Syntheses of Isosophoramine and Lycopodinoid Hydrojulolidines

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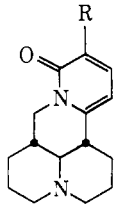
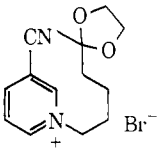
Abstract: A seven-step, stereoselective, total synthesis of *dl*-isosophoramine from nicotinonitrile is presented. It is based on the general scheme of alkaloid synthesis involving initially partial hydrogenation of 1-alkyl-3-acylpyridinium or related salts and acid-catalyzed cyclization of the resultant 2-piperideines and incorporates stereochemically diagnosed 1-cyano-9-acetylquinolizidine ketals and 8-methyl-9-aza-7a,10,10a,10b-tetrahydrojulolidine as crucial intermediates. The synthesis of three isomeric 10b-carbomethoxy-7a,8,10a,10b-tetrahydro-8-julolidones from dimethyl quinolinate is described. The construction of these crucial intermediates on route to the *Lycopodium* bases follows the general scheme of alkaloid synthesis. Carbon-13 nmr spectroscopy has been used for the determination of the structure of a tetrahydropyridine dimer and the stereochemistry of complex, heavily substituted quinolizidines and hydrojulolidines. This constitutes an early example of the application of cmr spectra to the routine analysis of structurally complicated intermediates in organochemical synthesis.

The general scheme of alkaloid synthesis based on the two-step reaction sequence of partial hydrogenation of *N*-alkyl salts of β-acylpyridines and acid-catalyzed cyclization of the resultant 1-alkyl-3-acyl-2-piperideines[2] has been expanded recently on discovery of the permissibility of replacing the β-acylpyridine by nicotinonitrile as starting material.[3] This change led to the synthesis of *rac*-lamprolobine[4] and opened the way for potentially facile syntheses of quinolizidine-based, dinitrogenous alkaloids. The following stereoselective synthesis of the matrine base isosophoramine (**1a**) represents a vivid example of the power of the expanded scheme of synthesis.

Alkylation of nicotinonitrile with 6-bromo-2-hexanone ethylene ketal yielded a salt (**2**) whose palladium-



1a, R = H
b, R = CO_2Et



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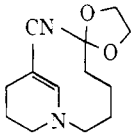
catalyzed hydrogenation produced piperideine **3**.[5] Acid-induced cyclization of the latter led to the quinolizidine system in form of three stereoisomers (**4a**, **4b**, and **4c**).



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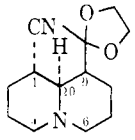
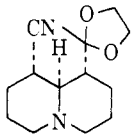
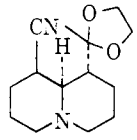


4a



4b

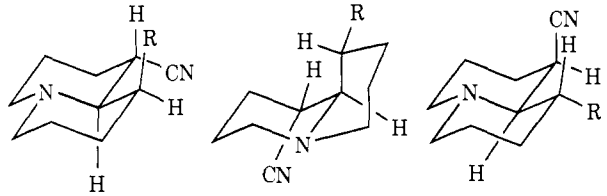


4c

The cyclization produced the isomers in 1:56:10 ratio, respectively, in chloroform solution at room temperature, while in 9:10:6 ratio in refluxing benzene.

Acid-catalyzed isomerization of either isomer **4a** or **4b** in refluxing benzene yielded a 1:1 mixture of the two substances, while similar treatment of **4c** left this isomer unchanged. Since these experiments indicate in light of the above product ratios that isomerization had occurred without the involvement of **3** and hence must have taken place by way of a ketal–enol ether equilibration route, quinolizidines **4a** and **4b** must be C(9) epimers. Base-induced isomerization of **4a** led to a greater than 90% recovery of starting material. But **4b** was converted into **4c** in this manner. These results indicate **4b** and **4c** to be C(1) epimers. The 220-MHz proton magnetic resonance spectra of the three isomers aided in the assignment of their stereochemistry. Both chemical shifts and coupling characteristics of the C(1) methines indicate **4a** to be different from the other isomers. Hydrogen 1 in the former [δ 3.03 (td, J = 12, 4 Hz)] is axially oriented, while the same hydrogen in **4b** [δ 3.48 (narrow m)] and **4c** [δ 3.57 (narrow m)] possesses equatorial conformation. Hydrogen 10 is not easily recognizable in the spectra of **4a** and **4c**, but appears at 3.10 ppm (dd, J = 10, 4 Hz), a low-field position indicative of a *cis*-quinolizidine fusion and coupling constants representative of a cis,trans or trans,-cis C(1)–C(10)–C(9) hydrogen arrangement. These facts determine the stereochemistry of **4b** as depicted in the formula and indicate **5b** as the conformation of this isomer. The pmr and chemical interconversion results, as a consequence, establish the stereostructures for **4a** and **4c** as depicted in their formulas. The appearance of 2.85 and 2.88 ppm signals, respectively characteristic of equatorial hydrogens at C(4) and C(6) in *trans*-quinolizidines,[6] show **4a** and **4c** to possess conformations **5a** and **5c**, respectively. Finally, the chemical shifts of the methyl group of the three isomers (**4a**, 1.57 ppm; **4b**, 1.26; **4c**, 1.25) show a distinctly different environment for the ketal side chain of **4a**. While the methyl function in the latter is strongly deshielded by

(1) (a) U. S. Public Health Service Predoctoral Fellow, 1966–1969; (b) U. S. Public Health Service Predoctoral Fellow, 1969–1972.
(2) E. Wenkert, *Accounts Chem. Res.*, 1, 78 (1968).
(3) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).
(4) E. Wenkert and A. R. Jeffcoat, *ibid.*, **35**, 515 (1970).
(5) In contrast to previous experience[3] the hydrogenation yields also a minor product, a dimer of **3** (see Experimental Section), whose cmr analysis (*vide infra*) proves the bond holding the two monomer units together to be at C(4). The hydrogenation of nicotinonitrile methobromide also yields a dimer, mp 144–145°, as minor by-product.
(6) F. Bohlmann, D. Schumann, and H. Schulz, *Tetrahedron Lett.*, 173 (1965).

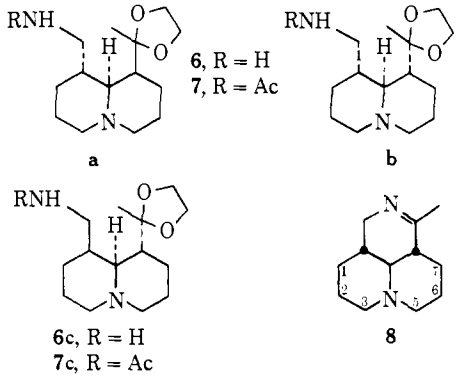


5a 5b 5c

R = $CMe(OCH_2)_2$

the nuclear nitrogen or the nitrile unit, the methyl group of **4b** and **4c** possesses a normal chemical shift (*cf.* 1.23 ppm for **2** and **3**). The ^{13}C nmr chemical shifts of the isomers (*vide infra*) confirm strongly their conformations.

Each of the isomeric aminonitriles was treated with lithium aluminum hydride and the reduction products (**6a**, **6b**, and **6c**) were characterized as their crystalline acetamides (**7a**, **7b**, and **7c**, respectively). In view of amide **7a** revealing an anomalously low-field pmr signal (1.61 ppm) for its ketal methyl group deshielding by the nuclear nitrogen must affect the methyl functions of both **4a** and **7a**. Acid hydrolysis of diamine **6a** or **6b** yielded tricyclic imine **8** whose all-trans stereochem-



6, R = H
7, R = Ac

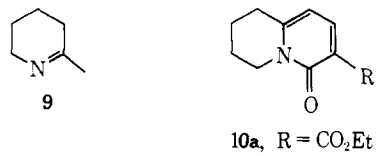
a b

6c, R = H
7c, R = Ac

8

istry was determined by the ^1H and ^{13}C nmr analyses (*vide infra*) revealing the presence of a *trans*-quinolizidine system.[7]

The last phase of the isosophoramine synthesis required grafting an α-pyridone unit onto **8**. This was tried first on the model 2-methyl-2-piperideine (**9**).[8] Base-induced condensation of the latter[9] with diethyl ethoxymethylenemalonate[10] and treatment of the Michael adduct with acid yielded ester **10a**, whose hydrolysis and decarboxylation in aqueous acid produced tetrahydroquinolizone **10b**.[11] As a consequence, imine **8**



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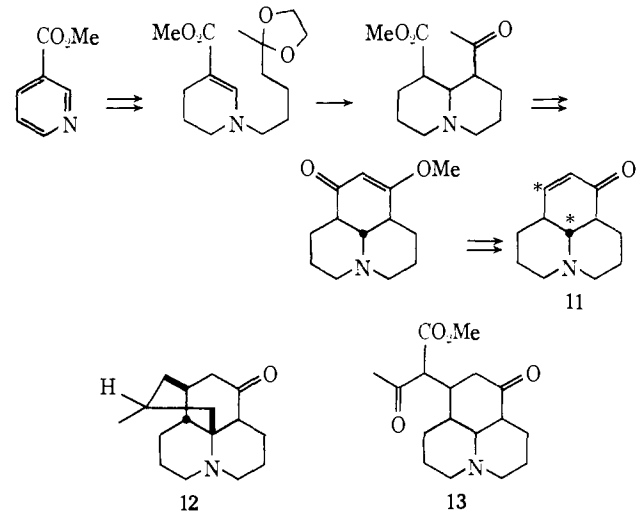
10a, R = CO_2Et
b, R = H

was exposed to a base-catalyzed condensation with diethyl ethoxymethylenemalonate and subsequent acid treatment. This sequence yielded the tetracyclic ester **1b** whose decarboxylative hydrolysis led to *dl*-isosophoramine (**1a**).[12]

Lycopodinoid Hydrojulolidines. The general scheme of alkaloid synthesis[2] has been applied recently to the construction of hydrojulolidine **11** from methyl nicotinate in a facile seven-step reaction sequence (Scheme I).[13] Ketone **11** represents a basic ring system common

Scheme I



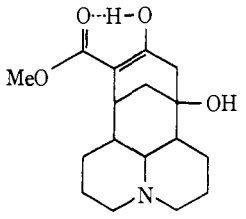
11

12 13

to many *Lycopodium* alkaloids, *e.g.*, lycopodine (**12**), and lacks only a C_1-substituted, three carbon bridge between its starred positions in order to possess a full lycopodinoid skeleton. The following discussion illustrates two pathways for the introduction of logical substituents and oxidation levels into the starred positions needed for completion of a total synthesis of a tetracyclic *Lycopodium* alkaloid.

