Amino-Claisen Rearrangements of *N*-Vinylisoquinuclidenes in Novel Approaches to the Synthesis of Hydroisoquinolines and Hydrophenanthridines[1]

Patrick S. Mariano,*[2] Debra Dunaway-Mariano, and Peter L. Huesmann

Department of Chemistry, Texas A&M University, College Station, Texas 77843

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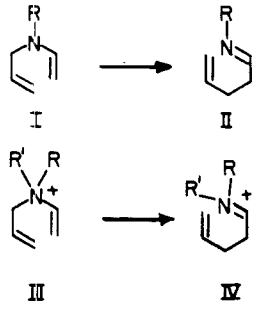
Model studies probing novel and potentially efficient approaches to the synthesis of hydroisoquinolines and hydrophenanthridines are described. Synthetic designs investigated employ amino-Claisen and related rearrangement reactions to transform easily prepared *N*-vinylisoquinuclidenes to these nitrogen containing, fused bicyclic and tricyclic systems. One approach developed utilizes nucleophilic substitution reactions of N-methylated isoquinuclidenes with β-chloro-α,β-unsaturated ketones to generate the transient N-vinylated quaternary ammonium salts. Rearrangements of these substances occur at room temperature and produce the hydroisoquinolines **12**, **13β**, and **13α**. This route fails when the β-halo enone precursors possess alkyl substitution at the β carbon. However, an alternate and more versatile procedure was developed utilizing acid-catalyzed rearrangements of β-amino-α,β-unsaturated ketones **20**, **22**, and **24**, derived from reactions of secondary isoquinuclidenes with β-chloro enones. The generality of this latter approach is demonstrated by its utility in preparation of hydrophenanthridines **21**, **23**, and **25** and phenanthridone **27**. The mechanistic features, synthetic potential, and possible limitations of these rearrangement reactions are discussed.

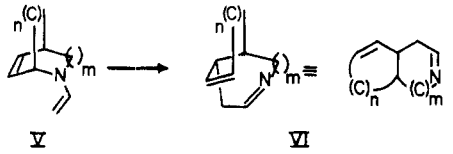
The Cope[3] and Claisen[4] rearrangements have found wide application in the synthesis of complex molecular systems. Indeed, the Claisen rearrangement which transforms allyl vinyl ethers into γ,δ-unsaturated carbonyl compounds has proven exceptionally useful as a general synthetic method due to its adaptability to a wide range of structural and functional variations.[5] In contrast, incorporation of the related amino-Claisen rearrangement, which converts *N*-allylenamines I or corresponding ammonium salts III to corresponding unsaturated imines or iminium salts II and IV, into preparative



I II III IV

sequences has occurred much less frequently. The limited utilization of this process in synthetic strategies targeted at the construction of nitrogen-containing natural products is surprising in light of reports describing the exceptional ease and high efficiency of rearrangements involving *N*-allyl-*N*-vinylammonium salts (III → IV).[6]

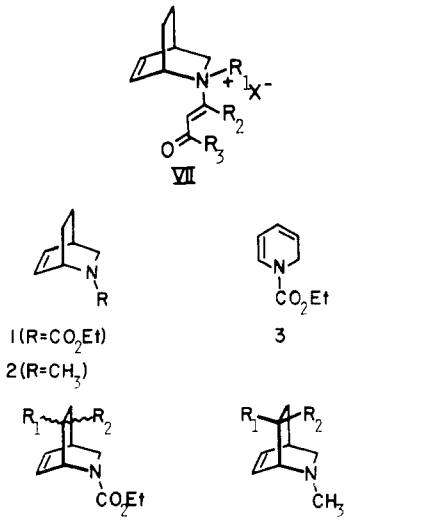
Recently, we initiated investigations to explore more thoroughly the scope and applications of amino-Claisen and related rearrangement reactions. We were particularly interested in transformations of this type with 2-vinyl-2-azabicycloalkenes of general structure V since these would provide reasonably simple routes to a series of complex and potentially important heterocyclic systems containing fused-polycyclic structures (VI). Our initial efforts have demon-



V VI

strated that this approach can be applied in the preparation of hydroisoquinolines and hydrophenanthridines from *N*-vinylisoquinuclidenes (V; $n = 2$, $m = 1$). Moreover, the studies described below demonstrate the utility of synthetic strategies that combine rearrangement reactions of this type with simple methods for generation of the intermediate isoquinuclidenes.[7]

***N*-Vinylammonium Salt Approach.** Our efforts were initially focused on an investigation of amino-Claisen rearrangements of the *N*-vinylisoquinuclideneammonium salts VII, which appeared synthetically accessible by reaction of N-alkylated isoquinuclidenes **2**, **6en**, and **6ex** with β-halo-



VII

1 (R=CO$_2$Et) 3

2 (R=CH$_3$)

4 (R$_1$=COCH$_3$, R$_2$=H) 6en (R$_1$=CH$_3$CO(CH$_2$)$_2$O, R$_2$=H)

5 (R$_1$=CH$_3$CO(CH$_2$)$_2$O, R$_2$=H) 6ex (R$_1$=H, R$_2$=CH$_3$CO(CH$_2$)$_2$O)

α,β-unsaturated ketones.[8] The sequences used to prepare the isoquinuclidenes **2** and **6** followed two basic designs. The simple *N*-methyl system **2**[7b] is obtained using the known Diels–Alder cycloaddition of *N*-(ethoxycarbonyl)formaldimine to 1,3-cyclohexadiene[7b] followed by lithium aluminium hydride reduction of the intermediate bicyclic carbamate **1**. An alternate route was employed to generate **6ex** and **6en**. Cycloaddition of methyl vinyl ketone to 1-(ethoxycarbonyl)-1,2-dihydropyridine (**3**)[9] furnished the 7-acetylisoquinuclidenes **4** as a 4:3 mixture of endo and exo isomers in an 89% yield. Epimerization of the ketone mixture with methanolic $NaOCH_3$ led to a thermodynamic distribution consisting of a 2:3 endo to exo isomeric ratio. Stereochemical assignments to the epimers of **4** are derived indirectly on the basis of evi-

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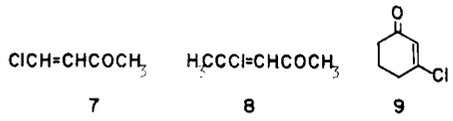
Table I. Selected Spectroscopic Properties of the Hexahydroisoquinolines 12, 13β, and 13α

spectroscopic data	hexahydroisoquinoline 12	13β	13α
IR (cm^{-1}) C=O	1582	1575	1575
UV (nm) (EtOH)	308 (ε 25 600)	307 (ε 15 800)	307 (ε 29 500)
^1H NMR (ppm)			
NCH=CCO	7.30	7.14	7.24
N-CH_3	3.04	2.98	3.00
H-5	5.60	6.37	5.68
H-6	5.44	5.63	5.49
^{13}C NMR (ppm)			
C=O	192	192	192
NC=CCO	112	112	112
NC=CCO	148	148	148

dence provided for the separated *N*-methylisoquinuclidenes **6** (vide infra). The ethylene ketals **5,** obtained from **4** by reaction with ethylene glycol (81%), were then reduced with $LiAlH_4$ to produce (99%) an epimeric mixture of the *N*-methylisoquinuclidenes **6** which could be separated by preparative GLC or Florisil column chromatography. Characteristic NMR data for the individual stereoisomers were used in making regiochemical and stereochemical assignments to **6en** and **6ex.** Of exceptional utility were the multiplicities of the H-1 resonances in the ^1H NMR spectra of these substances. Accordingly, the H-1 resonances of these isomers appeared as a triplet of doublets, indicating the presence of a single proton on C-7. In addition, the chemical shifts of the *N*-methyl protons and carbon in the spectra of **6ex** and **6en** (2.14 and 2.23 ppm for ^1H NMR and 45.07 and 46.02 ppm for ^{13}C NMR, respectively) reflect the effect of the bulky dioxolane group on N-CH_3 conformations which have the methyl protons and carbon in the exo isomer residing in the deshielding region of the C-5, C-6 π bond. Also, the dioxolane methyl and H-7 proton resonances for **6ex** (1.55 and 1.75 ppm, respectively) and **6en** (1.12 and 1.98 ppm, respectively) appear again to reflect C-5, C-6 π bond deshielding effects. Further confirmation of these stereochemical assignments was obtained using LIS ^1H NMR spectroscopic measurements. The dioxolane methyl proton chemical shift changes, induced by continuous variation of the $Eu(fod)_3$ to isoquinuclidene molar ratios in the range of 0.0 to 0.45, were found to be 0.33 ppm for **6ex** and 0.13 ppm for **6en.** The *N*-methyl proton resonances experienced equivalent induced shifts of 1.3 ppm over the same region. Thus, assignment of the *exo*-dioxolane configuration to **6ex** appears reasonable since it would place the methyl group in closer proximity to the site of ligation in the lanthanide–amine complex. It is interesting to note that the preferred regiochemical and stereochemical modes for methyl vinyl ketone cycloaddition to 1-(ethoxycarbonyl)-1,2-dihydropyridine are those predicted using FMO considerations[10] and are analogous to results from a study of Diels–Alder additions to *N*-acylaminodienes[11] and 1-benzyl-5-cyano-1,2-dihydropyridine.[12]

Efforts then turned to generation of *N*-vinylisoquinuclideneammonium salts of general structure VII by reaction of the *N*-methylisoquinuclidenes **2, 6en,** and **6ex** with a series of β-chloro enones, including 4-chlorobut-3-en-2-one (**7**),[13] 4-chloropent-3-en-2-one (**8**),[14] and 3-chlorocyclohex-2-en-1-one (**9**).[15] Precedent for this approach is found in several



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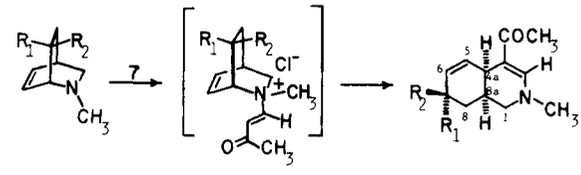
reports which describe the preparation of a series of related quaternary ammonium salts by reaction of tertiary amines with a variety of chlorovinyl ketones.[8] However, under the reaction conditions employed we were unable to isolate the *N*-vinylisoquinuclidene salts **10** and **11** which were almost certainly produced by addition of the *N*-methylisoquinuclidenes **2, 6ex,** and **6en** to the simple chlorovinyl ketone **7.** Accordingly, formation and ensuing rearrangement of these salts were carried out in one step by stirring THF solutions of **2, 6ex,** or **6en** and **7** containing suspended K_2CO_3 at 25 °C. Pu-



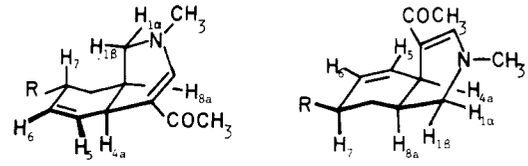
2 10 (R1=R2=H) 12

6en 11en (R1=CH3CO(CH2)2O, R2=H) 13α

6ex 11ex (R1=H, R2=CH3CO(CH2)2O) 13β

rification of the reaction mixtures by silica gel chromatography afforded the corresponding hexahydroisoquinolines **12, 13α,** and **13β,** respectively, in yields after purification ranging from 30–60%.

