Hz), 7.0 (4 H, m). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.31; H, 6.48; N, 3.63.

Dimethyl 1,2,4,6a,7,12-Hexahydro-4,6-dimethyl-2-ethoxy-4,7-methano-3a*H*-benzo[*g*]furo[2,3-*d*]isoquinoline-6a,13β-dicarboxylate (23). Reaction was carried out in a similar fashion as for **24** except that chloroform containing 0.75% ethanol as stabilizer was used as solvent. Workup gave an oil that was purified by flash chromatography on silica gel (230–400 mesh) eluting with 1% methanol/chloroform to provide 0.029 g (45%) of **23** as a single isomer of undetermined stereochemistry at C-2: NMR ($CDCl_3$, 360 MHz) δ 1.22 (3 H, t, CH_3^e, J = 9 Hz), 1.55 (3 H, s, CH_3^a), 2.02 (1 H, d of d, H^g, J = 15, 6 Hz), 2.14 (3 H, s, CH_3^b), 2.21 (1 H, d, H^f, J = 15 Hz), 2.68 (1 H, d, H^b, J = 12 Hz), 3.20 (1 H, d, H^c, J = 18 Hz), 3.26 (3 H, s, CH_3^c), 3.43 (1 H, d, H^d, J = 18 Hz), 3.44 (1 H, m, H^j), 3.65 (3 H, s, CH_3^d), 3.73 (1 H, m, H^i), 3.75 (1 H, d, H^c, J = 12 Hz), 4.74 (1 H, s H^e), 5.03 (1 H, d, H^h, J = 6 Hz), 7.1 (4 H, m); mass spectrum, 427 (M^+).

2-(3-Thienyl)toluene (17). To 2.0 g (0.012 mol) of 2-bromotoluene dissolved in 20 mL of tetrahydrofuran and cooled to −78 °C under nitrogen was added via syringe 0.012 mol of *n*-butyllithium in hexane, and the resulting suspension was stirred for 45 min at −78 °C. Then, 2.76 g (0.015 mol) of magnesium bromide etherate was added through Gooch tubing in portions such that the temperature was kept <−65 °C. After stirring for 10 min at −78 °C the reaction mixture was allowed to warm to room temperature over 1 h to afford a clear, green solution. This solution was added via syringe to a suspension of 1.79 g (0.011 mol) of 3-bromothiophene and 0.26 g (0.05 mmol) of bis(1,2-diphenylphosphino)ethanenickel(II) chloride[33] in 25 mL of ether that had been stirred for 10 min. As the Grignard reagent was added dropwise over 10 min, the reaction mixture turned dark and a mild exotherm developed. This solution was heated at reflux for 18 h.

The reaction mixture was cooled and quenched with dilute hydrochloric acid. The organic phase was separated and washed with aqueous sodium bicarbonate and brine and the solvent removed in vacuo to give a brown oil. This was fractionated to give 1.28 g (67%) of pure **17** as a clear oil, bp 110–114 °C (7 mm). This material was a single spot on TLC (silica gel) with R_f 0.6, eluting with 2% ethyl acetate/hexane: NMR ($CDCl_3$, 60 MHz) δ 2.30 (3 H, s, CH_3), 7.20 (7 H, m, aromatic); mass spectrum, 174 (M^+). Anal. Calcd for $C_{11}H_{10}S$: C, 75.82; H, 5.78. Found: C, 75.88; H, 5.76.

2-(3-Thienyl)benzaldehyde (18). To 12.6 g (0.0723 mol) of 2-(3-thienyl)toluene (**17**) dissolved in 150 mL of carbon tetrachloride was added 13.35 g (0.075 mol) of *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide. This solution was heated at reflux under nitrogen with irradiation from a 250-W sunlamp for 2 h. The reaction mixture was cooled and passed through a pad of silica gel on a filter funnel to remove succinimide. The pad was thoroughly washed with ether, and the filtrate was stripped in vacuo to give an orange oil. This was fractionated to give 14.2 g (76%) of the desired bromomethyl compound, bp 100–103 °C (0.1 mm) as a clear oil. This compound was converted to aldehyde **18** by utilizing the standard Krohnke method. Crude material was purified by flash chromatography on silica gel eluting with 3% ethyl acetate/hexane to give 0.25 g (66%) of pure **18** as a clear oil (R_f 0.4): NMR ($CDCl_3$, 60 MHz) δ 7.40 (5 H, m, aromatic), 7.95 (2 H, m, aromatic), 10.13 (1 H, s, CHO); mass spectrum, 188 (M^+). Anal. Calcd for $C_{11}H_8OS$: C, 70.18; H, 4.28. Found: C, 70.01; H, 4.33.