One reaction route involves placement of a nucleophilic side chain on the circumference of ketone **11** and conversion of its central bridgehead into an electrophilic site. Base-catalyzed condensation of **11** with methyl acetoacetate yielded adduct **13**. On occasion the product was tetracycle **14**, a substance obtained also on extended exposure of **13** to base.[14,15] Acid-catalyzed hydrolysis and decarboxylation of either product gave diketone **15**, whose all-trans configuration was determined by ^{13}C nmr spectroscopy (*vide infra*).[16] Oxidation of the diketone with *m*-chloroperbenzoic acid produced its amine oxide (**16**), whose dehydration with trifluoroacetic anhydride[17] led to the desired vinylogous amide **17**. In analogy with previous experience[18] with the Potier modification of the Polonovsky reaction,[17] the minor products of the dehydration were fluoro compounds **18** and **19**, products of dehydration along the periphery of the ring system

(7) Diamine **6c** could serve in the future as an intermediate in a stereospecific synthesis of all-*cis*-tetrahydrojulolidines and matrine alkaloids derived therefrom.
(8) M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 2445 (1964).
(9) D. A. Evans, *J. Amer. Chem. Soc.*, **92**, 7593 (1970).
(10) V. Boekelheide and J. P. Lodge, Jr., *ibid.*, **73**, 3681 (1951).
(11) F. Bohlmann, N. Ottawa, and R. Keller, *Justus Liebigs Ann. Chem.*, **587**, 162 (1954).
(12) S. Okuda, H. Kamata, and K. Tsuda, *Chem. Pharm. Bull.*, **11**, 1349 (1963), and references therein.
(13) E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Amer. Chem. Soc.*, **90**, 6177 (1968).
(14) The stereochemistry of **13** and **14** remains undetermined.
(15) *Cf.* E. Wenkert and T. E. Stevens, *J Amer. Chem. Soc.*, **78**, 5627 (1956); E. Wenkert, F. Haviv, and A. Zeitlin, *ibid.*, **91**, 2299 (1969).
(16) The bisdioxalane derivative of **15** is described in the Experimental Section.
(17) A. Ahond, A. Cavé, C. Kan-Fan, H.-P. Husson, J. de Rostolan, and P. Potier, *J. Amer. Chem. Soc.*, **90**, 5622 (1968); A. Ahond, A. Cavé, C. Kan-Fan, Y. Langlois, and P. Potier, *Chem. Commun.*, 517 (1970); H.-P. Husson, L. Chevolot, Y. Langlois, C. Thal, and P. Potier, *J. Chem. Soc., Chem. Commun.*, 930 (1972).
(18) E. Wenkert, B. Chauncy, and S. H. Wentland, *Syn. Commun.*, **3**, 73 (1973).



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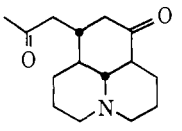

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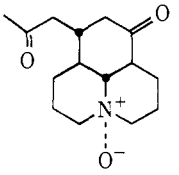

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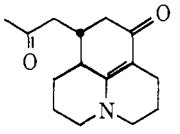

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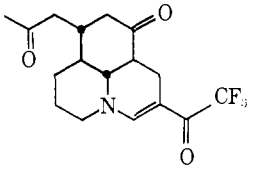

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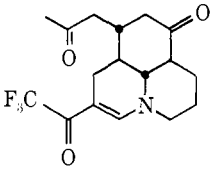

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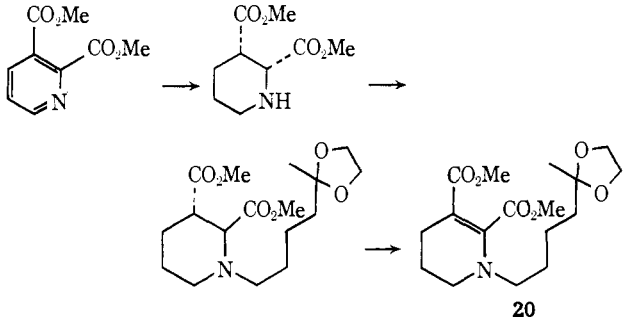
and trifluoroacetylation of the resulted enamines. The functional groups of the diketo compound **17** are ideally situated and electronically favorable to encourage interaction of the side chain with the central carbon site *via* a minimal number of operations leading to the *Lycopodium* alkaloid skeleton.

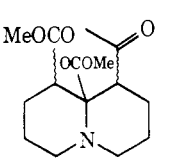
The second reaction route toward a useful lycopodinoid hydrojulolidine inverts the electronic environment of the target product of the first route and involves the introduction of a substituent, capable of being altered readily into a three-carbon, nucleophilic chain, into the central bridgehead of **11** without modifying the electrophilic sites on the periphery of the tricyclic system. This objective required replication of Scheme I with an α-substituted nicotinic ester serving as starting material. Since long α-alkyl groups might block the initial N-alkylation of the pyridine nucleus and subsequently present alternate sites for intramolecular condensation, the innocuous carbomethoxy group was chosen as the α substituent and dimethyl quinolinate as starting compound. The transformation of the latter into the crucial tetrahydropyridine intermediate **20** was described earlier[18] and is portrayed in Scheme II. Treatment of ketal **20** with acid under a variety

Scheme II



20

of conditions yielded keto diester **21** in two isomeric forms or **21** and ketal **22**, which could be converted into **21** on acid-induced hydrolysis. Base-catalyzed cyclization of the keto diester led to diketo ester **23** whose all-trans configuration was proved by its ^{13}C-nmr analysis (*vide infra*).[19] Interestingly, in contrast



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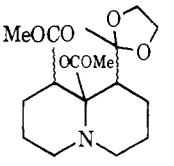

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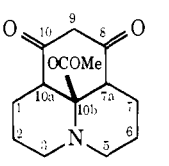

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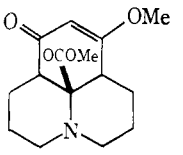
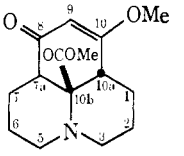
to most previous experience, the β-diketone (**23**) is completely nonenolic both in the solid state and in solution.

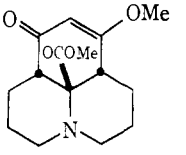
Treatment of diketo ester **23** with diazomethane yielded enol ether **24a**, while exposure of **23** to methanolic hydrogen chloride produced a mixture of enol ether isomers, **24a**, **24b**, and **24c** in 1:13:5 ratio, respectively. The latter proved to be the thermodynamic product mixture, since enol ether **24b** was converted into an enol ether mixture with the same isomer ratio on treatment with methanolic hydrogen chloride. The first indication regarding the stereochemistry of the three isomers came from the pmr δ and J values of the olefinic hydrogen. Its signal appeared at 5.27 ppm in the spectra of **24a** and **24b**, but at 5.50 ppm in the spectrum of **24c**, indicating a different conformational disposition of the ester function to the enone-incorporating ring in isomers **24a** and **24b** *vs.* **24c**. If it be assumed that coupling by the olefinic hydrogen can take place appreciably only with the allylic, bridgehead hydrogen and is at its maximum in case of a dihedral angle relationship of 90° between the interacting hydrogens,[20] the 2-Hz coupling exhibited by the olefinic hydrogens of **24a** and **24c** reveals the allyl hydrogen to be quasi-axial toward its olefinic ring in these isomers, a conformational restraint shown also by the stereochemically known decarbomethoxy derivative of **24a** [δ 5.38 (d, J = 2.5 Hz, olefinic H)].[13] The complete absence of any olefinic hydrogen coupling in the spectrum of **24b** shows its allyl hydrogen to be quasiequatorial toward the oxygenated ring. The assignment of the configuration of the isomers **24a**, **24b**, and **24c** and their conformations depicted in **25a**, **25b**, and **25c**, respectively,



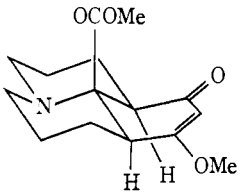
24a



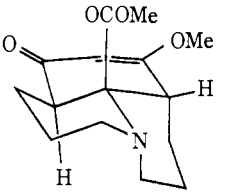
24b



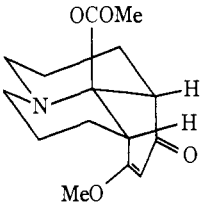
24c



25a



25b



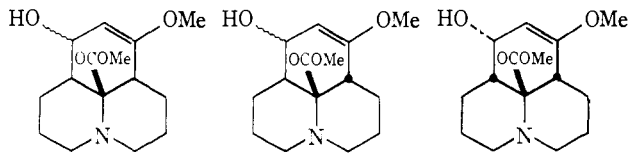
25c

(19) No cyclopentano-β-diketo Dieckmann product was detected.
(20) M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

is substantiated by their ^{13}C nmr analysis (*vide infra*) and by the pmr analysis of their reduction products.