Structural and stereochemical assignments for these hexahydroisoquinolines were made on the basis of their spectroscopic properties, summaries of which are included in Table I. As can be seen by inspection of this data, the rearrangement products from these reactions all contain the *N*-methylenamino ketone function spanning the N-2 to C-4 centers of the fused bicyclic system. In addition, the locations of the unconjugated π bonds in **13β** and **13α** were made in a similar



12 (R=H) 13β(R=CH3CO(CH2)2O)

13α(R=CH3CO(CH2)2O)

fashion using characteristic ^1H NMR spectroscopic parameters (see Table II) in conjunction with the expectation that the relative stereochemistries at C-7 and C-8a would be governed by the C-7 stereochemistries in the isoquinuclidene precursors **6ex** and **6en,** respectively, and that the bulky methyldioxolyl grouping will control preferred conformations of the hexahydroisoquinoline ring systems. In the spectrum of the 7α-dioxolyl epimeric hexahydroisoquinoline, **13α,** vicinal coupling between H-5 and H-4a and between H-6 and H-7 is small, as would be expected if both H-4a and H-7 are disposed axially on the A-ring. In addition, the H-1, H-8a cou-

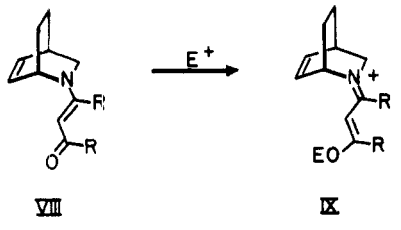
Table II. ^{1}H NMR Spectroscopic Data Used in Assignments of Relative Stereochemistries to 12, 13β, and 13α

^{1}H NMR parameters	hexahydroisoquinoline 12	13β	13α
chemical shifts (ppm)			
H-1α	2.84	2.95	2.82
H-1β	3.16	3.15	3.11
coupling constants (Hz)			
J(1α–1β)	12	12	12
J(1α–8a)	4	5	4.5
J(1β–8a)	12	4	12
J(1α–4a)	2	0	2
J(4a–5)	2	5	1

pling pattern contains a large axial–axial coupling (12 Hz), indicating the B-ring axial location of H-8a in this isomer and thus the cis H-4a, H-8a relationship. This data points to a preferred conformation of **13α** in which the bulky dioxolane grouping and C-4 are equatorial with respect to the A-ring. Further confirmation of this is found in the observation of a reasonably large (2 Hz) long range coupling between H-1 and H-4a, a result of their location at the terminii of the familiar W-bonded network. In contrast, J(4a-5) in the spectrum of **13β** is large and consistent with the equatorial location of H-4a on the A-ring of this isomer. Similarly, the H-1, H-8a coupling pattern lacking a large axial–axial coupling constant can be used, along with the near 0 long range coupling constant between H-1 and H-4a, to assign a cis ring fusion and a preferred equatorial dioxolane, axial C-4 conformation to **13β**. Supportive evidence for these assignments derives from the unusual downfield location of the H-5 resonance in the spectrum of **13β** which models suggest should be the case since H-5 lies in the nodal plane of the acetyl carbonyl function at C-4. Lastly, the exceptionally close similarities between the ^{1}H NMR parameters of **12** and **13α** suggest a cis-fused C-4 equatorial stereochemistry for the former hexahydroisoquinoline also.

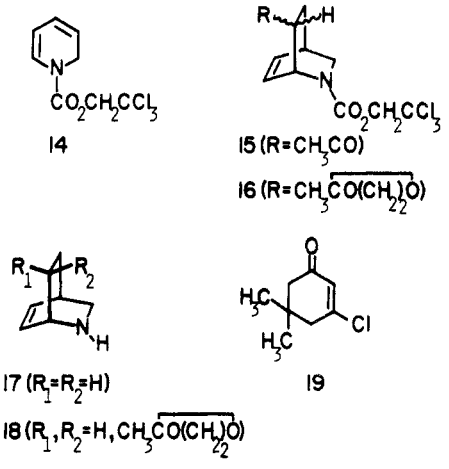
This method for generation of hydroisoquinolines through rearrangement of intermediates produced by ketovinylation of tertiary Δ^5-isoquinuclidenes appears to be limited to systems utilizing β-chloro enones lacking β-alkyl substitution. This conclusion arises as a result of observations which show that the N-methylisoquinuclidenes **6en** and **6ex** fail to react with either 4-chloropent-3-en-2-one or 3-chlorocyclohex-2-en-1-one. Thus, although the literature holds several reports indicating that simple tertiary amines react with these more hindered β-chloro enones,[8] the potentially less nucleophilic N-methylisoquinuclidenes appear to resist Michael addition.

Protonated Enamino Ketone Approach. A more general approach to this problem, based upon a similar strategy, has been developed. We envisaged that N-vinylisoquinuclidenes of general structure VIII, prepared by reaction of the corresponding secondary bicyclic amines with β-halo enones or β-diketones and having the vinyl moiety as part of a β-enamino ketone function, would undergo O-addition of strongly electrophilic reagents. Indeed, Leonard[16] has shown that simple enamino ketones undergo O-protonation. Iminium salt intermediates IX formed in this way would be likely precursors to hydroisoquinolines or more highly annelated analogues due to the potential for heterolytic cleavage and cyclization. Examples which serve to demonstrate the applications and generality of this methodology are found in the acid-catalyzed rearrangements of a series of N-ketovinylated isoquinuclidenes leading to the generation of decahydrophenanthridines.



VIII IX

The enamino ketones used to test this strategy were produced in the familiar manner by ketovinylation of the corresponding isoquinuclidenes. For example, addition of the parent azabicyclooctene **17**[7b] to 3-chloro-5,5-dimethylcyclohex-2-en-1-one (**19**)[17] furnished the crystalline N-vinyliso-



quinuclidene **24**. The more highly functionalized enamino ketone **20** can be prepared as a C-7 epimeric mixture using a reaction sequence beginning with Diels–Alder cycloaddition of methyl vinyl ketone to 1-(trichloroethoxycarbonyl)-1,2-dihydropyridine (**14**), which was obtained from pyridine and trichloroethoxycarbonyl chloride using the sodium borohydride reduction procedure developed by Fowler.[18] In this sequence, the trichloroethoxycarbonyl function serves as a model blocking group, selected on the basis of its rather mild removal using activated zinc. This feature would be particularly attractive when sequences utilizing more elaborate and highly functionalized substances are investigated. Ketalization of the intermediate carbamate **15** produced the epimeric ketals **16** which were deprotected using the reported conditions[19] to furnish the isoquinuclidenes **18**. The desired enamino ketone **20** (C-7 epimeric mixture) was then prepared by addition of **18** to the β-chlorocyclohexenone **9**.

Acid-catalyzed rearrangements were then explored. A moist benzene solution of the cyclohexenonylisoquinuclidene **20** containing p-TsOH was refluxed for 8 h, giving, after chromatographic purification, a 70% yield of a substance which had spectroscopic properties fully consistent with assignment of its structure to the decahydrophenanthridine **23** (see Table III). Deketalization almost certainly preceeds rearrangement under these reaction conditions. Indeed, the 7-acetylisoqui-

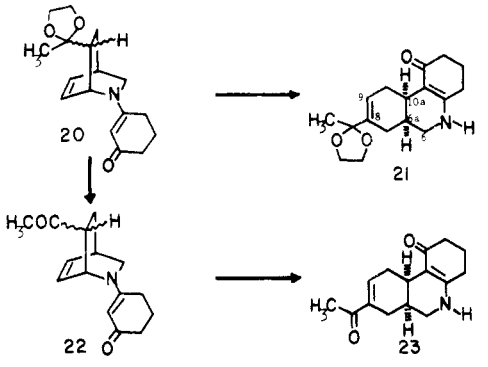
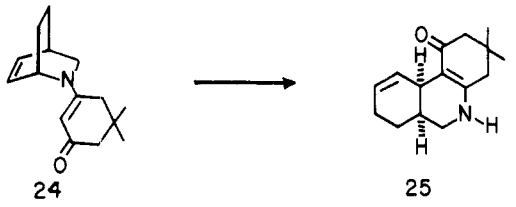


Table III. Characteristic Spectroscopic Properties of the Decahydrophenanthridines 21, 23, and 25

spectroscopic parameters	decahydrophenanthridine 21	23	25
UV (nm) (EtOH)	301 (ε 26 100)	298 (ε 25 400)	302 (ε 22 300)
IR (cm^{-1})			
α,β-unsatd C=O		1650	
enamino ketone C=O	1575	1575	1580
^1H NMR (ppm) vinyl H	5.72 (1 H)	6.77 (1 H)	5.64 (1 H)
			5.46 (1 H)
^{13}C NMR (ppm) (multiplicity)			
NC=CC=O	159.5 (s)	158.7 (s)	158.8 (s)
NC=CC=O	192.9 (s)	193.3 (s)	192.9 (s)
C=CC=O		199.1 (s)	
C=C, C-8	134.2 (s)	136.6 (s)	
C=C, C-9	119.7 (d)	138.6 (d)	130.9 (d)
C=C, C-10			128.8 (d)

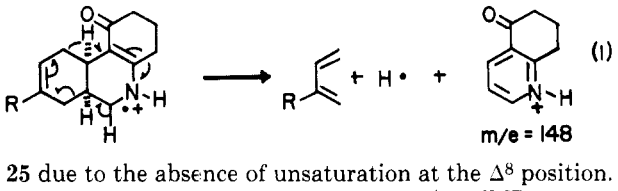
nuclidene **22** can be produced at 25 °C by stirring **20** in an acidic aqueous THF solution. Rearrangement of this new *N*-vinylisoquinuclidene **22** to produce **23** (79%) requires refluxing benzene temperatures and *p*-TsOH as catalyst. Rearrangement of the ketal **20** to the Δ^8-decahydrophenanthridine ketal **21**, on the other hand, can be performed under anhydrous conditions (HCl, C_6H_6, reflux), but requires much more lengthy reaction times (3.5 days) for completion. The structural similarities between **21** and **23** are demonstrated by the ready interconversion of the ketal to methyl ketone functionalities under aqueous acid hydrolytic conditions. Lastly, in the case of the *N*-vinylisoquinuclidene **24**, which



24 **25**

lacks acetyl substitution at C-7, exceedingly long reaction times (7 days) and high temperatures (refluxing toluene) are required in order to drive acid-catalyzed rearrangement to the crystalline Δ^9-decahydrophenanthridine **25**.

Structural assignments to the decahydrophenanthridines produced by the procedures detailed above were based upon characteristic spectroscopic properties and comparisons with those of related hydroisoquinolines. A summary of the data which was most informative is included in Table III. The location of the π bond within the A-ring of these fused tricyclic substances is worthy of comment. Clearly, the ^{13}C and ^1H NMR data presented in Table III are consistent in an unambiguous way with structures having the olefinic moiety at the Δ^8 position in both the acetyl- and methyldioxolyl-substituted systems, **21** and **23**. For the hydrophenanthridine **25**, indirect evidence is available to assist in assigning Δ^9 as the site of A-ring unsaturation. As expected, the base peak (*m/e* 148) in the mass spectrometric fragmentation patterns of the two Δ^8-unsaturated hydrophenanthridines **21** and **23** results from retro-Diels–Alder cleavage at C-6a–C-7 and C-10–C-10a as shown in eq 1. A similar process is not seen in fragmentation



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of **25** due to the absence of unsaturation at the Δ^8 position. The exceptionally close similarities of the ^1H NMR spectra of **25** and its hexahydroisoquinoline analogue **12** (see Figure 1) give further support to this assignment.