Dimethyl 2,6-Dimethyl-4-[2-(3-thienyl)phenyl]-1,4-dihydropyridine-3,5-dicarboxylate (19). To 2.0 g (10.6 mmol) of **18** dissolved in 10 mL of methanol was added 1.23 g (10.6 mmol) of methyl acetoacetate, 1.23 g (10.6 mmol) of methyl 3-aminocrotonate, and a drop of concentrated aqueous ammonium hydroxide. The resulting solution was refluxed for 4 days. The solvent was removed in vacuo and the residue purified by flash chromatography on silica gel (230–400 mesh) eluting with 1/2 hexane/ether. Solvent removal afforded a pale yellow foam which was triturated with 2/1 hexane/ether to give 1.5 g (37%) of **19** as a pale yellow solid, mp 155–164 °C. Recrystallization from ether–hexane gave analytically pure material, mp 164–166 °C: NMR ($CDCl_3$, 90 MHz) δ 2.18 (6 H, s), 3.40 (6 H, s), 5.40 (1 H, s), 5.60 (1 H, br s), 7.05–7.60 (7 H, m, aromatic). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.83; H, 5.66; N, 3.50.

Dimethyl 5,8-Dihydro-4,6-dimethyl-4,5-methano-4*H*-thieno[3,2-*a*][4]benzazonine-7,13β-dicarboxylate Hemihydrate (27). To a solution of 0.32 g (0.83 mmol) of **19** in 20 mL

of chloroform was added 0.134 g (1.0 mmol) of aluminum chloride through Gooch tubing. After being stirred for 24 h at room temperature under nitrogen, the reaction was quenched by the addition of water and neutralized with the addition of saturated sodium bicarbonate solution. The resulting 2-phase mixture was extracted with 3 × 25 mL portions of methylene chloride, and the combined organic phases were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded crude **27** which was purified by flash chromatography on silica gel eluting with 1/1 hexane/ether to give 0.22 g (69%) of pure **27**, mp 223–233 °C: NMR ($CDCl_3$, 360 MHz) δ 1.55 (3 H, s, CH_3^d), 2.08 (3 H, s, CH_3^c), 3.29 (3 H, s, CH_3^b), 3.55 (3 H, s, CH_3^a), 3.31 (1 H, d, H^b, J = 8 Hz), 4.42 (1 H, s, NH), 4.50 (1 H, d, H^a, J = 8 Hz), 7.08–7.53 (6 H, m, aromatic). Anal. Calcd for $C_{21}H_{21}NO_4S \cdot {}^1/_2H_2O$: C, 64.26; H, 5.65; N, 3.57. Found: C, 64.36; H, 5.65; N, 3.64.

2-(2-Thienyl)benzaldehyde (29). To 4.89 g (0.03 mol) of 3-bromothiophene dissolved in tetrahydrofuran and cooled to −78 °C under nitrogen was added dropwise 0.03 mol of *n*-butyllithium in hexane while keeping the internal temperature less than −72 °C. After 10 min of stirring, 11.7 g (0.045 mol) of magnesium bromide etherate was added portionwise through Gooch tubing, and the temperature of the reaction mixture was allowed to rise to −20 °C over 45 min. Transmetalation carried out at this temperature allows the formation of the thermodynamically more stable 2-thienylmagnesium species as the major product. This mixture was then added via syringe to a suspension of 16.2 g (0.015 mol) of bis(μ-acetato)bis[2-(*N*-phenylformimidoyl)phenyl]dipalladium[27] and 15.74 g (0.06 mol) of triphenylphosphine in 250 mL of benzene which had been previously stirred for 1 h. The reaction mixture was then stirred at room temperature overnight.

The cooled reaction mixture was quenched with 175 mL of 1 N hydrochloric acid with stirring for 2.5 h. This was filtered and the phases were separated. The aqueous phase was extracted with 2 × 150 mL of ether, and the combined organic phases were washed with brine and acid over anhydrous sodium sulfate. The solvent was removed on the rotary evaporator to give an oil which was purified by flash chromatography on silica gel (230–400 mesh), eluting with 3% ethyl acetate/hexane to give **29** (R_f 0.4) as a clear oil, 1.57 g (27% yield): NMR ($CDCl_3$, 90 MHz) δ 10.2 (1 H, s, −CHO), 6.95–8.1 (7 H, m, aromatic).