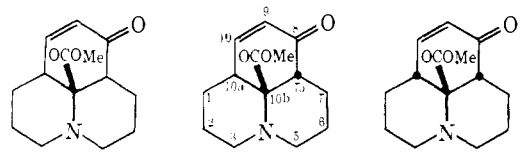
Reduction of **24a** with diisobutylaluminum hydride yielded two isomeric alcohols (**26a**), while similar reduction of **24b** and **24c** gave one alcohol each (**26b** and **26c**, respectively). The coupling characteristics of the oxymethine hydrogen of **26c** with its neighbors indicate the stereochemistry shown in formula **26c**, whereas the fine structure of the oxymethine signals of the other alcohols is too diffuse to permit assignment of the stereochemistry of the new chiral center. The configuration of the other asymmetric carbon sites remains the same as that in the ketonic precursors (**24**), as indicated by like allylic coupling of the olefinic hydrogens.

Mild acid treatment of one of the isomeric alcohols **26a** and of **26b** and **26c** yielded enones **27a**, **27b**, and



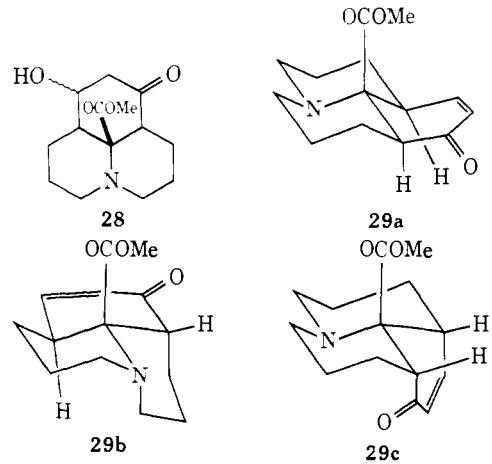
26a **26b** **26c**

27c, respectively. Similar demethanolation of the



27a **27b** **27c**

other **26a** isomer gave a mixture of **27a** and ketol **28**.[21,22] The olefinic α and β hydrogens couple equally in the three isomeric unsaturated ketones to the γ hydrogen by 3 and 2 Hz, respectively, indicating the presence of a quasiaxial allyl, bridgehead hydrogen with respect to the olefinic ring in each of the ketone isomers. This fact implies further that despite the change in functional groups the conformations of the ring system (**29a**, **29b**, and **29c**) do not change from those of the enol ether



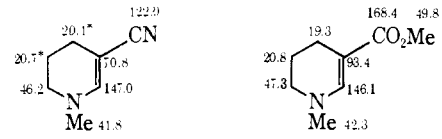
28 **29a**

29b **29c**

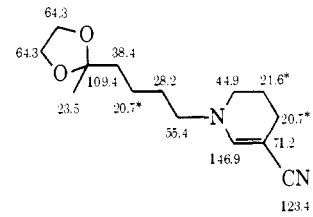
precursors (**25**), an argument confirmed by ^{13}C nmr analysis (*vide infra*). In view of the ease of interconvertibility of the isomeric, unsaturated ketones (**27**) (at the enol ether stage)[23] and the potential for conversion of the central ester unit into a three-carbon nucleophilic chain the ketones are ideal intermediates for the completion of the synthesis of a *Lycopodium* base.

^{13}C Nmr Analyses. While cmr spectroscopy is becoming a popular method of analysis of structure problems,[24] it only rarely has been applied to problems of organochemical synthesis.[25] The present work represents one of the early examples of the continuous use of the new structure tool in a project of synthesis of structurally complex compounds.

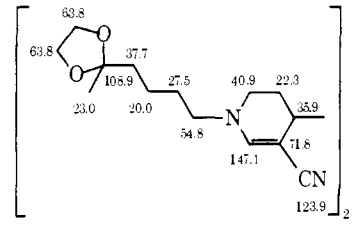
In connection with the analysis of the dimer accompanying the production of the cyanamide vinylog **3** (*vide supra*) the ^{13}C nmr spectrum of 1-methyl-**1**,4,5,6-tetrahydronicotinonitrile (**30**) was inspected. Its chemical shift assignment follows readily that executed earlier for the nicotinic ester equivalent (**31**)[24b,26] and that of **3** (**32**) from application of standard chemical shift theory.[27] The presence of only 13 signals in the cmr spectrum of the dimer indicate the latter to possess monomeric units symmetrically disposed toward each other. The shift of the point of their attachment was revealed by the identification of the signal as that of a methine in the single-frequency off-resonance decoupled spectrum. Since the δ values of the side chain, the olefinic carbons, and the cyano group of the dimer (**33**) are



30 **31**



32



33

similar to those in **32**, the site of junction of the monomer units must be at C(4), C(5), or C(6). Carbon 5 is excluded in view of predicted equality of substituent

(21) *Cf.* E. Wenkert and D. P. Strike, *J. Amer. Chem. Soc.*, 86, 2044 (1964).

(22) If it be assumed that a *quasiaxial* hydroxy group is needed for facile transformation of **26a** into **27a** *via* the β-methoxyallyl cation intermediate,[21] the precursor of the ketol possesses a *quasiequatorial* hydroxy function. In this event ketol **28** has its alcohol group α oriented.

(23) Short treatment of **27b** with base yielded **27c**.

(24) *Inter alia:* (a) A. Rabaron, M. Koch, M. Plat, J. Peyroux, E. Wenkert, and D. W. Cochran, *J. Amer. Chem. Soc.*, 93, 6270 (1971); (b) E. Wenkert, D. W. Cochran, E. W. Hagaman, F. M. Schell, N. Neuss, A. S. Katner, P. Potier, C. Kan, M. Plat, M. Koch, H. Mehri, J. Poisson, N. Kunesch, and Y. Rolland, *ibid.*, 95, 4990 (1973).

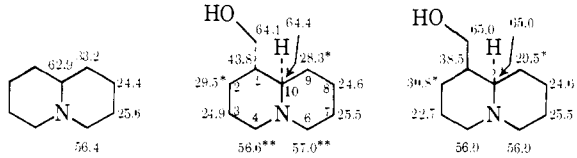
(25) *Cf.* G. Magnusson and S. Thorén, *J. Org. Chem.*, 38, 1380 (1973).

(26) Starred δ values may be reversed.

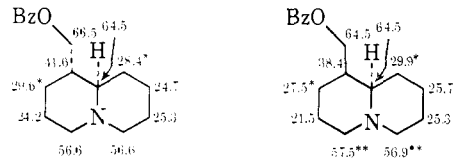
(27) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N. Y., 1972; G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972.

effects on C(4) and C(6). Since the methine shift is not that of an aminomethine, the attachment must be at C(4) and the structure of the dimer as depicted in **33**.[28]

^{13}C nmr spectroscopy became most important in connection with the analysis of the above quinolizidine and hydrojulolidine synthetic intermediates. Chemical shifts were determined from proton-decoupled and single-frequency off-resonance decoupled cmr spectra and correlated with previously obtained shift data on quinolizidine (**34**).[29] Furthermore, a study of the shift assignments for the alkaloids epilupinine (**35**) and lupinine (**36**) and their benzoates (**37** and **38**, respectively) helped in this connection. The chemical shifts were assigned on the following basis. The aminomethine is expected downfield of the other methine and the aminomethylenes and oxymethylene are similarly distinct from the other methylenes in all four substances.[27] The shifts of C(7) and C(8) of the four compounds must be close to those of their equivalent sites in quinolizidine (**34**). The C(3) shifts of epilupinine (**35**) and its benzoate (**37**), quinolizidines with equatorial side chains, need to be close to the C(3) shift of quinolizidine (**34**) itself, while the signal of the same carbon in lupinine (**36**) and its benzoate (**38**) would be expected to be moved



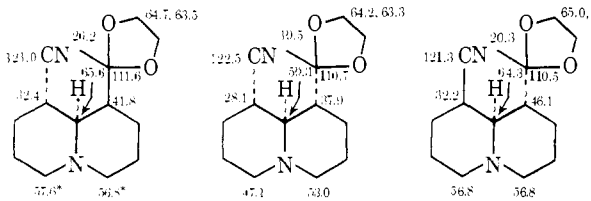
34 **35** **36**



37 **38**

upfield by the γ effect exerted by their axial side chains. Assignment of the δ values for C(2) and C(9) is only tenuous, at best, at this time.

The availability of the shift data for quinolizidines **34–38** encouraged the analysis of the cmr spectra of the three cyanoquinolizidine ketals **4** (**5**). The assignment of the δ values for the methyl and cyano groups, the nonprotonated ketal carbon, and the three methines are based on expectation from theory,[27] while the oxymethylenes and aminomethylenes can be recognized from their normal low-field signals. The chemical shifts, listed on formulas **39a** (**4a**, **5a**), **39b** (**4b**, **5b**), and **39c** (**4c**, **5c**), yield several important details on the structures of the compounds. Both the bridgehead methine and aminomethylene shifts reveal unambiguously the *trans*-quinolizidine conformation of **39a** and **39c** and the *cis*-quinolizidine conformation for **39b**. The aminomethine resonance of the cis form is *ca.* 6 ppm upfield of that of the trans form.[30] While the aminomethylene shift of *trans*-quinolizidines is constant at 57 ppm, the signals for the cis conformation are strongly upfield. The extraordinarily high field position (47.1 ppm) of one of the aminomethylene signals in the spectrum of the *cis*-quinolizidine **39b** reflects two γ effects exerted by carbons of the neighboring ring, *i.e.*, 1,3-diaxial nonbonded interactions of H(4) with hydrogens of the neighboring ring. This effect is exhibited also by the anomalously high-field shift of C(9) of **39b** (with respect to the shifts of the ketal α-methines of **39a** and **39c**), one of the recipients of the nonbonded interactions, indicating the axial nature of H(9) and the consequent equatorial orientation of the ketal side chain in **39b** (**4b**, **5b**). The 4 ppm difference of C(9) in **39a** *vs.* C(9) of **39c** reveals the ketal group to be axial in the former and equatorial in the latter substance. The anomalous methyl shift of **39a** is in agreement with the axial nature of the ketal function in this compound.[32] The chemical shift difference of 4 ppm of C(1) for **39b** and **39c** reflects the difference of *cis- vs. trans*-quinolizidines without alteration of the conformation environment of the α-cyano carbon site. All these facts gleaned from the cmr spectra of the isomeric cyanoquinolizidine ketals (**4**) are in accord with the conformations projected in formulas **5a–c**. Since the remaining methylene shifts (**39a**: 29.7, 25.6, 24.0, 21.6 ppm; **39b**: 25.9, 23.1, 20.9, 19.5 ppm; **39c**: 27.8, 26.8, 24.5, 22.1 ppm) are difficult to assign with certainty, they are not being used as corroborative evidence.