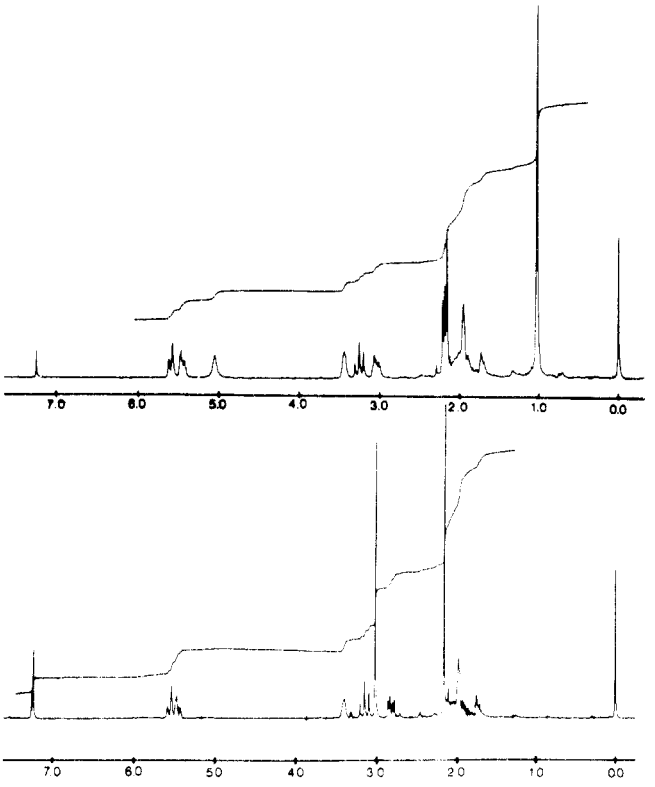
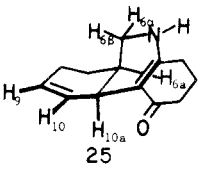


Figure 1. The 200-MHz ^1H NMR spectra of hexahydroisoquinoline **12** (bottom) and decahydrophenanthridine **25** (top) taken in $CDCl_3$ with chemical shift scales in ppm relative to $(CH_3)_4Si$.

Unfortunately, the ^1H NMR spectra of **21** and **23** are not well resolved, thus making ring-fusion stereochemistry difficult to discern. On the other hand, the Δ^9-hydrophenanthridine **25** gives a near first-order 200-MHz spectrum which



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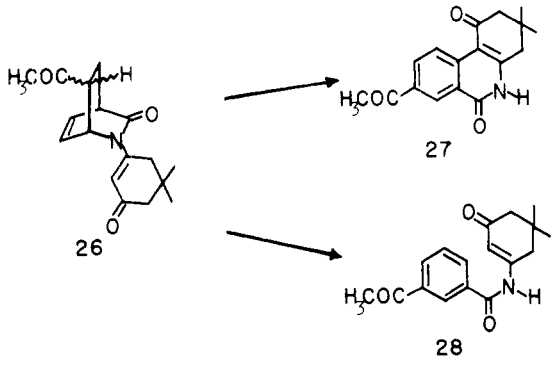
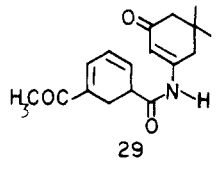
is useful in determining the relative configurations at C-6a and C-10a and thus the stereochemical course of this novel rearrangement reaction. Of exceptional utility are the H-6β, H-6a coupling constant of 12 Hz, indicating a 1,2-diaxial alignment of these protons, the near 0 coupling between H-10 and H-10a, a result of an axial orientation of H-10a, and the chemical shift for the H-10 resonance (5.64 ppm), which in the closely related hydroisoquinoline systems indicated that the carbonyl-

bearing B-ring carbon was bridged equatorial with respect to the A-ring. This data and comparison with that obtained for the cis-fused Δ^5-hydroisoquinoline **12** (see Figure 1) suggest that the hydrophenathridine **25** and most probably **21** and **23** contain cis-AB ring fusions and exist preferentially in a conformation having C-6 directed axially from the A-ring.

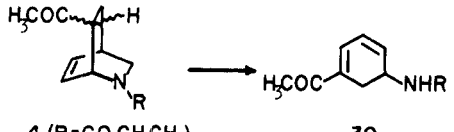
Related Observations. In order to briefly explore the applicability of this acid-catalyzed rearrangement reaction of N-ketovinylated isoquinuclidenes to closely related systems, the chemistry of the 7-acetylisoquinuclidenone **26** was investigated. The synthesis of this substance by methyl vinyl ketone cycloaddition to the corresponding dimedonyl-2-pyridone has been described previously.[10] Acid-catalyzed rearrangement of **26** is less efficient than that of analogues lacking the amide functionality. Accordingly, the tetrahydrophenanthridone **27** is obtained in low yield (10%) by reaction of **26** in benzene containing *p*-toluenesulfonic acid at 60 °C. Attempted rearrangements at higher temperatures (80 °C) gave the acetylbenzamide derivative **28** in a 13% yield after



chromatographic purification. The benzamide product isolated from the high temperature reaction is most likely arising from fragmentation of either the ring oxygen or the enamido ketone oxygen protonated system via cleavage of the carbon-1 nitrogen bond followed by rapid oxidation[20] of the intermediate acetylcyclohexadiene derivative **29.** Interestingly, similar



fragmentation reactions have been observed in the acid-catalyzed reactions of the 7-acetylisoquinuclidene carbamates **4** and **15.** The cyclohexadienes **30** and **31** are obtained in high yield (ca. 90%) from reactions of the respective bicyclic carbamate starting materials conducted in refluxing benzene containing *p*-toluenesulfonic acid. The relationship of these observations to the mechanistic course of the acid-catalyzed conversions of *N*-vinylisoquinuclidenes to decahydrophenanthridines is considered below.

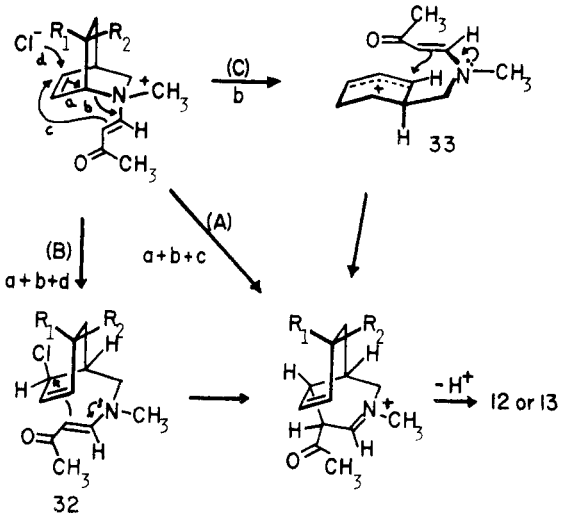


4 (R=$CO_2CH_2CH_3$) 30

15(R=$CO_2CH_2CCl_3$) 31

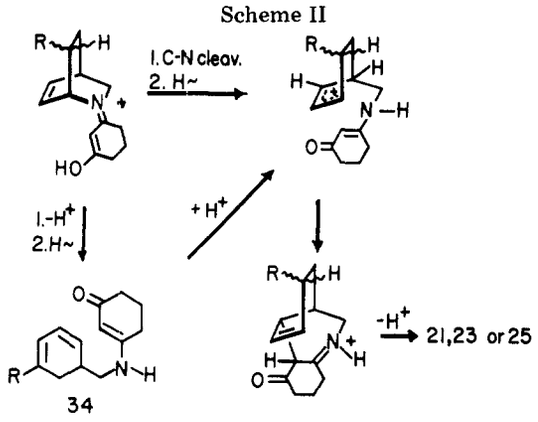
Mechanistic Discussion. Several mechanisms for conversion of the *N*-vinylisoquinuclideneammonium salts to hexahydroisoquinolines, described above, appear reasonable. The first of these involves concerted amino-Claisen rearrangement from the endo-ketovinylated systems formed in a reversible fashion by addition of the *N*-methylisoquinuclidines to β-chloroenone (Scheme I, pathway A). Analogous substances containing the *N*-allylenammonium salt moiety are known to be exceptionally prone to rearrangement by this pathway.[4,6] Likewise, it does not appear that the bicyclic framework of these systems would serve to prevent good orbital overlap in the transition state for the pericyclic process since Cope and oxy-Cope rearrangements occur readily on closely related 2-*endo*-vinylbicyclo[2.2.*n*]alk-5-enes.[3,21] Alternatively, a nonconcerted pathway involving sequential nucleophilic substitution reactions might be operating (Scheme I, pathway B). In this pathway, S_N2' attack by chloride at C-5 of the initially formed ammonium salt would lead to the allylic chloride **32,** which could then cyclize by internal C-alkylation of the enamino ketone moiety.[22] The observed hydroisoquinoline stereochemistry would require the less likely[23] exo attack (inversion) of chloride at C-5 in the initial S_N2' step. A third mechanistic alternative can be envisaged (Scheme I, pathway C). Heterolytic cleavage of the carbon-1 nitrogen bond in the ammonium salt would produce an intermediate allylic cation **33,** capable of cyclizing to product by attack of the enamino ketone at C-5. Interestingly, the final step of this mode closely mimics analogous processes in polyolefin cationic cyclizations[24] and thus should display similar stereochemical preferences for production of the cis ring fusion via axial addition to the allyl cation through a transition state having the enamino ketone side chain equatorially disposed.[25]

Scheme I



The acid-catalyzed transformation of N-ketovinylated isoquinuclidenes to hydrophenanthridines can also be rationalized by several possible mechanisms all starting with the O-protonated salts. Thus, although kinetic protonation of several enamines has been shown to be selective for nitrogen,[26] acid-base theory and experimental observations[16] suggest that the carbonyl oxygen of enamino ketones is the site protonated. On the basis of this, it seems doubtful that these rearrangements follow concerted, amino-Claisen reaction pathways. More likely, step-wise processes are involved. Initial cleavage of the carbon-1 nitrogen bond in the O-protonated salts would lead to an allylic cation similar to **33** which would undergo stereoelectronically controlled cyclization to generate the A–B cis-fused hydrophenanthridines (Scheme II). Alternatively, deprotonation either following or in concert with C–N bond cleavage leads to the cyclohexadienylenamino ketones **34,** which can reprotonate under the acidic reaction conditions and cyclize. The latter pathway would more likely operate in the case of the 7-acetyl system **22,** where indirect precedence is available for formation of a cyclohexadiene intermediate in observations made with the isoquinuclidenone **26** and carbamate **4** and **15** analogues. Lastly, formation of the

Scheme II



Δ^8-hydrophenanthridine **21** from rearrangement of **20** most probably is the result of acid-catalyzed isomerization of the initially formed Δ^9 regioisomer.