Dimethyl 2,6-Dimethyl-4-[2-(3-thienyl)phenyl]-1,4-dihydropyridine-2,6-dicarboxylate (30). To 0.095 g (0.5 mmol) of **29** dissolved in 5 mL of methanol were added 0.116 g (1.0 mmol) of methyl acetoacetate and 1.0 mmol of concentrated aqueous ammonium hydroxide and this was refluxed for 4 days. The solvent was removed on the rotary evaporator, and the residue was purified by flash chromatography on silica gel (230–400 mesh) eluting with 50% hexane/ether. Solvent removal afforded a pale yellow solid which was triturated with 2/1 hexane/ether to give 0.105 g (55%) of pure **30** as a white solid, mp 173–175 °C: NMR ($CDCl_3$, 90 MHz) δ 7.0–7.5 (7 H, m, aromatic), 5.5 (1 H, s, −CH−), 5.4 (1 H, br s, −NH), 3.4 (6 H, s, 2-CH_3), 2.25 (6 H, s, 2 −$COOCH_3$). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.89; H, 5.70; N, 3.60.

Dimethyl 5,8-Dihydro-4,6-dimethyl-4,8-methano-4*H*-thieno[3,2-*a*][4]benzazonine-7,13β-dicarboxylate (32) and Dimethyl 3a,4,6a,7-Tetrahydro-4,6-dimethylindeno[2,1-*c*]-thieno[3,2-*c*]pyridine-6a,12-dicarboxylate (33, 33b). To 0.32 g (0.8 mmol) of **30** in 20 mL of chloroform at room temperature under nitrogen was added 0.134 g (1.0 mmol) of aluminum chloride through Gooch tubing and the resulting suspension was stirred overnight.

The cooled reaction mixture was quenched with 20 mL of ice water, made basic with saturated sodium bicarbonate solution, and diluted with 100 mL of chloroform. The organic phase was separated, washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed to give a viscous yellow oil, which from TLC analysis was shown to be three components. This material was separated into these components by flash chromatography on silica gel (230–400 mesh) eluting with 1/2 hexane/ether. The first component to elute had R_f 0.4 in this system and was shown to be **32**, 0.052 g (16%) mp 185–193 °C. The second component to elute from the column was **33a** the β-isomer from biscyclization, 0.110 g (34%), mp 169–174 °C. The final component to elute was **33b**, 0.015 g (5%), mp 172–175.5 °C.

33a: NMR ($CDCl_3$, 360 MHz), δ 1.62 (3 H, s, CH_3^a), 2.27 (3 H, s, CH_3^b), 2.42 (1 H, d, H^b), 3.51 (3 H, s, CO_2CH_3), 3.65 (3 H, s, CO_2CH_3), 3.68 (1 H, d, H^a), 3.96 (1 H, dd, H^c), 5.33 (1 H, dd, H^e), 5.98 (1 H, dd, H^d), 7.0–7.43 (4 H, m, aromatic). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.57; H, 5.41; N, 3.81.

33b: NMR ($CDCl_3$, 360 MHz), δ 1.64 (3 H, s, CH_3^a), 2.30 (3 H, s, CH_3^b), 2.54 (1 H, s, H^b), 3.14 (1 H, dd, H^c), 3.72 (4 H, s, H^a and CO_2CH_3), 3.69 (3 H, s, CO_2CH_3), 5.31 (1 H, dd, H^e), 6.03 (1 H, dd, H^d), 7.14–7.43 (4 H, m, aromatic); mass spectrum, 383 (M^+).

32: NMR ($CDCl_3$, 360 MHz) δ 1.80 (3 H, s, CH_3^d), 2.08 (3 H, s, CH_3^c), 3.23 (1 H, d, H^b), 3.25 (3 H, s, CH_3^b), 3.55 (3 H, s, CH_3^a), 4.33 (1 H, br s, NH), 4.50 (1 H, d, H^a), 7.0–7.58 (7 H, m, aromatic); mass spectrum, 383 (M^+). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; N, 5.52; N, 3.65. Found: C, 65.55; H, 5.49; N, 3.61.

Acknowledgment. We thank Dr. D. W. Cochran for his analysis of NMR spectra, J. P. Moreau for elemental analyses, Dr. H. Ramjit for mass spectral determinations, and M. Banker for the typing of this manuscript. We also thank Dr. G. M. Smith of the Merck Molecular Systems Department for helpful discussions.

Supplementary Material Available: Crystallographic data including tables of the atomic postional and thermal parameters, bond distances, and bond angles and a diagram of the structure for **32** (5 pages). Ordering information is given on any current masthead page.