39a **39b** **39c**

As part of the cmr analysis of tricycle **8** and carboethoxyisosophoramine (**1b**) the spectrum of 2-methyl-2-piperideine (**9**) was inspected. The chemical shifts of the latter are depicted on formula **40** and indicate that an imino group, as an olefinic linkage, exerts the shielding endocyclic homoallyl effect described earlier.[24b,29] The shift assignment of the methines, aminomethylenes, methyl group, and iminocarbon of imine **41** (**8**) follows standard theory.[27] The C(2) and C(6) shifts are similar to those of equivalent carbons of quinolizidine (**34**) and the contrast between the C(1) and C(7) shifts reflects the dissimilarity of attachment of the piperideine unit to the quinolizidine nucleus. The shift data establish fully the stereochemistry of the tricyclic compound (**41**). The C(3) and C(5) shifts indicate the presence of a *trans*-quinolizidine unit and the C(2) and C(6) shifts show the piperideine attachment to be doubly equatorial to the quinolizidine moiety, thereby constraining the tricycle to an all-trans configuration. The chemical shift assignment and consequent determination of the stereochemistry of **1b** follow nearly the identical arguments as put forth for imine **8**. The δ values are indicated on formula **42**,

(28) For 2,2′- and 4,4′-coupled dimers produced by various reductions of pyridinium salts, see U. Eisner and J. Kuthan, *Chem. Rev.*, 72, 1 (1972).

(29) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Accounts Chem. Res.*, in press.

(30) This is the identical $\Delta\delta$ value for the difference of shifts of yohimbine, a *trans*-indoloquinolizidine, and pseudoyohimbine, a *cis*-indoloquinolizidine.[31]

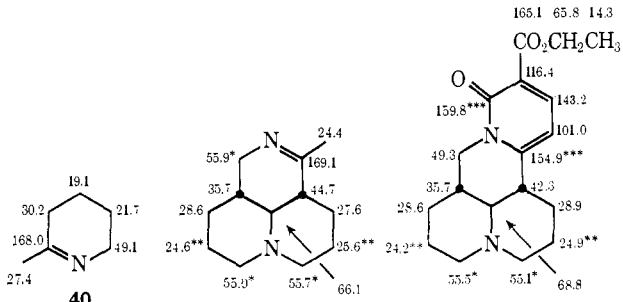
(31) D. W. Cochran, Ph.D. Dissertation, Indiana University, 1971.

(32) While the origin of this apparent δ effect is unclear, similarly deshielded methyl groups have been observed previously in 1,3-diaxial methyl–methyl nonbondedly interacting situations.[33]

(33) E. Wenkert and B. L. Buckwalter, *J. Amer. Chem. Soc.*, **94**, 4367 (1972).

those for the α-pyridone ring being based on shift theory.[27]

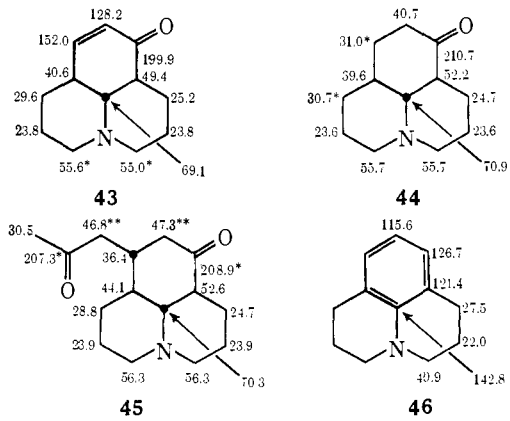
The data from **41** and **42** are directly applicable to



40 **41** **42**

cmr analyses of ketone **11**, its dihydro derivative, and diketone **15**. Thus all quinolizidine carbon shifts of **43** (**11**) are apparent, if the shielding effect of the keto group on its peri neighbor is taken into consideration, while the shifts of the three enone carbons are taken from theory.[27] As in the case of **41** and **42**, tricyclic **43** possesses an all-trans configuration. Removal of the double bond of **43** has a minimal effect on the quinolizidine carbons (*cf.* **44**). Finally, application of shift theory[27] to the analysis of **45** (**15**) puts all numbers into place in this ketone also. The shifts depicted in **45** indicate without doubt an all-trans configuration for the diketone. This constitutes the only proof of stereochemistry of **15** at the present time and illustrates the power of ^{13}C nmr spectroscopy for the solution of stereostructure problems.

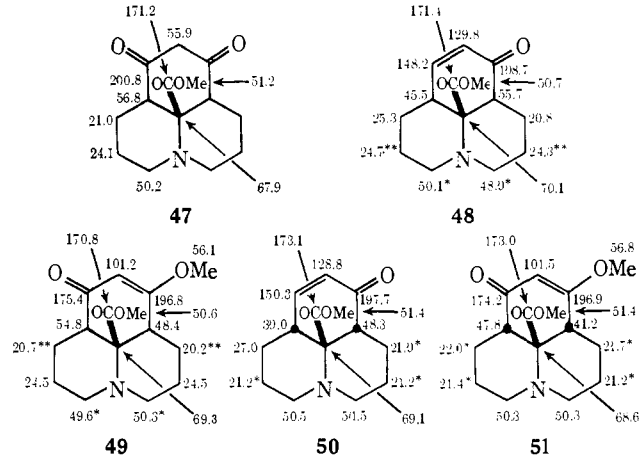
As an adjunct study to the above analyses of hydrojulolidones the cmr analysis of the basic compound, julolidine (**46**), was undertaken. The shifts were as-



43 **44** **45** **46**

signed on the basis of the above discussion and theory[27] and reveal the endocyclic homoallyl effect especially on the aminomethylenes.[24b,29]

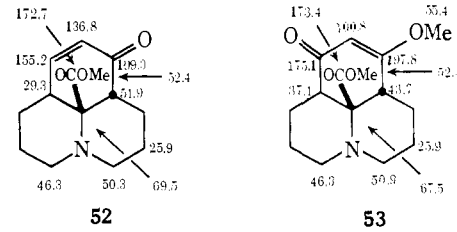
The simplest of the carbomethoxyhydrojulolidines to be analyzed by cmr means is diketone **23**. By taking advantage of its symmetry and by the use of **44** as a model the δ values portrayed in **47** (**23**) can be assigned. The ester function exerts normal γ effects on C(5) and C(7) and the overall data support unambiguously an all-trans configuration for **23**. With **43** and **47** as models the chemical shifts of **27a** and subsequently **24a** can be ascertained (*cf.* **48** and **49**, respectively). The data reveal all-trans configurations for these substances also. The assignments on **48** and **49** lead directly to the analysis of **27c** and subsequently **24c**. As formulas **50** and **51**, respectively, indicate, these ketones are *trans*-quin-



47 **48** **49** **50** **51**

olizidines with a cis,cis C(7a)–C(10b)–C(10a) configuration. The enone unit being axially oriented toward the quinolizidine ring exerts a γ effect on C(2) and C(6), the carbons with which it is in 1,3-diaxial nonbonded interaction.

The trans,cis hydrojulolidones **24b** and **27b** are the most difficult tricycles to evaluate stereochemically by cmr spectral means. While the assignment of the chemical shifts of the nonprotonated aminocarbon and the carbons of the methoxyenone[34] or enone and carbomethoxy units follows the aforementioned pattern, distribution of the methine and methylene shifts, which contain most of the stereochemistry information, among individual carbon centers requires great care. Two shift pairs, those of the aminomethylenes and methines, are strongly stereochemically diagnostic. As figures **52** (**27b**) and **53** (**24b**) illustrate the aminomethy-



52 **53**

lene shifts reveal the presence of a *cis*-quinolizidine structure without differentiating a trans,cis from a cis,trans hydrojulolidine configuration. If 50 ppm is accepted as the base value for an aminomethylene which is part of a *trans*-quinolizidine system but shielded by the central carbomethoxy group, the 46-ppm signal must represent the amino carbon which is part of a *trans*-hydroquinoline unit experiencing a lowered β effect from its neighboring, now axial aminomethylene group.[35] This δ value thus becomes the property of C(3) of **52** (**27b**, **29b**) and C(5) of **53** (**24b**, **25b**). The fact of the other aminomethylene shift undergoing no change from the base value appears to be the fortuitous consequence of the removal of the influence of the γ effect of the carbomethoxy group in the piperidine unit fused diaxially to the *trans*-hydroquinoline moiety being balanced by a γ effect of one of the methines. This last effect must express itself also by one of the

(34) The added conjugation of the α,β-unsaturated ketone unit by the methoxy group leads to strong shielding of the carbonyl group (E. Wenkert and H. Gottlieb, unpublished observations).