Conclusion

The results presented above demonstrate that rearrangement reactions of appropriately substituted N-ketovinylated isoquinuclidenes offer a novel, efficient, and reasonably versatile method for construction of highly functionalized hydroisoquinoline and hydrophenanthridine systems. The availability of simple procedures for construction of isoquinuclidenes by Diels–Alder cycloadditions of dienophiles to 1,2-dihydropyridines or of imine derivatives to cyclohexadienes and for ketovinylation combine to indicate that synthetic strategies for the preparation of important heterocyclic compounds based on this design will find unique applications.

Experimental Section

General. ^{1}H NMR spectra were recorded using a Varian T-60 or HA-100 spectrometer with $(CH_3)_4Si$ as an internal standard. Chemical shifts are recorded in parts per million relative to $(CH_3)_4Si$. ^{13}C NMR spectra were recorded using a JEOL PS-100 spectrometer with a dedicated probe and Nicolet pulsed FT data collection system at operating frequencies of 25.0337–25.0347 MHz with $(CH_3)_4Si$ as an internal standard. ^{13}C NMR chemical shifts are reported in parts per million relative to $(CH_3)_4Si$. Mass spectra were obtained at 70 eV using a DuPont CEC21-110B high-resolution spectrometer. IR spectra were measured on a Perkin-Elmer 237B or Beckman IR-8 spectrophotometer. UV spectra were obtained on a Beckman ACTA-III spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Preparative chromatographic separations were accomplished using the following absorbents: for TLC, EM type 60 CF-254 silica gel; for column chromatography, either Grace silica gel (Davison grade 923, 100–200 mesh) or Fisher Florisil (100–200 mesh). Unless otherwise noted, Na_2SO_4 was routinely used as drying agent in the workup of reaction mixtures. Analytical GLC measurements were made using a Varian-940 chromatograph, and preparative GLC was done using a Varian-2400 chromatograph. Melting points were measured on a Griffin Mel-Temp apparatus and are reported uncorrected.

2-(Ethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (4). A mixture of 21.1 g (0.317 mol) of 1-(ethoxycarbonyl)-1,2-dihydropyridine[9] and 33 mL of methyl vinyl ketone was heated at 50 °C for 6 days under an Ar atmosphere. Purification of the reaction mixture by Florisil column chromatography (elution gradient from 1:9 to 3:7 ether–hexane) yielded a clear oil (27.2 g, 89%) which contained a 3:4 epimeric mixture (GLC) of the 7-acetyl-1-(ethoxycarbonyl)isoquinuclidene **4:** IR (CCl_4) 3020, 2950, 2925, 2900, 2850, 1720, 1695, 1414, 1370, 1105 cm^{-1}; UV (CH_3CN) max 199 nm (ϵ 3940); ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 4 H, H-8 endo and OCH_2CH_3), 1.80 (m, 1 H, H-8 exo), 2.13 and 2.29 (s, 3 H, $-COCH_3$), 2.56–3.36 (m, 4 H, H-3, H-7, and H-4), 4.12 (m, 2 H, $-OCH_2CH_3$), 5.00 and 5.14 (m, 1 H, H-1), 6.40 (m, 2 H, H-5 and H-6); ^{13}C NMR ($CDCl_3$) characteristic resonances at 14.6 and 14.8 (q, OCH_2CH_3), 30.3 and 30.8 (d, C-4), 47.1 (t, NCH_2), 52.5 (d, C-1), 61.0 (t, $-OCH_2CH_3$), 130.0, 132.0, 135.0, 135.5 (d, C-5 and C-6), 155.4 (s, NCO), 206.1, and 206.4 (s, $COCH_3$) ppm; mass spectrum *m/e* (relative intensity) 223 (P, 19), 178 (4), 153 (100), 124 (63), 108 (9); high-resolution mass spectrum, *m/e* 223.12027 ($C_{12}H_{17}NO_3$ requires 223.12083).

Interconversion of *endo*- and *exo*-7-Acetylisoquinuclidenes 4. A solution containing 150 mg (0.67 mmol) of the 7-acetylisoquinuclidene carbamates **4** in an exo–endo ratio of 3:4 and ethanolic sodium methoxide (from 900 mg, 0.04 g-atom of sodium and 70 mL of ethanol) was stirred under Ar at 25 °C for 15 h. The mixture was poured into ice water and neutralized with concentrated HCl and chloroform was extracted. The extracts were dried and concentrated in vacuo, giving 120 mg of an oil characterized by ^{1}H NMR to contain a mixture of *exo*- and *endo*-acetylisoquinuclidenes in a ratio of 3:2.

2-(Ethoxycarbonyl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (5). A solution of 5.06 g (22.7 mmol) of 2-(ethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene, 10 mL (179 mmol) of ethylene glycol, and 59 mg (0.31 mmol) of *p*-toluenesulfonic acid in 200 mL of anhydrous benzene was refluxed for 6 h under an Ar atmosphere in an apparatus equipped with a Dean-Stark trap. After cooling to 25 °C, the reaction mixture was washed with saturated $NaHCO_3$ and dried. Concentration of the resulting solution in vacuo yielded 6.17 g of a yellow oil which was further purified by Florisil column chromatography utilizing a gradual increase in the concentration of eluent from 1:9 to 3:7 ether–hexane. This yielded a clear oil (4.85 g, 80.0%) which consisted of an epimeric mixture of the isoquinuclidene ketals **5:** IR (CCl_4) 3020, 2950, 1695, 1425, 1110 cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.10–3.32 (m, 9 H, H-3, -4, -7, -8, and $-OCH_2CH_3$), 1.16 and 1.30 (s, 3 H, O_2CCH_3), 3.80–4.25 (m, 6 H, $-OCH_2CH_2O-$ and $-OCH_2CH_3$), 4.76 and 4.90 (m, 1 H, H-1), 6.34 (m, 2 H, H-5 and -6); mass spectrum, *m/e* (relative intensity) 267 (P, 5), 222 (2), 153 (57), 124 (29), 87 (100); high-resolution mass spectrum, *m/e* 267.14763 ($C_{14}H_{21}NO_4$ requires 267.14704).

2-Methyl-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (6en and 6ex). To a suspension of 120 mg (3.20 mmol) of lithium aluminium hydride in 50 mL of ether at 0 °C under Ar was added 539 mg (2.02 mmol) of the isomeric 2-(ethoxycarbonyl)-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-enes (**5**) in 10 mL of ether. The reaction mixture was stirred at 25 °C for 3 h, cooled to 0 °C, and mixed with 0.7 mL of 20% aqueous NaOH. The ethereal solution was then filtered and concentrated in vacuo yielding 4.5 mg of a clear oil which was purified by Kugelrohr distillation to yield 372 mg (88%) of a mixture of the epimeric *N*-methylisoquinuclidene ketals **6en** and **6ex.** The individual epimers were separated by preparative GLC (14% SE-60, 15 ft × 5/16 in. column, 190 °C). These isomers can also be separated by Florisil column chromatography. This technique leads to extensive loss of materials due to what appears to be irreversible adsorption. The spectral data for the individual isomers were as follows.

Exo isomer **6ex:** IR (CCl_4) 3020, 2925, 1435, 1365, 1200, 1060 cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.36 (m, 2 H, H-8 endo and exo), 1.55 (s, 3 H, O_2CCH_3), 1.60 (dd, 1 H, J = 9 and 2 Hz, H-3 endo), 1.75 (m, 1 H, H-7), 2.14 (s, 3 H, $-NCH_3$), 2.45 (m, 1 H, H-4), 3.08 (dd, 1 H, J = 9 and 2 Hz, H-3 exo), 3.37 (ddd, 1 H, J = 4, 3, and 2 Hz, H-1), 3.94 (m, 4 H, $-OCH_2CH_2O-$), 6.32 (m, 2 H, H-5 and -6); ^{13}C NMR ($DCCl_3$) 21.9 (q, O_2CCH_3), 23.4 (t, C-8), 31.4 (d, C-4), 45.1 (q, $-NCH_3$), 47.3 (d, C-7), 54.9 (d, C-1), 56.1 (d, C-3), 64.2 (t, $-OCH_2CH_2O-$), 65.2 (t, $-OCH_2CH_2O-$), 111.6 (s, $-O-C-O-$), 132.4 (d, C-5 or -6), 132.7 (d, C-5 or -6) ppm; mass spectrum, *m/e* (relative intensity) 208 (P, 10), 166 (2), 122 (4), 95 (69), 94 (100); high-resolution mass spectrum, *m/e* 209.14126 ($C_{12}H_{19}NO_2$ requires 209.14157).

Endo isomer **6en:** IR (CCl_4) 3020, 2925, 1435, 1365, 1150, 1060 cm^{-1}; ^{1}H NMR ($DCCl_3$) δ 1.12 (s, 3 H, O_2CCH_3), 1.21 (m, 1 H, H-8 endo), 1.70 (m, 1 H, H-8 exo), 1.98 (m, 1 H, H-7), 2.23 (s, 3 H, $-NCH_3$), 2.45 (dd, 1 H, J = 10 and 2 Hz, H-3 endo), 2.53 (m, 1 H, H-4), 2.97 (dd, 1 H, J = 10 and 2 Hz, H-3 exo), 3.44 (ddd, 1 H, J = 5, 2.5, and 2 Hz, H-1), 3.89 (m, 4 H, $-OCH_2CH_2O-$), 6.19 (m, 1 H, H-5 or -6), 6.37 (m, 1 H, H-5 or -6); ^{13}C NMR ($DCCl_3$) 22.44 (q, O_2CCH_3), 26.9 (t, C-8), 31.3 (d, C-4), 44.0 (d, C-7), 46.2 (q, $-NCH_3$), 54.2 (t, C-3), 54.8 (d, C-1), 64.3 (t, $-OCH_2CH_2O-$), 64.6 (t, $-OCH_2CH_2O-$), 110.7 (s, $-OCO-$), 130.4 (d, C-5 or -6), 132.5 (d, C-5 or C-6) ppm; mass spectrum *m/e* (relative intensity) 209 (P, 8), 95 (68), 94 (100); high-resolution mass spectrum *m/e* 209.14105 ($C_{12}H_{15}NO_2$ requires 209.14157).