(35) This is the same relationship as that of a peri carbon set in *cis*- *vs. trans*-decalins: D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Amer. Chem. Soc.*, **95**, 3718 (1973).

methine shifts. If configurations **27b** and **24b** and hence conformations **29b** and **25b**, respectively, are correct, the allylic methine C(10a) of **27b** must exhibit a shift at least 10 ppm upfield that of the equivalent carbon of the all-trans model **27a** as a consequence of the γ effects exercised by C(5) and C(7) and the same relationship must hold for the α-ketomethine C(7a) of **24b** because of the γ effects of C(1) and C(3). Were the structures incorrect and the trans,cis arrangement actually a cis,trans combination, the ketomethine C(7a) of **27b** and the allylic methine C(10a) of **24b** would be expected to experience strong upfield shifts. As the placement of the δ values in formulas **52** and **53** indicates and the similarity of only the $\Delta\delta$ values of the allylic methine (16 ppm) of **27b** and **27a** and the α-ketomethine (18 ppm) of **24b** and **24a** portrays, only one combination of numbers yields a logical pattern thus confirming the stereochemistry outlined in **27b** and **24b**.

All carbon shifts of **52** and **53** not mentioned heretofore, except those of the methylenes, are assigned on the basis of previous arguments (*vide supra*). While the 18.8, 23.7, and 24.0-ppm signals of **52** and the 19.4, 22.2, and 24.5-ppm signals of **53** can be associated with certain carbon centers only with great difficulty, the 25.9-ppm signal in the spectra of both compounds undoubtedly represents C(6) of **52** (**27b**) and C(2) of **53** (**24b**), since these carbons suffer from neither an environmental change nor from strong 1,3-diaxial interactions in the two substances.

Experimental Section

Melting points were determined on a Reichert micro hot-stage and are uncorrected. Infrared and ultraviolet spectra were recorded on Perkin-Elmer 137 and Cary 14 spectrophotometers. Mass spectra were obtained on Varian CH-7 and AEI MS-9 spectrometers. Unless otherwise noted, ^{1}H nmr spectra of deuteriochloroform solutions with TMS as internal standard (δ 0 ppm) were recorded on Varian A-60, HA-100, and HR-220 spectrometers. The ^{13}C nmr spectra of chloroform or deuteriochloroform solutions were taken on an nmr instrument consisting of a Varian Associates DP-60 magnet working at 14 kG with an external ^{19}F lock, a white-noise generator and adjustable, home-built crystal oscillator for proton decoupling, a Fabri-Tek 1074 time-averaging computer and Digital Electronics Corp. PDP-8/1 computer for signal averaging and Fourier transformation of the free induction decay. The samples were spun in 13-mm o.d. tubes and the solvent signal was used as internal standard. All δ values denoted on the formulas are in ppm downfield from TMS; $\delta^{TMS} = \delta^{CHCl_3} + 77.2$ ppm; $\delta^{TMS} = \delta^{CDCl_3} + 76.9$ ppm.

3-Cyano-1-(5-ketohexyl)pyridinium Bromide Ethylene Ketal (2). A mixture of 10.0 g of nicotinonitrile and 22.0 g of 6-bromo-2-hexanone ethylene ketal was stirred at 70° for 3 days. Ether was added and the mixture shaken and filtered. The residue was stored in a desiccator to prevent moisture-induced deketalation and the filtrate evaporated. The overall reaction process was repeated twice on the residue, yielding a total of 27.2 g of crude salt. While the latter could be utilized in this form in the next reaction, it was purified by crystallization from anhydrous methanol–ether. Drying at 110° (0.005 Torr) for 1 day yielded colorless crystals of **2**: mp 138–140°; ir (KBr) C≡N 4.47 (w) and C=C 6.12 (m) μ; pmr δ 1.23 (s, 3, Me), 1.3–2.2 [m, 6, $(CH_2)_3$], 3.86 [s, 4, $(OCH_2)_2$], 4.81 (t, 2, J = 7 Hz, NCH_2), 8.43 [dd, 1, J = 8, 6 Hz, H(5)], 9.17 [d, 1, J = 8 Hz, H(4)], 9.62 [d, 1, J = 6 Hz, H(6)], 10.08 [s, 1, H(2)].

Anal. Calcd for $C_{14}H_{19}O_2N_2Br$: C, 51.39; H, 5.85; N, 8.56; Br, 24.42. Found: C, 51.15; H, 5.98; N, 8.52; Br, 24.60.

1-(5-Ketohexyl)-1,4,5,6-tetrahydronicotinonitrile (3). A mixture of 15.0 g of **2**, 2 g of 10% palladium/charcoal, and 15 ml of triethylamine in 300 ml of methanol was hydrogenated at 50 psi for 14 hr. It was filtered through Celite and the filtrate evaporated under reduced pressure. The residual mixture of trimethylammonium bromide precipitate and orange oil was washed repeatedly with benzene and the solution concentrated to a volume of 100 ml which was passed through alumina (activity IV) and eluted with benzene. Evaporation of the eluates and drying of the residue at 0.05 Torr gave 10.0 g of yellow oil which darkened on standing but could be used in the next reaction. A more stable, pale yellow liquid, 8.9 g, was obtained on passage of a chloroform solution through silica gel or by distillation. Chromatography on a preparative tlc plate of alumina and redistillation gave **3**: bp 179–181° (0.5 Torr); ir (neat) C≡N 4.58 (s) and C=C 6.14 (s) μ; pmr δ 1.23 (s, 3, Me), 1.3–2.4 (m, 10, $(CH_2)_5$], 3.10 [t, 4, $(NCH_2)_2$], 3.86 [s, 4, $(OCH_2)_2$], 6.77 (s, 1, olefinic H).

Anal. Calcd for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19. Found: 67.34; H, 8.82; N, 11.02.

An ether solution of the oil from the silica gel chromatography was kept at 0° for 12 hr and the resultant precipitate (1.2 g from 15 g of unpurified **2**) crystallized from methylene chloride. Preparative tlc of the needles, mp 110–111°, and crystallization from chloroform–pentane gave crystalline **33**: mp 111–112°; ir (KBr) C≡N 4.60 (s) and C=C 6.14 (s) μ; pmr δ 1.30 (s, 6, Me_2), 1.4–1.7 [m, 14 $(CH_2)_5$], 2.2–3.2 [m, 10, $(NCH_2)_4$, $H(4)_2$, for both *dl* and meso forms], 3.91, 3.93 [s each, 4, $(OCH_2)_4$], 6.77 (s, 2, olefinic H).

Anal. Calcd for $C_{28}H_{42}O_2N_4$: C, 67.44; H, 8.49; N, 11.24. Found: C, 67.52; H, 8.59; N, 11.18.

9-Acetyl-1-cyanoquinolizidine Ethylene Ketals (4). A solution of 1.0 g of **3** and 3 g of anhydrous *p*-toluenesulfonic acid in 500 ml of dry benzene was refluxed for 24 hr. The mixture of pale yellow solution and separated oil was concentrated to a volume of 100 ml, treated with 10 ml of triethylamine, and taken up in methylene chloride. The solution was washed vigorously with 5% sodium hydroxide solution, dried over potassium carbonate, and evaporated. Chromatography of a methylene chloride solution of the residue [1.1 g of a 9:10:6 mixture of **4a**, **4b**, and **4c**, respectively, by gc (5% Carbowax at 225°)] on alumina (activity IV) and elution with benzene yielded 803 mg of pale yellow oil whose rechromatography under identical means and elution with benzene and subsequently with 50:1 benzene–ether gave 228 mg of **4a**, 222 mg of **4b**, 58 mg of a mixture of **4b** and **4c**, 50 mg of **4c**, and 112 mg of a mixture of **4c** and uncharacterized material. Each isomer crystallized on standing and was purified further by rechromatography on alumina and sublimation. Cyanide **4a**: mp 65–66°; ir (KBr) NCH 3.65 (m), 3.72 (w)[36] and C≡N 4.50 (w) μ; pmr δ 1.3–2.3 (m, 12 H), 1.57 (s, 3, Me), 2.85 [m, 2, equatorial H(4), H(6)], 3.03 [td, 1, J = 12, 4 Hz, H(1)], 3.8–4.1 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.19; H, 8.64; N, 11.19.

Cyanide **4b**: mp 86–86.5°; ir (KBr) NCH absent[36] and C≡N 4.51 (w) μ; pmr δ 1.26 (s, 3, Me), 1.3–3.0 (m, 13 H), 3.10 [dd, 1, J = 10, 4 Hz, H(10)], 3.48 [m, 1, H(1)], 3.8–4.1 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.22; H, 8.89; N, 11.29.

Cyanide **4c**: mp 77–78°; ir (KBr) NCH 3.61 (m), 3.68 (m), 3.75 (w),[36] and C≡N 4.51 (w) μ; pmr δ 1.25 (s, 3, Me), 1.4–2.2 (m, 12 H), 2.88 [m, 2, equatorial H(4), H(6)], 3.57 [m, 1, H(1)], 3.8–4.2 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.20; H, 8.83; N, 11.19.