Δ^3,Δ^5-2-Methyl-4-acetylhexahydro-*cis*-isoquinoline (12). To a solution of 414 mg (3.36 mmol) of 2-methyl-2-azabicyclo[2.2.2]oct-5-ene (**2**)[7b] in 10 mL of anhydrous THF containing 1.19 g (8.6 mmol) of suspended K_2CO_3 was added 679 mg (6.50 mmol) of 1-chlorobut-1-en-3-one.[14] The resulting mixture was stirred at 25 °C under an Ar atmosphere for 8.5 h, filtered to remove insoluble salts, and concentrated in vacuo, yielding 767 mg of a red viscous oil which was purified by preparative TLC on silica gel (3:7 $HCCl_3$–ether). An orange oil (150 mg, 28%) was obtained from a band at R_f 0.4 which was characterized

as the hydroisoquinoline **12**: IR ($HCCl_3$) 2967, 2899, 2841, 2825, 1631, 1582, 1414, 1393, 1351, 1335, 1294, 1264, 1183, 1110, 938 cm^{-1}; UV (EtOH) max 308 nm (ϵ 25 600); ^1H NMR ($DCCl_3$) δ 1.64–2.26 (m, 5 H, H-8a, -7α, -7β, -8α, and -8β), 2.13 (s, 3 H, $-COCH_3$), 2.84 (ddd, 1 H, J = 12, 4, and 2 Hz, H-1α), 3.04 (s, 3 H, $-NCH_3$), 3.16 (t, 1 H, J = 12 Hz, H-1β), 3.39 (m, 1 H, H-4a), 5.44 (dt, 1 H, J = 10.5 and 2.5 Hz, H-6), 5.60 (d, 1 H, J = 10.5 Hz, H-5), 7.30 (s, 1 H, H-3); ^{13}C NMR ($DCCl_3$) 20.8 (t, C-8), 23.9 (q, $COCH_3$), 24.5 (t, C-7), 29.0 (d, C-8a), 30.4 (d, C-4a), 43.0 (q, $-NCH_3$), 48.2 (t, C-1), 111.5 (s, C-4), 122.8 (d, C-5), 130.9 (d, C-6), 148.3 (d, C-3), 192.4 (s, $-COCH_3$) ppm; mass spectrum *m/e* (relative intensity) 191 (p, 86), 190 (19), 176 (34), 162 (23), 148 (100), 136 (15), 120 (14), 112 (58), 91 (20), 77 (27), 43 (65), 42 (66), 39 (32); high resolution mass spectrum *m/e* 191.13044 ($C_{12}H_{17}NO$ requires 191.13101).

Δ^3,Δ^5-2-Methyl-4-acetyl-7β-(1,1-ethylenedioxyeth-1-yl)hexahydroisoquinoline (13β). To a solution of 187 mg (0.89 mmol) of 2-methyl-*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**6ex**) in 10 mL of anhydrous THF containing 155 mg (1.2 mmol) of suspended K_2CO_3 was added 121 mg (1.2 mmol) of 1-chlorobut-1-en-3-one.[13] This mixture was then stirred at 25 °C for 18 h under an Ar atmosphere, filtered to remove insoluble salts, and concentrated in vacuo. Preparative TLC on silica gel of the residue (1:1 $HCCl_3$–ether) gave 93 mg (38%) of the hydroisoquinoline **13β** as an oil: IR ($HCCl_3$) 2960, 2905, 2850, 1625, 1575, 1345 cm^{-1}; UV (EtOH) max 307 nm (ϵ 15 800); ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H, O_2CCH_3), 2.12 (s, 3 H, $COCH_3$), 1.20–2.62 (m, 4 H, H-7, -8, and -8a), 2.98 (s, 3 H, $-NCH_3$), 2.95 (dd, 1 H, J = 12 and 5 Hz, H-1α), 2.95 (br m, 1 H, H-4a), 3.15 (dd, 1 H, J = 12 and 4 Hz, H-1β), 3.95 (s, 4 H, OCH_2CH_2O), 5.63 (d, 1 H, J = 10 Hz, H-6), 6.37 (ddd, 1 H, J = 10, 5, and 2.5 Hz, H-5), 7.14 (s, 1 H, H-3); ^{13}C NMR ($CDCl_3$) 20.9 (q, O_2CCH_3), 24.5 (q, $COCH_3$), 26.0 (t, C-8), 31.5 (d, C-8a or -7), 31.9 (d, C-8a or -7), 43.3 (q, NCH_3), 44.0 (d, C-4a), 53.0 (t, C-1), 64.6 (t, $-OCH_2CH_2O-$), 111.4 (s, –OCO–), 112.5 (s, C-4), 125.0 (d, C-5 or -6), 132.1 (d, C-5 or -6), 147.8 (d, C-3), 192.3 (s, $COCH_3$) ppm; mass spectrum, *m/e* (relative intensity) 227 (P, 5), 273 (5), 272 (5), 258 (4), 191 (18), 190 (18), 137 (9), 136 (6), 87 (100), 43 (32); high-resolution mass spectrum, *m/e* 277.16829 ($C_{16}H_{23}NO_3$ requires 277.16778).

Δ^3,Δ^5-2-Methyl-4-acetyl-7α-(1,1-ethylenedioxyeth-1-yl)hexahydroisoquinoline (13α). To a solution of 253 mg (1.2 mmol) of 2-methyl-*endo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]-oct-5-ene (**6en**) in 10 mL of anhydrous THF containing 209 mg (1.6 mmol) of suspended K_2CO_3 was added 164 mg (1.6 mmol) of 1-chlorobut-1-en-3-one. This mixture was then stirred at 25°C for 1.5 h under an Ar atmosphere, filtered to remove insoluble salts, and concentrated in vacuo. Preparative TLC on silica gel of the residue (1:1 $HCCl_3$–ether) gave 345 mg of partially crystalline material which was recrystallized (C_6H_6–pentane) to yield 201 mg (60.5%) of the hydroisoquinoline **13α**: mp 156–158 °C; IR ($HCCl_3$) 2995, 2975, 2910, 2860, 1625, 1575, 1335 cm^{-1}; UV (EtOH) max 307 nm (ϵ 29 500); ^1H NMR ($DCCl_3$) δ 1.26 (s, 3 H, O_2CCH_3), 1.86 (m, 2 H, H-8), 2.14 (s, 3 H, $COCH_3$), 2.28 (m, 2 H, H-7 and -8a), 2.82 (ddd, 1 H, J = 12, 4.5, and 2 Hz, H-1α), 3.00 (s, 3 H, $-NCH_3$), 3.11 (t, 1 H, J = 12 Hz, H-1β), 3.40 (m, 1 H, H-4a), 3.93 (s, 4 H, $-OCH_2CH_2O-$), 5.49 (d, 1 H, J = 10 Hz, H-6), 5.68 (d, 1 H, J = 10 Hz, H-5), 7.24 (s, 1 H, H-3); ^{13}C NMR ($DCCl_3$) 20.8 (q, O_2CCH_3), 23.9 (q, $COCH_3$), 26.8 (t, C-8), 29.4 (d, C-7 or -8a), 30.4 (d, C-7 or -8a), 40.3 (d, C-4a), 43.0 (q, $-NCH_3$), 48.3 (t, C-1), 64.6 (t, $-OCH_2CH_2O-$), 64.8 (t, $-OCH_2CH_2O-$), 111.2 (s, –OCO–), 111.6 (s, C-4), 122.8 (d, C-5 or -6), 132.8 (d, C-5 or -6), 148.5 (d, C-3), 192.3 (s, $-COCH_3$) ppm; mass spectrum, *m/e* (relative intensity) 277 (P, 57), 232 (20), 191 (17), 190 (41), 137 (7), 136 (6), 112 (17), 87 (100), 43 (54); high-resolution mass spectrum, *m/e* 277.16856 ($C_{16}H_{23}NO_3$ requires 277.16778).

1-(Trichloroethoxycarbonyl)-1,2-dihydropyridine (14). The general procedure described by Fowler[18] for preparation of analogous substances was employed. To 10.63 mL (0.132 mol) of distilled pyridine and 4.99 g (0.132 mol) of sodium borohydride in 50 mL of absolute ethanol was added dropwise at −78 °C 18.2 mL (0.132 mol) of trichloroethyl chloroformate in 12 mL of anhydrous ether. After stirring for an additional 1.5 h under argon, the reaction mixture was poured into 300 mL of ice water. The ether layer was separated, washed thoroughly with water, and then dried and concentrated in vacuo to give 32.0 g of a clear, sweet-smelling liquid. ^1H NMR analysis of the liquid indicated that it was essentially pure except for the presence of 5–10% of the 1,4-dihydropyridine: ^1H NMR ($CDCl_3$) δ 6.58 (d, 1 H, H-6, J = 8 Hz), 5.60 (m, 2 H, H-3 and H-4), 5.10 (m, 1 H, H-5), 4.71 (s, 2 H, CH_2), 4.33 (m, 2 H, H-2).

2-(Trichloroethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]-oct-5-ene (15). A mixture of 31.2 g (0.122 mol) of 1-(trichloroethoxycarbonyl)-1,2-dihydropyridine (**14**) and 40 mL (0.49 mol) of methyl vinyl ketone was heated at 53 °C under an Ar atmosphere for 7 days. Purification of the reaction mixture by Florisil column chromatography (utilizing a gradual increase in the concentration of eluent from 1:9 to 3:7 ether–hexane) yielded 23.0 g (58%) of the 7-acetylisoquinuclidene **15** as a 1:3.2 epimeric mixture[27a] (GLC): IR ($HCCl_3$) 3000, 2930, 2860, 1720, 1715, 1420, 1370, 1130 cm^{-1}; UV (CH_3CN) max 206 nm (ϵ 3050); ^1H NMR ($DCCl_3$) δ 1.32 (m, 1 H, H-8 endo), 1.84 (m, 1 H, H-8 exo), 2.13 and 2.27 (s, 3 H, $COCH_3$), 2.63–3.52 (m, 4 H, H-7, -4, and -3), 4.80 (m, 2 H, $-OCH_2CCl_3$), 5.13 (m, 1 H, H-1), 6.42 (m, 2 H, H-5 and -6); ^{13}C NMR ($DCCl_3$) characteristic resonances at 23.2 and 24.7 (t, C-8), 28.1 and 28.7 (q, $COCH_3$), 30.1 and 30.6 (d, C-4), 52.1 and 52.5 (d, C-1), 74.8 (t, $-CH_2CCl_3$), 95.8 (s, $-CCl_3$), 129.4, 129.9, 131.5, 135.1, 135.5, and 135.7 (d, C-5 and -6),[27b] 152.5, 153.2, 153.7 (s, $-NCO(OCH_2CCl_3)$,[27b] 205.7, 206.2, 206.5 (s, $COCH_3$) ppm;[27b] mass spectrum, *m/e* (relative intensity) 329 (3), 327 (9), 325 (P, 10), 290 (5), 255 (100), 178 (24), 131 (34), 124 (76); high-resolution mass spectrum, *m/e* 325.00304 ($C_{12}H_{14}NO_3Cl_3$ requires 325.00390).

2-(Trichloroethoxycarbonyl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (16). A solution of 10.1 g (31.1 mmol) of 2-(trichloroethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (**15**), 22 mL (0.39 mol) of ethylene glycol, and 75 mg (0.39 mmol) of *p*-toluenesulfonic acid in 250 mL of anhydrous benzene was refluxed for 8 h under an Ar atmosphere in an apparatus equipped with a Dean-Stark trap. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo to yield 12.05 g (ca. 100%) of a yellow oil containing an epimeric mixture of the isoquinuclidene ketals (**16**): IR ($CHCl_3$) 2990, 2960, 2930, 2870, 1710, 1420, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3 H, O_2CCH_3), 1.24–2.01 (m, 2 H, H-7), 2.44 (ddd, 1 H, J = 9.0, 7.0, and 2.5 Hz), 2.79 (m, 1 H, H-4), 2.79–2.97 (m, 2 H, H-3), 3.88 (s, 4 H, OCH_2CH_2O), 4.71 (s, 2 H, CH_2CCl_3), 4.88 (m, 1 H, H-1), 6.36 (m, 2 H, H-5 and H-6); ^{13}C NMR ($CDCl_3$) characteristic resonances at 22.5 (q, O_2CCH_3), 26.6 (t, C-7), 30.8 and 31.0 (d, C-8), 46.1 and 46.6 (t, C-3), 46.8 and 47.0 (d, C-1), 69.2 and 64.6 ($O-CH_2CH_2-O$), 74.6 and 74.7 (t, CH_2CCl_3), 95.9 (s, CCl_3), 109.7 (s, O–C–O), 130.5, 131.0, 133.3, and 133.8 (d, C-5 and C-6), 152.3 and 152.9 (NCO_2) ppm; mass spectrum, *m/e* (relative intensity) 369 (P, 1), 259 (3), 257 (10), 255 (10), 87 (100), 43 (72); high-resolution mass spectrum on P − 114, *m/e* 254.96252 ($C_8H_8NO_2Cl_3$ requires 254.96205).