A reaction between **3** and anhydrous *p*-toluensulfonic acid in chloroform at room temperature gave **4a**, **4b**, and **4c** in 1:56:10 ratio, respectively. Refluxing of 25 mg of **4a** and anhydrous *p*-toluenesulfonic acid in 2.5 ml of benzene for 1.5 hr and gc analysis of the products revealed the presence of a 1:1 mixture **4a** and **4b**. No change occurred after refluxing for 3 and for 8 hr. Refluxing of 25 mg of **4c** and anhydrous *p*-toluenesulfonic acid in 2.5 ml of benzene and gc product analysis after 1 and 14 hr showed the presence of only starting **4c**. A solution of 35 mg of **4a** and potassium *tert*-butoxide (from 20 mg of potassium) in 1.1 ml of *tert*-butyl alcohol was kept at room temperature under nitrogen for 26 hr. Ether, 5 ml, was added and the mixture washed with water, dried over potassium carbonate, and evaporated. Analysis of the residue, 34 mg, by gc showed the presence of **4a** (93%) and an uncharacterized material (7%). The identical reaction with **4b**, 50 mg, and potassium *tert*-butoxide (from 40 mg of potassium) in 4 ml of *tert*-butyl alcohol and gc product analysis revealed the presence of more than 95% of **4c**. Passage of an ether solution of the product through a short alumina column led to 48 mg of crystalline **4c**.

1-Aminomethyl-9-acetylquinolizidine Ethylene Ketals (6) and Their *N*-Acetyl Derivatives (7). A solution of 400 mg of cyanide

(36) E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956).

4a in 25 ml of ether was added slowly to a mixture of 400 mg of lithium aluminum hydride in 100 ml of refluxing ether and the mixture refluxed for 50 hr. Enough 25% sodium hydroxide solution then was added cautiously to decompose the excess hydride but to retain the inorganic salts as gritty precipitate. The solution was decanted and the precipitate washed with fresh ether. Evaporation of the combined organic solutions yielded 387 mg of colorless, oily diamine **6a** which could be used without further purification for the preparation of **8** or converted into its *N*-acetyl derivative in the following manner. A solution of 150 mg of **6a** and 0.3 ml of acetic anhydride in 5 ml of ether was kept standing for 12 hr. A 10% potassium carbonate solution, 5 ml, was added and the mixture stirred for 2 hr. The aqueous solution was separated and extracted with methylene chloride and the combined organic solutions were dried over potassium carbonate. Evaporation of the solvent yielded 140 mg of solid whose crystallization from methylene chloride–hexane gave needles of amide **7a**: mp 135–136°; ir ($CHCl_3$) NH 2.95 (w), 3.05 (w), NCH 3.61 (w), 3.69 (m), 3.75 (w),[36] and C=O 6.03 (s) μ; pmr δ 0.8–2.3 (m, 13 H), 1.61 (s, 3, Me), 1.97 (s, 3, Ac Me), 2.82 [m, 2, equatorial H(4), H(6)], 3.1–3.4 (m, 2, $AcNCH_2$), 3.8–4.0 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{16}H_{28}O_3N_2$: C, 64.83; H, 9.52; N, 9.45. Found C, 64.90; H, 9.64; N, 9.38.

Cyanide **4b**, 50 mg, was reduced as **4a** and the resultant colorless, liquid diamine **6b**, 50 mg, acetylated as **6a**. Crystallization of the product from hexane gave 45 mg of amide **7b**: mp 123.5–124.5°; ir ($CHCl_3$) NH 2.95 (w), 3.05 (w), NCH absent,[36] and C=O 6.03 (s) μ; pmr δ 1.25 (s, 3, Me), 1.3–3.0 (m, 15 H), 1.95 (s, 3, Ac Me), 3.2–3.4 (m, 1, $AcNCH_2$ H), 3.4–3.6 (m, 1, $AcNCH_2$ H), 3.8–4.0 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{16}H_{28}O_3N_2$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.73; H, 9.45; N, 9.35.

Cyanide **4c**, 50 mg, was reduced as **4a** and the resultant colorless, oily diamine **6c**, 50 mg, acetylated as **6a**. Crystallization of the product from heptane yielded 47 mg of needles of amide **7c**: mp 99–100°; ir ($CHCl_3$) NH 2.95 (w), 3.02 (w), 3.16 (w), NCH 3.61 (m), 3.68 (m),[36] and C=O 6.05 (s) μ; pmr δ 1.0–2.2 (m, 13 H), 1.23 (s, 3, Me), 1.94 (s, 3, Ac Me), 2.79, 2.87 [m, each, 1 each, equatorial H(4), H(6)], 3.2–3.4 (m, 1, $AcNCH_2$ H), 3.6–3.8 (m, 1, $AcNCH_2$ H), 3.8–4.0 [m, 4, $(OCH_2)_2$].

Anal. Calcd for $C_{16}H_{28}O_3N_2$: C, 64.83; H, 9.52; N, 9.45. Found: C, 64.65; H, 9.47; N, 9.26.

9-Aza-8-methyl-7a,10,10a,10b-tetrahydrojulolidine (8). A solution of 387 mg of diamine **6a** in 10 ml of 20% hydrochloric acid was allowed to stand at room temperature for 16 hr. It then was neutralized slowly by a 25% potassium hydroxide solution and the mixture extracted exhaustively with methylene chloride. The extract was dried over potassium carbonate and evaporated. Chromatography of the residual, yellow oil, 295 mg, on alumina (activity IV) yielded colorless, liquid imine **8**: ir (neat) NCH 3.54 (m), 3.62 (m),[36] and C=N 6.02 (m) μ; pmr δ 0.8–2.3 (m, 13 H), 1.93 (br s, 3, Me), 2.86 [m, 2, equatorial H(3), H(5)], 3.0–3.2 (m, 2, imino CH_2); *m/e* 192.1618 (calcd for $C_{12}H_{20}N_2$, 192.1626). The imine darkens rapidly and must be stored as hydrochloride salt or as its dipicrate, mp 248–249° dec.

Anal. Calcd for $C_{24}H_{26}O_{14}N_8$: C, 44.31; H, 4.03; N, 17.22. Found: C, 44.45; H, 4.13; N, 17.09.

3-Carbomethoxy-6,7,8,9-tetrahydro-4*H*-quinoliz-4-one (10a). A hexane solution of 1.6 *M* *n*-butyllithium, 7 ml, was added to a solution of 1.4 ml of disopropylamine (freshly distilled from calcium hydride) in 12 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) kept under nitrogen at −10°. Imine **9**, 1.11 ml, was added to the mixture at −30° and the combination stirred for 15 min. Diethyl ethoxymethylenemalonate, 2.12 ml, was added rapidly to the mixture at −78° and stirring continued at this temperature for 6 hr. Acetic acid, 10 ml, was added to the suspension and the resultant orange solution heated at 100° for 30 min. Application of reduced pressure removed the solvents, but kept the orange residual syrup at 100° for 2 hr. Water, 30 ml, was added and the solution basified with solid potassium carbonate and extracted with methylene chloride. The extract was dried over potassium carbonate and evaporated. Filtration of a benzene solution of the residual red oil through a short alumina column (activity IV) provided 2.1 g of a solid whose sublimation and crystallization from ether–pentane gave long needles of **10a**: mp 74–75°; ir ($CHCl_3$) C=O 5.78 (s), 5.91 (s), 6.03 (s), and C=C 6.41 (s) μ; pmr δ 1.35 (t, 3, J = 7 Hz, Me), 1.80 and 1.95 [pent. each, 2 each, J = 7 Hz, C(7) and C(8) methylenes], 2.82 [t, 2, J = 7 Hz, $H(9)_2$], 4.01 [t, 2, J = 7 Hz, $H(6)_2$], 4.33 (q, 2, J = 7 Hz, OCH_2), 6.05 [d, 1, J = 8 Hz, H(1)], 8.08 [d, 1, J = 8 Hz, H(2)].

Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.99; H, 7.09; N, 6.41.

6,7,8,9-Tetrahydro-4*H*-quinoliz-4-one (10b). A mixture of 200 mg of **10a** and 8 ml of concentrated hydrochloric acid was refluxed for 3 hr and then evaporated to dryness. The residue was taken up in a solution of potassium carbonate and the mixture extracted with methylene chloride. The extract was dried over magnesium sulfate and evaporated. Distillation of the residual oil, 90 mg, gave colorless solid pyridone **10b**, mp 45–47° (lit.[11] mp 46–47°), and picrate, mp 104.5–105.5° (lit.[11] mp 107°).

11-Carboethoxyisosophoramine (1b). A hexane solution of 1.6 *M* *n*-butyllithium, 2.1 ml, was added to a solution of 0.5 ml of diisopropylamine (freshly distilled from calcium hydride) in 2 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) maintained under nitrogen at 0°. A solution of 460 mg of imine **8** in 2 ml of dry tetrahydrofuran was added at −30° and the mixture stirred for 10 min. Diethyl ethoxymethylenemalonate, 0.7 ml, was added to the mixture at −78° and stirring continued at this temperature for 8 hr. Glacial acetic acid, 10 ml, was added and the mixture stirred at room temperature for 3 hr and at 100° for 1.5 hr. Upon being kept at room temperature for 12 hr the mixture was evaporated to dryness under reduced pressure. A methylene chloride solution of the residual oil was extracted with 5% hydrochloric acid and the extract made alkaline with potassium carbonate and extracted with methylene chloride. The latter extract was dried over potassium carbonate and evaporated. An ether solution of the oily residue, 602 mg, was passed through an alumina (activity IV) column and evaporated. Crystallization of the crystalline residue, 404 mg, yielded ester **1b**: mp 67–69°; ir ($CHCl_3$) NCH 3.61 (w), 3.67 (w),[36] C=O 5.80 (s), 5.92 (s), 6.05 (s), and C=C 6.45 (s) μ; pmr δ 1.0–3.0 (m, 15 H), 1.34 (t, 3, J = 7 Hz, Me), 3.61 (dd, 1, J = 16, 11 Hz, axial $CONCH_2$ H), 4.32 (q, 2, J = 7 Hz, OCH_2), 4.43 (dd, 1, J = 16, 5 Hz, equatorial $CONCH_2$ H), 6.20 (dd, 1, J = 8, 1 Hz, pyridone γ-H), 8.24 (d, 1, J = 8 Hz, pyridone β-H); *m/e* 316.1790 (calcd for $C_{18}H_{24}O_3N_2$, 316.1787).