***endo*- and *exo*-7-(1,1-Ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (18).** To a suspension of 22.8 g (349 mg-atom) of activated zinc in 150 mL of anhydrous methanol was added 6.0 g (16.3 mmol) of 2-(trichloroethoxycarbonyl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**16**). The resulting mixture was then refluxed under an Ar atmosphere for 1 h, cooled to 25 °C, and filtered through Celite. The filtrate was diluted with chloroform to give approximately a 3:7 methanol–chloroform mixture and perculated through an alumina (Alcoa F-20) column followed by washing with three bed volumes of 3:7 methanol–chloroform. The combined eluant was concentrated in vacuo, yielding 3.1 g (98%) of an oil containing an epimeric mixture of the deblocked isoquinuclidine **18**. This material was further purified by alumina column chromatography (Alcoa F-20) (1:1 ether–hexane followed by 3:7 methanol–chloroform). Concentration of the methanol–chloroform fraction in vacuo gave 1.5 g (47%) of pure **18**: IR ($HCCl_3$) 3010, 2960, 2925, 2850, 1375, 1150 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.08 and 1.34 (s, 3 H, O_2CCH_3), 1.00–1.52 (m, 2 H, H-8), 1.78 (m, 2 H, H-7 and H-3 endo), 2.24–2.98 (m, 4 H, H-3 exo, −4 and –NH), 3.56 and 3.78 (m, 1 H, H-1), 3.88 and 3.95 (m, 4 H, $-OCH_2CH_2O-$), 6.32 (m, 2 H, H-5 and -6); ^{13}C NMR ($DCCl_3$) 22.2 and 22.7 (q, O_2CCH_3), 24.9 and 28.9 (t, C-8), 30.4 and 30.9 (d, C-7), 44.3 and 46.1 (t, C-3), 46.6 and 47.1 (d, C-1), 63.8, 64.3, 64.6, and 65.3 (t, $-OCH_2CH_2O-$), 110.7 and 111.5 (s, –OCO–), 131.6, 133.2, 134.2, and 135.2 (d, C-5 and -6) ppm; mass spectrum *m/e* (relative intensity) 195 (P, 9), 108 (3), 87 (32), 81 (100), 80 (95); high-resolution mass spectrum, *m/e* 195.12615 ($C_{11}H_{12}NO_2$ requires 195.12592).

2-(Cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (20). To a solution of 360 mg (1.85 mmol) of *endo*- and *exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**18**) in 15 mL of anhydrous THF containing 374 mg (2.71 mmol) of suspended K_2CO_3 under an Ar atmosphere was added 360 mg (2.77 mmol) of 3-chlorocyclohex-2-en-1-one.[15] The resulting solution was stirred at 25 °C for 3 days and then filtered. The filtrate was concentrated in vacuo, giving a residue which was purified by preparative TLC on silica gel (1:19 methanol–ether) to yield 320 mg (60%) of an oil that was characterized as an epimeric mixture of cyclohexenonylisoquinuclidenes **20**: IR ($HCCl_3$) 3020, 2980, 2925, 1590, 1540, 1435, 1200 cm^{-1}; UV (EtOH) max 304 nm (ϵ 14 009); ^1H NMR ($DCCl_3$) δ 1.12 and 1.20 (s, 3 H, O_2CCH_3), 1.20–3.20 (m, 11 H, H-3, -7, -8, and cyclohexenonyl methylenes), 3.92 (m, 4 H, $-OCH_2CH_2O-$), 4.68 (m, 1 H, H-1), 5.00 (m, 1 H, –COCH=), 6.38

(m, 2 H, H-5 and -6); ^{13}C NMR ($DCCl_3$) characteristic resonances at 21.7 and 22.1 (q, O_2CCH_3), 30.7 and 31.3 (d, C-4), 64.0 and 64.5 (t, $-OCH_2CH_2O-$), 97.3 and 97.5 (d, -COCH=), 109.6 and 110.0 (s, -OCO-), 130.0, 132.8, and 134.3 (d, C-5 and C-6), 161.9 and 162.9 (s, -NC=CHCO-), 195.7 and 195.9 (s, -COCH=) ppm; mass spectrum, *m/e* (relative intensity) 289 (P, 17), 246 (14), 195 (9), 174 (40), 87 (55), 81 (100); high-resolution mass spectrum, *m/e* 289.16684 ($C_{17}H_{23}NO_3$ requires 289.16778).

$\Delta^{4a,10b}\Delta^{8}$-8-(1,1-Ethylenedioxyeth-1-yl)-1-oxodecahydrophenanthridine (21). A solution of 412 mg (1.43 mmol) of 2-(cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**20**) in 50 mL of benzene was saturated with anhydrous (passed first through concentrated H_2SO_4) HCl and refluxed for 3.5 days. The reaction mixture was cooled to 25 °C, added dropwise to 40 mL of a stirred, ice-cooled solution of saturated $NaHCO_3$, and extracted with $HCCl_3$. The chloroform layer was washed with saturated $NaHCO_3$, dried, and concentrated in vacuo, giving a dark red oil that was purified by preparative TLC on silica gel (9:1 ether–methanol) to yield from a band at R_f 0.39 a yellow oil which crystallized on standing, mp 201–204 °C (137 mg, 33%), characterized as the phenanthridine ketal **21:** IR ($HCCl_3$) 3401, 3279, 2959, 2915, 2865, 2817, 1575, 1513, 1398, 1377, 1266, 1241, 1181, 1041 cm^{-1}; UV (EtOH) max 301 nm (ϵ 26 100); ^1H NMR ($DCCl_3$) δ 1.42 (s, 3 H, O_2CCH_3), 1.52–2.13 (m, 5 H, H-3, -10, and -6a), 2.13–2.62 (m, 6 H, H-2, -4, and -7), 2.80–3.22 (m, 3 H, H-2 and -10a), 3.66–4.04 (m, 4 H, $-OCH_2CH_2O-$), 5.72 (m, 1 H, H-9), 6.62 (s, 1 H, -NH); ^{13}C NMR ($DCCl_3$) 21.9 (t, C-3), 23.8 (q, O_2CCH_3), 26.3 (d, C-6a), 6.3 (t, C-10), 27.7 (t, C-7), 28.8 (d, C-10a), 28.9 (t, C-4), 36.4 (t, C-2), 42.2 (t, C-6), 64.0 (t, $-OCH_2CH_2O-$), 64.2 (t, $-OCH_2CH_2O-$), 109.1 (s, -OCO-), 109.4 (s, C-10b), 119.7 (d, C-9), 134.2 (s, C-8), 159.5 (s, C-4a), 192.9 (s, C-1) ppm; mass spectrum, *m/e* (relative intensity) 289 (P, 16), 244 (49), 149 (43), 148 (100), 87 (39), 43 (48); high-resolution mass spectrum *m/e* 289.16799 ($C_{17}H_{23}NO_3$ requires 289.16778).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.69; H, 8.17; N, 4.75.

2-(Cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (22). A solution of 55 mg (0.190 mmol) of 2-(cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**20**) and 33 mg (0.74 mmol) of *p*-toluenesulfonic acid in 2.5 mL of 4:1 THF–H_2O was stirred at 25 °C under an Ar atmosphere for 10 days. The reaction mixture was poured into 10 mL of saturated $NaHCO_3$ and extracted with chloroform. The combined chloroform extracts were dried and concentrated in vacuo yielding 36 mg of an oil which was purified by preparative TLC on silica gel (19:1 ether–methanol). A yellow oil (15.9 mg, 34%) obtained from a band at R_f 0.12 was characterized as the deblocked isoquinuclidene **22:** ^1H NMR ($DCCl_3$) δ 1.54–2.72 (m, 8 H, H-8 and cyclohexenonyl methylenes), 2.10 and 2.20 (s, 3H, $COCH_3$), 2.72–3.28 (m, 4 H, H-7, -4 and, -3), 4.85 (m, 1 H, H-1), 5.07 (m, 1 H, -NC=CHCO), 6.20–6.73 (m, 2 H, H-5 and -6); mass spectrum, *m/e* (relative intensity) 245 (P, 22), 175 (67), 174 (100), 80 (15), 79 (12), 43 (17), 41 (12), 39 (13); high resolution mass spectrum, *m/e* 245.14088 ($C_{15}H_{19}NO_2$ requires 245.14157).

$\Delta^{4a,10b}\Delta^{8}$-8-Acetyl-1-oxodecahydrophenanthridine (23). A solution of 290 mg (0.997 mmol) of 2-(cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-(1,1-ethylenedioxyeth-1-yl)-2-azabicyclo[2.2.2]oct-5-ene (**20**), 0.5 mL of H_2O, and 191 mg (1.0 mmol) of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed for 8 h under an Ar atmosphere. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. This gave an oil which was subjected to preparative TLC on silica gel (1:9 methanol–ether), yielding 125 mg (51%) of a white powder characterized as the 8-acetylphenanthridine **23:** mp 200–205 °C dec (C_6H_6); IR ($HCCl_3$) 3400, 2980, 2925, 2900, 1660, 1640, 1575, 1515 cm^{-1}; UV (EtOH) max 231 nm (ϵ 13 048), 298 (25 372); ^1H NMR ($DCCl_3$) δ 2.27 (s, 3 H, $-COCH_3$), 1.7–3.2 (m, 14 H, H-3, -4, -6a, -7, -10, and -10a), 6.34 (m, 1 H, NH), 6.77 (m, 1 H, H-9); ^{13}C NMR ($DCCl_3$) 21.9 (t, C-3), 25.2 (q, $COCH_3$), 25.5 (t, C-7), 26.0 (d, C-6a), 28.4 (d, C-10a), 29.2 (t, C-7 and C-10), 36.5 (t, C-4), 42.4 (t, C-6), 109.2 (s, C-10b), 136.6 (s, C-8), 138.6 (d, C-8), 158.7 (s, C-4a), 193.3 (s, C-1), 199.1 (s, $COCH_3$) ppm; mass spectrum *m/e* (relative intensity) 245 (P, 69), 202 (14), 149 (66), 148 (100), 43 (10); high-resolution mass spectrum, *m/e* 245.14113 ($C_{15}H_{19}NO_2$ requires 245.14157).

Conversion of $\Delta^{4a,10b}\Delta^{8}$-8-(1,1-Ethylenedioxyeth-1-yl)-1-oxodecahydrophenanthridine (21) to $\Delta^{4a,10b}\Delta^{8}$-8-Acetyl-1-oxodecahydrophenanthridine (23). A solution of 107 mg (0.346 mmol) of the phenanthridine ketal **21** and 66.8 mg (0.351 mmol) of *p*-toluenesulfonic acid in 16 mL of 15:1 THF–H_2O was stirred at 25 °C under an Ar atmosphere for 17 h. The reaction mixture was poured into 25 mL of saturated $NaHCO_3$ and extracted with $HCCl_3$. The chloroform layer was washed with saturated $NaHCO_3$, dried, and concentrated in vacuo to yield 83 mg (98%) of the acetylphenanthridine **23.**

Conversion of 2-(Cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (22) to $\Delta^{4a,10b}\Delta^{8}$-8-Acetyl-1-oxodecahydrophenanthridine (23). A solution of 14.4 mg (0.059 mmol) of 2-(cyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (**22**) and 9.7 mg (0.051 mmol) of *p*-toluenesulfinic acid in 4 mL of anhydrous benzene was refluxed under an Ar atmosphere for 13.5 h. The reaction was cooled to 25 °C, diluted with chloroform, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo to yield 11.3 mg (79%) of pure acetylphenanthridine **23.**

2-(5,5-Dimethylcyclohex-2-en-1-on-3-yl)-2-azabicyclo[2.2.2]-oct-5-ene (24). To a solution of 493 mg (4.52 mmol) of 2-azabicyclo[2.2.2]oct-5-ene (**17**) in 5 mL of anhydrous benzene containing 969 mg (7.01 mmol) of suspended K_2CO_3 was added 841 mg (5.32 mmol) of 5,5-dimethyl-3-chlorocyclohex-2-en-1-one.[17] The resulting mixture was refluxed for 19.5 h under an Ar atmosphere, cooled to 25 °C, and filtered to remove insoluble salts. The filtrate was concentrated in vacuo, giving an oil which was purified by preparative TLC on silica gel (ether). A yellow crystalline material (465 mg, 45%) obtained from a band at R_f 0.10 was characterized as the dimedonylisoquinuclidene **24:** mp 146–148 °C; IR ($HCCl_3$) 2933, 2857, 1590, 1536, 1439, 1393, 1374, 1289, 1256, 1154, 1006 cm^{-1}; UV (EtOH) max 306 nm (ϵ 36 400); ^1H NMR ($DCCl_3$) δ 1.06 (s, 6 H, *gem*-dimethyl), 1.36–2.06 (m, 4 H, H-7 and -8), 2.12 (s, 2 H, $=CHCOCH_2-$), 2.32 (s, 2 H, $-CO-CH=CCH_2$), 2.85 (m, 1 H, H-4), 2.89 (m, 1 H, H-3 endo), 3.15 (m, 1 H, H-3 exo), 4.56 (m, 1 H, H-1), 5.01 (s, 1 H, COCH=), 6.44 (m, 2 H, H-5 and -6); ^{13}C NMR ($DCCl_3$) 21.8 (t, C-8), 28.5 (t, C-7), 29.2 (q, $-C(CH_3)_2-$), 30.7 (d, C-4), 32.5 (s, $C(CH_3)_2$), 40.7 (t, C-3), 47.4 (d, C-1), 49.5 (t, $=CHCOCH_2-$), 50.8 (t, $-COCH=CCH_2-$), 96.3 (d, -COCH=), 131.2 (d, C-5 or -6), 134.9 (d, C-5 or -6), 161.1 (s, -NC=CHCO-), 195.6 (s, -COCH=) ppm; mass spectrum, *m/e* (relative intensity) 231 (P, 8), 203 (67), 202 (100), 152 (14), 80 (33), 79 (25), 77 (18), 67 (24), 41 (18), 39 (19); high-resolution mass spectrum, *m/e* 231.16161 ($C_{15}H_{21}NO$ requires 231.16231).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.60; H, 9.29; N, 5.90.

$\Delta^{4a,10b}\Delta^{9}$-3,3-Dimethyl-1-oxodecahydrophenanthridine (25). A solution of 93 mg (0.40 mmol) of 2-(5,5-dimethylcyclohex-2-en-1-on-3-yl)-2-azabicyclo[2.2.2]oct-5-ene (**24**) and 76.9 mg (0.40 mmol) of *p*-toluenesulfonic acid in 10 mL of toluene was refluxed for 7 days under an Ar atmosphere. The reaction mixture was cooled to 25 °C, poured into saturated $NaHCO_3$, and extracted with chloroform. The chloroform extracts were washed with saturated $NaHCO_3$, dried, and concentrated in vacuo to yield 81.9 mg of material which was purified by preparative TLC on silica gel (9:1 ether–methanol). A white crystalline material (45 mg, 48%) was obtained from a band at R_f 0.60 which was characterized as the phenanthridine **25:** mp 210–213 °C; IR ($HCCl_3$) 3401, 3268, 2959, 2933, 2899, 1580, 1513, 1389, 1259 cm^{-1}; UV (EtOH) max 302 nm (ϵ 22 300); ^1H NMR ($DCCl_3$) δ 1.02 (s, 6 H, *gem*-dimethyl), 1.56–2.14 (m, 5 H, H-6a, -7, and -8), 2.24 (s, 2 H, H-4), 3.07 (dd, 1 H, J = 12 and 3 Hz, H-6α), 3.26 (t, 1 H, J = 12 Hz, H-6β), 3.44 (m, 1 H, H-10a), 5.46 (dt, 1 H, J = 10 and 3 Hz, H-9), 5.64 (d, 1 H, J = 10 Hz, H-10), 6.59 (s, 1 H, NH); ^{13}C NMR ($DCCl_3$) 20.9 (t, C-7), 24.7 (t, C-8), 28.1 (q, *gem*-dimethyl), 28.5 (q, $C(CH_3)_2$), 29.3 (d, C-6a), 30.6 (d, C-10a), 32.3 (s, C-3), 41.4 (t, C-2), 42.8 (t, C-4), 50.6 (t, C-6), 105.8 (s, C-10b), 128.8 (d, C-10), 130.9 (d, C-9), 158.8 (s, C-4a), 192.9 (s, C-1) ppm; mass spectrum, *m/e* (relative intensity) 231 (P, 100), 230 (29), 216 (12), 202 (22), 147 (43), 91 (12), 77 (14), 41 (16), 39 (18); high-resolution mass spectrum, *m/e* 231.16346 ($C_{15}H_{21}NO$ requires 231.16231).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.68; H, 9.25; N, 5.99.

3,3-Dimethyl-8-acetyl-1,6-dioxohexahydrophenanthridine (27). A solution of 298 mg (1.01 mmol) of 2-(5,5-dimethylcyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-en-3-one (**26**)[10] and 200 mg (1.06 mmol) of *p*-toluenesulfonic acid in 15 mL of anhydrous benzene was heated at 60 °C for 24 h, cooled to 25 °C, poured into saturated $NaHCO_3$, and separated. The aqueous phase was acidified to pH 3 with concentrated HCl and extracted with chloroform. The chloroform extracts were dried and concentrated in vacuo giving a yellow oil which was crystallized from methanol. This yielded 30.5 mg (10.4%, mp 232 °C dec) of a white crystalline material which was characterized as the phenanthridine **27:** IR (KBr) 3450, br 3370–2090, 2920, 1680, 1150, 1390, 1370, 1280, 1200 cm^{-1}; UV (EtOH) max 258 nm (ϵ 49 400); ^1H NMR (Me_2SO-d_6) 0.69 (s, 6 H, *gem*-dimethyl), 2.29 (s, 2 H, $-CH_2COC=$), 2.63 (s, 3 H, $-COCH_3$), 2.77 (s, 2 H, $-COC=CCH_2-$), 7.57 (d, 1 H, J = 9 Hz, H-10), 7.87 (dd, 1 H,

J = 9 and 2 Hz, H-9), 8.47 (d, 1 H, J = 2 Hz, H-7); ^{13}C NMR (Me_2SO-d_6) 15.4 (q, $COCH_3$), 27.7 (q, $C(CH_3)_2$), 31.6 (s, $C(CH_3)_2$), 47.6 (t, C-2), 53.8 (t, C-4), 124.2 (s, C-10b), 126.1 (s, C-6a), 128.0 (d, C-10), 128.3 (s, C-8), 129.0 (d, C-9), 130.4 (d, C-7), 149.2 (s, C-10a), 149.6 (s, C-4a), 163.1 (s, C-6), 166.7 (s, $COCH_3$), 199.6 (s, C-1) ppm; mass spectrum, m/e (relative intensity) 283 (P, 100), 268 (22), 255 (39), 228 (41), 227 (83), 154 (19); high-resolution mass spectrum, m/e 283.12208 ($C_{17}H_{17}NO_3$ requires 283.12082).

***N*-(5,5-Dimethylcyclohex-2-en-1-on-3-yl)-3-acetylbenzamide (28).** A solution of 515 mg (1.79 mmol) of 2-(5,5-dimethylcyclohex-2-en-1-on-3-yl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-en-3-one (**26**)[10] and 359 mg (1.89 mmol) of *p*-toluenesulfonic acid in 35 mL of anhydrous benzene was refluxed under an Ar atmosphere for 24 h, cooled to 25 °C, and poured into saturated $NaHCO_3$. This material was extracted with chloroform, and the chloroform extracts were washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. This yielded 380 mg of a red oil which was purified by preparative TLC on silica gel (19:1 ether–methanol), giving a yellow oil (65 mg, 13%) from a band at R_f 0.57 which was characterized as the benzamide **28:** IR ($HCCl_3$) 3401, 3279, 2985, 2941, 1684, 1637, 1610, 1497, 1374, 1284, 1222 cm^{-1}; UV (EtOH) max 222 nm (ϵ 19 900), 291 (18 800); ^1H NMR ($DCCl_3$) δ 1.07 (s, 6 H, *gem*-dimethyl), 2.17 (s, 2 H, $-CH_2COCH=$), 2.59 (s, 3 H, $-COCH_3$), 2.61 (s, 2 H, $-CO-CH=CCH_2-$), 6.87 (s, 1 H, $-COCH=$), 7.53 (t, 1 H, Ar H-5), 8.08 (d, 2 H, Ar H-4 and H-6), 8.42 (s, 1 H, Ar H-2), 9.42 (s, 1 H, NH); ^{13}C NMR ($DCCl_3$) 26.9 (q, $-COCH_3$), 28.4 (q, $C(CH_3)_2$), 33.1 (s, $C(CH_3)_2$), 42.4 (t, $-CH_2COCH=$), 50.7 (t, $-COCH=CCH_2-$), 111.8 (d, $-COCH=$), 127.3 (d, Ar C-5), 129.3 (d, Ar C-2), 132.1 (d, Ar C-6), 132.5 (d, Ar C-4), 134.7 (s, Ar C-1), 137.3 (s, Ar C-3), 154.7 (s, $-NC=CHCO-$), 166.0 (s, $-CONH-$), 197.5 (s, $=CHCO-$), 200.9 (s, $-COCH_3$) ppm; mass spectrum, m/e (relative intensity) 285 (P, 8), 284 (8), 201 (12), 148 (9), 147 (100), 91 (10), 77 (6), 76 (7), 43 (11); high-resolution mass spectrum, m/e 285.13560 ($C_{17}H_{19}NO_3$ requires 285.13648).