***dl*-Isosophoramine (1a).** A solution of 25 mg of ester **1b** in 10 ml of 20% sulfuric acid was refluxed for 14 hr. The solution was basified with 10% potassium hydroxide solution and extracted with methylene chloride. Drying of the extract with potassium carbonate and evaporation yielded 5 mg of **1a**: ir ($CHCl_3$) NCH 3.60 (w), 3.68 (w),[36] C=O 6.06 (s), C=C 6.39 (m), and 6.50 (s) μ; uv (MeOH) λ_{max} 233 nm (log ϵ 3.76), 310 (3.79); pmr δ 1.0–3.0 (m, 15 H), 3.15 (dd, 1, J = 16, 13 Hz, axial $CONCH_2$ H), 4.40 (dd, 1, J = 16, 5 Hz, equatorial $CONCH_2$ H), 6.15 (d, 1, J = 6 Hz, pyridone γ-H), 6.41 (d, 1, J = 8 Hz, pyridone α-H), 7.29 (dd, 1, J = 8, 6 Hz, pyridone β-H); ir and pmr spectra identical with those of an authentic sample of allosophoramine (= isosophoramine); *m/e* 244.1566 (calcd for $C_{15}H_{20}ON_2$, 244.1576).

Diketo Ester 13. A solution of sodium methoxide (from 25 mg of sodium) in 10 ml of methanol was added to a solution of 1.07 g of ketone **11** and 0.65 g of methyl acetoacetate in 20 ml of methanol and the mixture kept at room temperature under nitrogen for 48 hr. It then was poured into water, brought to pH 6.8 with glacial acetic acid, and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. Passage of a benzene solution of the residual oil through alumina (activity III) and evaporation yielded a colorless oil, 1.50 g, whose distillation gave liquid **13**: ir ($CHCl_3$) NCH 3.55 (w), 3.67 (w),[36] C=O 5.77 (s), and 5.82 (s) μ; uv (MeOH) λ_{max} 255 nm (log ϵ 3.28); pmr δ 1.5–3.0 (m, 19 H); 2.19, 2.23 (s, total of 3, Me of keto and enol forms), 3.75 (s, 3, OMe); *m/e* 307 (M^+), 306, 263, 222, 190 (base): *m/e* 307.1802 (calcd for $C_{17}H_{25}O_4N$, 307.1783).

Anal. Calcd for $C_{17}H_{25}O_4N$: N, 4.56. Found: N, 4.53.

Amino Ester 14. A solution of 672 mg of **13** and sodium methoxide (from 51 mg of sodium) in 30 ml was kept at room temperature under nitrogen for 4 days. It then was poured into water and the pH adjusted to 6.5–7.8. The solution was extracted with chloroform. Drying of the extract over sodium sulfate and evaporation led to 554 mg of starting diketo ester **13**. The aqueous solution was adjusted to pH 8.5 and reextracted with chloroform. The extract was dried and evaporated yielding 93 mg of crystalline **14**: mp 160–163° dec; ir (Nujol) OH 3.05 (m), C=O, C=C 6.08 (s), and 6.19 (s) μ; uv (MeOH) λ_{max} 256 nm (log ϵ 4.04), (0.1 *N* KOH/MeOH) 282 (4.29); pmr δ 1.0–3.0 (m, 20 H), 3.73, 3.74 (s, 3, OMe); *m/e* 307 (M^+), 306, 249, 248, 233, 232, 187 (base), 186; *m/e* 307.1777 (calcd for $C_{17}H_{25}O_4N$, 307.1783).

10-Acetonyl-7a,8,9,10,10a,10b-hexahydro-8-julolidone (15). A solution of 2.00 g of **13** in 15 ml of concentrated hydrochloric acid was refluxed for 4 hr and then poured onto ice–water. It was adjusted to pH 8–9 with ammonium hydroxide and extracted with

chloroform. The extract was dried over sodium sulfate and evaporated. Passage of a benzene solution of the residue through a short alumina (activity III) column and evaporation gave a solid, 1.36 g, whose sublimation and crystallization from hexane afforded diketone **15**: mp 94–96°; ir ($CHCl_3$) NCH 3.60 (w), 3.67 (w),[36] and C=O 5.85 (s) μ; pmr δ 1.0–3.0 (m, 20 H), 2.12 (s, 3, Me).

Anal. Calcd for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.29; N, 5.62. Found: C, 72.26; H, 8.98; N, 5.57.

A solution of 45 mg of **14** in 2 ml of concentrated hydrochloric acid was refluxed for 3 hr. Work-up as above, chromatography on 1 g of alumina (activity III), and elution with ether gave 28 mg of diketone **15**, identical with the above sample by mixture melting point, ir, and tlc in four systems. Elution with 9:1 ether–methanol yielded 10 mg of an uncharacterized product [ir ($CHCl_3$) C=O 5.87 (s) μ; pmr no Me peaks] whose greater abundance after a 2-hr run indicated it to be a precursor of **15**.

Bisdioxalane of Diketone 15. A solution of 2.6 g of **15**, 2.4 g of *p*-toluenesulfonic acid, and 2.0 g of ethylene glycol in 100 ml of benzene was refluxed in the presence of a Dean–Stark water separator for 15 hr. It then was poured into cold aqueous ammonia and extracted with chloroform. The extract was dried and evaporated and a benzene solution of the oily residue filtered through a short alumina (activity III) column. Evaporation yielded a colorless, viscous oil, 3.2 g, which solidified on cooling. Crystallization of the solid gave **15** bisketal: mp 73–75°; ir (Nujol) NCH 3.62 (w) and 3.69 (w);[38] pmr δ 0.7–2.4 (m, 20 H), 1.28 (s, 3, Me), 2.80 [m, 2, equatorial H(3), H(5)], 4.89 and 4.91 [s, 4 each, $(OCH_2)_4$].

Anal. Calcd for $C_{19}H_{31}O_4N$: C, 67.62; H, 9.26; H, 4.15. Found: C, 67.54; H, 9.43; N, 4.25.

***N*-Oxide 16.** A solution of 0.54 g of 84% *m*-chloroperbenzoic acid in 20 ml of methylene chloride was added to a solution of 0.60 g of diketone **15** in 40 ml of methylene chloride at 0° and the mixture allowed to warm to room temperature for 0.5 hr. It then was stirred for 3 hr and evaporated to dryness. Chromatography of the residue on alumina (activity III) and elution with benzene gave a trace of **15**. Elution with 19:1 chloroform–methanol yielded 638 mg of solid product whose crystallization from ether afforded **16**: mp 230–232° dec; ir (Nujol) C=O 5.85 (s) μ; pmr δ 0.7–3.4 (m, 20 H), 2.16 (s, 3, Me).

Anal. Calcd for $C_{15}H_{23}O_3N$: C, 67.90; H, 8.74; N, 5.28. Found: C, 68.07; H, 8.54; N, 5.01.

Fluoro Compounds 18 and 19. Trifluoroacetic anhydride (freshly distilled from phosphorus pentoxide), 1.0 ml, was added to a solution of 0.61 g of dry *N*-oxide **16** (kept in a vacuum desiccator over phosphorus pentoxide) in 30 ml of dry methylene chloride (filtered through neutral, activity I alumina) at 0°. After 15 min the mixture was poured into a 10% sodium bicarbonate solution and extracted with chloroform. The extract was dried and evaporated and the residue, 0.43 g, chromatographed on silica gel. Elution with ether gave 70 mg of a solid whose crystallization from methanol yielded **18** (or **19**): mp 216–217°; ir (Nujol) C=O 5.84 (s), C=O, C=C 6.22 (s), and 6.32 (s) μ; uv (MeOH) λ_{max} 321 nm (log ϵ 4.50); pmr δ 0.8–3.5 (m, 17 H), 2.16 (s, 3, Me), 7.42 (s, 1, olefinic H); *m/e* 343 (M^+), 342 (very weak), 285, 274 (base), 216.

Anal. Calcd for $C_{17}H_{20}O_3NF_3$: C, 59.47; H, 5.87; N, 4.08. Found: C. 59.37; H, 6.10; N, 4.32.

Further elution with ether gave 63 mg of a solid whose crystallization from benzene–hexane yielded **19** (or **18**): mp 164–166°; ir (Nujol) C=O 5.86 (s), C=O, C=C 6.11 (w), and 6.29 (s) μ; uv (MeOH) λ_{max} 322 nm (log ϵ 4.44); pmr δ 0.8–3.7 (m, 17 H), 2.14 (s, 3, Me), 7.36 (s, 1, olefinic H); *m/e* 343 (M^+), 342 (50% of M^+), 299, 284, 274 (base), 216.

Anal. Calcd for $C_{17}H_{20}O_3NF_3$: C, 59.47; H, 5.87; N, 4.08. Found: C, 59.75; H, 5.90; N, 3.91.

10-Acetonyl-8,9,10,10a-tetrahydro-8-julolidone (17). Elution with 9:1 chloroform–methanol gave 275 mg of a solid whose crystallization from benzene–hexane yielded crystalline **17**: mp 138–139°; ir (Nujol) C=O 5.84 (s), C=O, C=C 6.24 (s), and 6.48 (s); uv (MeOH) λ_{max} 319 nm (log ϵ 4.40); pmr δ 1.0–2.8 (m, 14 H), 2.12 (s, 3, Me), 3.1–3.3 [m, 4, $(NCH_2)_2$]; *m/e* 247 (M^+), 232, 204, 190, 189, 188, 162.