***O*-Ethyl *N*-(3-Acetyl-1,2-dihydrobenzyl)carbamate (30).** A solution of 1.02 g (4.6 mmol) of 2-(ethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (**4**) and 75 mg (0.39 mmol) of *p*-toluenesulfonic acid in 50 mL of anhydrous benzene was refluxed under an Ar atmosphere for 20 h. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. This gave a brown oil which was purified by preparative TLC on silica gel (1:1 ether–hexane), yielding a clear oil (0.93 g, 91%) characterized as the cyclohexadiene derivative **30:** IR (CCl_4) 3440, 3025, 2970, 2945, 1730, 1665, 1510, 1250 cm^{-1}; UV (CH_3CN) max 299 nm (ϵ 9465); ^1H NMR ($DCCl_3$) δ 1.22 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.32 (s, 3 H, $COCH_3$), 2.06–2.80 (m, 3 H, H-1 and -2), 3.06 (dd, 1 H, J = 13.5 and 6 Hz, $-NCH-H$), 3.31 (dd, 1 H, J = 13.5 and 6 Hz, $-NCH-H$), 4.12 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.31 (m, 1 H, $-NH-$), 6.16 (m, 2 H, H-5 and -6), 6.89 (m, 1 H, H-4); ^{13}C NMR ($DCCl_3$) 14.6 (q, $-OCH_2CH_3$), 23.4 (t, C-2), 25.1 (q, $COCH_3$), 34.5 (d, C-1), 43.6 (t, $-NCH_2-$), 60.7 (t, $-OCH_2CH_3$), 124.7 (d, C-5), 133.4 (d, C-6), 135.3 (s, C-1), 136.4 (d, C-4), 156.9 (s, $-NHCO-$), 198.3 (s, $-COCH_3$) ppm; mass spectrum, m/e (relative intensity) 223 (P, 9), 178 (10), 134 (21), 122 (100); high-resolution mass spectrum, m/e 223.12114 ($C_{12}H_{17}NO_3$ requires 223.12084).

***O*-(2,2,2-Trichloroethyl) *N*-(3-Acetyl-1,2-dihydrobenzyl)-carbamate (31).** A solution of 375 mg (1.15 mmol) of 2-(trichloroethoxycarbonyl)-*endo*- and -*exo*-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene (**15**) and 15 mg (0.079 mmol) of *p*-toluenesulfonic acid in 50 mL of anhydrous benzene was refluxed for 15 h under an Ar atmosphere. The reaction mixture was cooled to 25 °C, washed with saturated $NaHCO_3$, dried, and concentrated in vacuo. The residue obtained was purified by preparative TLC on silica gel (3:7 ether–hexane), yielding 345 mg (92%) of a clear oil which was characterized as the cyclohexadiene derivative **31:** IR (CCl_4) 3420, 3010, 2925, 2900, 2850, 1740, 1660, 1510, 1245 cm^{-1}; UV (CH_3CN) max 298 nm (ϵ 8607); ^1H NMR ($DCCl_3$) δ 2.33 (s, 3 H, $COCH_3$), 2.64 (m, 3 H, H-1 and -2), 3.28 (m, 2 H, $-NHCH_2-$), 4.73 (s, 2 H, $-OCH_2-$), 5.80 (m, 1 H, $-NH-$), 6.18 (m, 2 H, H-5 and -6), 6.91 (m, 1 H, H-4); ^{13}C NMR ($DCCl_3$) 23.5 (t, C-2), 25.1 (q, $-COCH_3$), 34.4 (d, C-1), 44.1 (t, $-NCH_2-$), 74.6 (t, $-OCH_2-$), 95.7 (s, $-CCl_3$), 125.1 (d, C-5), 128.0 (s, C-3), 133.2 (d, C-6), 135.7 (d, C-4), 154.8 (s, $-NHCO-$), 198.2 (s, $COCH_3$) ppm; mass spectrum, m/e (relative intensity) 325 (2), 178 (17), 134 (14), 122 (100); high-resolution mass spectrum, m/e 325.00304 ($C_{12}H_{14}NO_3Cl_3$ requires 325.00392).

Attempted Reactions of the Isomeric *N*-Methylisoquinuclidenes 6 with Other β-Chloro Enones 8 and 9. To 107 mg (0.5 mmol) of the *endo*-methylisoquinuclidene **6en** in 10 mL of benzene was added 130 mg of 3-chlorocyclohex-2-en-1-one.[15] The resulting solution was stirred at reflux under Ar for 5 days and concentrated in vacuo, giving an oil shown by ^1H NMR analysis to be a mixture of starting chloro enone and isoquinuclidene. Similar attempted reactions conducted in dimethoxyethane and neat failed to lead to detectable quantities of the desired hydroisoquinoline product. In a similar fashion, 109 mg (0.5 mmol) of the *endo*-methylisoquinuclidene **6en** and 98 mg (0.8 mmol) of 4-chloropent-3-en-2-one[14] in 10 mL of carbon tetrachloride were refluxed under Ar for 15 h. The white crystalline material obtained was isolated and shown by ^1H NMR analysis to be the hydrochloride salt of the isoquinuclidene **6en:** ^1H NMR ($CDCl_3$) δ 6.56 and 6.17 (m, 2 H, H-5 and -6), 2.76 and 2.63 (s, 3 H, NCH_3) (sets of resonances resulting from endo, exo isomer at quaternary amine center which is chiral). This structural assignment was confirmed by quantitative reconversion of the salts to **6en** by treatment with 10% aqueous KOH.

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Registry No.—**2,** 3693-61-6; **3,** 57956-33-9; **4en,** 66531-14-4; **4ex,** 66574-55-8; **5en,** 67938-79-8; **5ex,** 67999-54-6; **6en,** 67938-80-1; **6ex,** 67999-08-0; **12,** 67938-81-2; **13α,** 66531-17-7; **13β,** 66531-18-8; **14,** 66531-21-3; **15en,** 66531-23-5; **15ex,** 66574-57-0; **16en,** 67938-82-3; **16ex,** 67999-09-1; **18en,** 67938-83-4; **18ex,** 67999-10-4; **20en,** 67999-11-5; **20ex,** 67999-12-6; **21,** 67938-84-5; **22en,** 67938-85-6; **22ex,** 67999-13-7; **23,** 67938-86-7; **24,** 67938-87-8; **25,** 67938-88-9; **26en,** 67938-93-6; **26ex,** 67999-14-8; **27,** 67938-89-0; **28,** 67938-90-3; **30,** 67938-91-4; **31,** 67938-92-5; 1-chlorobut-1-en-3-one, 7119-27-9; 5,5-dimethyl-3-chlorocyclohex-2-en-1-one, 17530-69-7; methyl vinyl ketone, 78-94-4; ethylene glycol, 107-21-1.

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(27) (a) This material was contaminated with small amounts of the 8-acetyl regioisomer. (b) The extra ^{13}C NMR resonances are due to the 8-acetyl isomer.

Structural Effects in Solvolytic Reactions. 30. Solvolysis of 2-(5′-Coumaranyl)-2-norbornyl *p*-Nitrobenzoates. Evidence for the Unimportance of σ Participation as a Factor in the High Exo/Endo Rate and Product Ratios Realized in the Solvolysis of Exceptionally Highly Stabilized Tertiary 2-Norbornyl Derivatives

Herbert C. Brown* and C. Gundu Rao[1]

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

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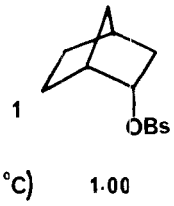
The 5-coumaranyl group, σ^+ −0.984, possesses electron-releasing properties considerably greater than those of *p*-anisyl, σ^+ −0.778. The solvolyses of *exo*- and *endo*-2-(5′-coumaranyl)-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone reveal a high exo/endo rate ratio of 240. The solvolysis of 2-(5′-coumaranyl)-*endo*-norbornyl *p*-nitrobenzoate in the presence of sodium acetate affords the exo-substituted alcohol in amounts greater than 99%. These highly stabilized norbornyl derivatives show high exo/endo rate ratios and high exo/endo product ratios, at one time considered essential criteria required for σ participation with formation of a σ-bridged intermediate. But σ participation cannot be a factor in the solvolysis of such highly stabilized tertiary norbornyl derivatives. These results must be accounted for alternatively in terms of steric effects.

The high exo/endo rate ratio and predominant exo substitution observed in the acetolysis of *exo*- (**2**) and *endo*-norbornyl (**1**) brosylates led to the postulation of σ participation



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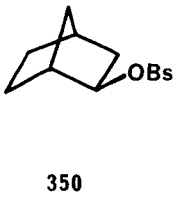


2

RR(25°C) 1.00 350

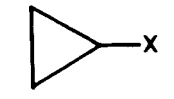
3

of the 1,6 bonding pair in the exo isomer **3** facilitating ionization.[2,3] It is a generally accepted postulate that the importance of neighboring group participation should diminish as the incipient carbonium ion center is stabilized by substitution.[4,5]

However, solvolysis of 2-aryl-2-norbornyl derivatives containing the substituents *p*-OCH_3, *p*-H, *p*-CF_3, and *m,m′*-$(CF_3)_2$ on the aromatic ring revealed essentially constant exo/endo ratios of 284, 127, 187, and 176, respectively. It is noteworthy that even the *p*-anisyl derivatives exhibit a high exo/endo rate ratio.[6,7]

In a previous paper we established the σ^+ constant for the 5-coumaranyl substituent.[8] It possesses a high negative value of −0.984, considerably more negative than that for *p*-anisyl, σ^+ −0.778. We also established that the 5-coumaranyl substituent (**5**) is capable of completely nullifying the rate enhancement of approximately 10^{12} observed in the solvolysis of secondary cyclopropyl derivatives[9] (**4**).

We decided to investigate whether the 5-coumaranyl substituent was also capable of completely nullifying the oft



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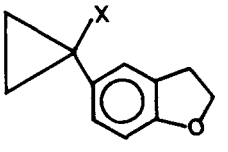

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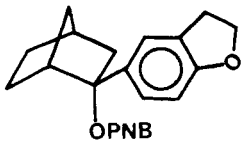
postulated σ participation in norbornyl derivatives. If the 5-coumaranyl group can cause the truly enormous π–σ participation (×10^{12}) observed in cyclopropyl derivatives to vanish, it should surely cause the much smaller σ participation (×350) proposed for *exo*-norbornyl to vanish.

Results

Synthesis. Addition of 5-coumaranyllithium to 2-norbornanone yielded 2-(5′-coumaranyl)-*endo*-norbornanol. Treatment with hydrogen chloride gave the exo chloride. Hydrolysis then yielded the 2-(5′-coumaranyl)-*exo*-norbornanol. The endo alcohol was converted into the *p*-nitrobenzoate by treating with *n*-butyllithium, followed by *p*-nitrobenzoyl chloride. The *exo*-*p*-nitrobenzoate was too unstable to be isolated, and hence the benzoate was synthesized for solvolytic studies.

Rate Studies. The rates of solvolysis of 2-(5′-coumaranyl)-2-norbornyl derivatives were measured in 80% aqueous acetone. The rate constant for the solvolysis of 2-(5′-coumaranyl)-*exo*-norbornyl *p*-nitrobenzoate (**7**) was determined



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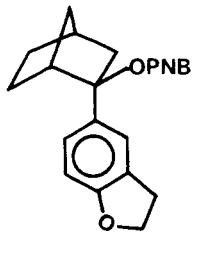

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RR(25°C) 1.00 240

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