Anal. Calcd for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.04; H, 8.63; N, 5.57.

Dimethyl 9-Acetylquinolizidine-1,10-dicarboxylate (21). A solution of 9.32 g of diester **20** in 200 ml of dry methanol was saturated with anhydrous hydrogen chloride gas at 0° and then kept at room temperature for 16 hr. It was poured into 1 l. of cold water, and the mixture was stirred for 1 hr, made alkaline with aqueous ammonia, and extracted with chloroform. The extract was dried and evaporated. Chromatography of the residue on alumina (activity I) and elution with benzene yielded a 3:1 mixture of stereoisomeric keto diesters **21** as colorless oil (the ratio of isomers varied from 2:1 to 4:1): ir ($CHCl_3$) C=O 5.76 (s, major) and 5.79 (s, minor) μ; pmr δ 1.4–3.0 (m, 14 H), 2.15 (s, 3, Me of major isomer), 2.24 (s, 3, minor Me), 3.54 (s, 3, major OMe), 3.62 (s, 3, minor OMe), 3.66 (s, 3, minor OMe), 3.72 (s, 3, major OMe).

Anal. Calcd for $C_{15}H_{23}O_5N$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.46; H. 7.84; N, 4.50.

Ketal 22. A solution of 5.83 g of diester **20** in 200 ml of 1:1 ether–methylene chloride was saturated with dry hydrogen chloride gas at 0° and kept at room temperature for 16 hr. It then was poured into cold water, and the mixture was stirred for 1 hr, basified with aqueous ammonia, and extracted with methylene chloride. The extract was dried and evaporated and the residual, red oil extracted exhaustively with boiling hexane. The hexane extract was evaporated, and a benzene solution of the residue was filtered through a short column of alumina (activity I). Chromatography of the resultant yellow oil, 2.5 g of a mixture of ketal and ketones according to pmr analysis, on alumina (activity III) and elution with 2:1 hexane–benzene yielded a solid, 0.60 g, whose crystallization from hexane gave crystalline, colorless ketal **22**: mp 105–106°; ir ($CHCl_3$) C=O 5.78 (s) μ; pmr δ 1.3–3.0 (m, 14 H), 1.41 (s, 3, Me), 3.59 (s, 3, OMe), 3.70 (s, 3, OMe), 3.84 [s, 4, $(OCH_2)_2$]; cmr δ 174.2 (C=O), 170.6 (C=O), 112.0 ($RR'CO_2$), 67.4 [C(10)], 51.0 [C(1) or C(9)], 46.6 [C(9) or C(1)], 51.0 (OMe), 50.0 (OMe), 22.3 (Me), 64.5 (OCH_2), 62.8 (OCH_2) 52.3 [C(4) or C(6)], 50.4 [C(6) or C(4)], 25.9 (CH_2), 24.3 (CH_2), 23.3 (CH_2), 22.3 (CH_2); *m/e* 341 (M^+), 282, 255, 254, 196, 87 (base).

Anal. Calcd for $C_{17}H_{27}O_6N$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.77; H, 7.92; N, 4.22.

Further elution with 1:1 hexane–benzene gave a mixture of ketone **21** isomers with the minor one in the preparation of **21** now predominating. When a methanol solution of 1.54 g of **22** was treated with hydrogen chloride and worked up in a manner described for the preparation of **21** (*vide supra*), 1.23 g of a 4:1 mixture of **21** isomers were obtained. The ketal **22** resisted ketal hydrolysis by all other methods.

Methyl *trans,trans*-7a,8,9,10,10a,10b-Hexahydro-8,10-julolidione-10b-carboxylate (23). A solution of 1.23 g of the keto diester isomer mixture **21** in 20 ml of 1,2-dimethoxyethane (freshly distilled from lithium aluminum hydride) was added dropwise to a stirring, refluxing suspension of 364 mg of sodium hydride in 40 ml of dimethoxyethane under nitrogen and the mixture refluxed for 5 hr. Glacial acetic acid, 0.49 ml, was added to the cooled mixture, the latter filtered, and the filtrate evaporated. A methylene chloride solution, 5 ml, of the residual oil was placed on a silica gel column and the latter eluted with ether. After the appearance of some starting diester and impurity there was obtained 855 mg of desired, solid product whose sublimation and crystallization from hexane gave diketo ester **23**: mp 160–161°; ir ($CHCl_3$) C=O 5.77 (s) and 5.84 (s) μ; pmr δ 1.0–3.3 (m, 14 H), 3.41 [br s, 2, $(CO)_2CH_2$], 3.59 (s, 3, Me); *m/e* 265 (M^+), 206 (base); no ir, pmr, and cmr evidence for enolization (even after extra base treatment).

Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.51; H, 7.31; N, 5.20.

In contrast to the above 78% yield the reaction between **21** and potassium *tert*-butoxide in refluxing *tert*-butyl alcohol for 16 hr led to only 22% of **23**.

Methyl *trans,trans*-10-Methoxy-7a,8,10a,10b-tetrahydro-8-julolidone-10b-carboxylate (24a). A solution of 0.50 g of diketo ester **23** in 1 ml of methanol was diluted with 50 ml of ether and treated with an excess of ethereal diazomethane. After 1 hr at room temperature it was evaporated and the solid residue sublimed at 130° and high vacuum yielding 0.52 g of colorless, crystalline **24a** (the latter could be recrystallized from acetone, ether, or methanol): mp 167–168°; ir (Nujol) C=O 5.78 (s), 6.02 (s), and C=C 6.26 (s) μ; uv (MeOH) λ_{max} 250 nm (log ϵ 4.12); pmr δ 1.5–3.0 (m, 14 H), 3.62, 3.66 [s each, 3 each, $(OMe)_2$], 5.27 (d, 1, J = 2 Hz, olefinic H); *m/e* 279 (M^+), 220 (base).

Anal. Calcd for $C_{15}H_{21}O_4N$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.82; H, 7.45; N, 4.90.

Enol Ethers 24b and 24c. A solution of 1.10 g of diketo ester **23** in 50 ml of methanol was treated with dry hydrogen chloride gas (saturation not needed) at 0° and kept at room temperature for 2 days. It was poured into ice-cold aqueous ammonia and the mixture of *ca.* pH 8.5 extracted exhaustively with chloroform. The extract was dried and evaporated yielding a colorless oil which solidified gradually. A solution of the latter in a minimum amount of methylene chloride was placed on a chromatographic column of silica (Mallinckrodt "SilicAR" cc-7, 200–300 mesh) and eluted

with dry ether. Vacuum sublimation of the first eluates, 300 mg, gave crystalline **24c** (crystallizable from hexane): mp 136–137°; ir (Nujol) C=O 5.78 (s), 6.08 (s), and C=C 6.23 (s) μ; uv (MeOH) λ_{max} 251 nm (log ϵ 4.03); pmr δ 1.0–3.3 (m, 13 H), 2.78 (dd, 1, J = 4, 2 Hz, COCH), 3.71, 3.73 [s each, 3 each, $(OMe)_2$], 5.50 (d, 1, J = 2 Hz, olefinic H).

Anal. Calcd for $C_{15}H_{21}O_4N$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.52; H, 7.59; N, 5.00.

Further elution with ether yielded 56 mg of **24a**, identical in all respects with the product of diazomethane treatment of **23** (*vide supra*). High vacuum sublimation and crystallization (from ether) of the solid product, 726 mg, from elution with 9:1 ether–methanol yielded **24b**: mp 188–190°; ir (Nujol) C=O 5.78 (s), 6.06 (s), and C=C 6.21 (s) μ; uv (MeOH) λ_{max} 245 nm (log ϵ 4.17); pmr δ 1.0–3.1 (m, 14 H), 3.65 and 3.74 [s each, 3 each, $(OMe)_2$], 5.27 (s, 1, olefinic H); *m/e* 279 (M^+), 220 (base).

Anal. Calcd for $C_{15}H_{21}O_4N$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.39; H, 7.48; N, 5.05.

Treatment of 2.08 g of **24b** with methanolic hydrogen chloride under the conditions of the above conversion of **23** into the isomers of **24** yielded 110 mg of **24a**, 1.40 g of **24b**, and 491 mg of **24c**.

Allyl Alcohols 26. A 0.7 *M* heptane solution of diisobutylaluminum hydride, 5.0 ml, was added to a solution of 713 mg of **24a** in 75 ml of dry toluene under nitrogen at −78° and the mixture kept at this temperature for 1 hr. The excess hydride was destroyed by the addition of 5 ml of methanol at −78° and the resultant clear solution poured into aqueous sodium citrate solution adjusted to *ca.* pH 8. It was extracted with chloroform and the extract dried and evaporated. Chromatography of the pale yellow, residual oil, 702 mg, on alumina (activity III) and elution with 1:1 benzene–methylene chloride gave 279 mg of solid alcohol whose high vacuum sublimation and crystallization from hexane yielded one isomer of **26a**: mp 108–110°; ir ($CHCl_3$) OH 2.82 (w), 290 (w), C=O 5.81 (s), C=C 6.03 (s), and 6.26 (w) μ; pmr δ 1.5–3.2 (m, 14 H), 3.51 and 3.66 [s each, 3 each, $(OMe)_2$], 4.18 (m, 1, OCH), 4.67 (dd, 1, J = 5, 3 Hz, olefinic H); *m/e*, no molecular ion peak 263.1561, (calcd $C_{15}H_{23}O_4N \cdot H_2O$: 263.1521).

Elution with 1:1 ether–methylene chloride gave 375 mg of solid alcohol whose high vacuum sublimation and crystallization from hexane yielded the other isomer of **26a**: mp 119–121°; ir ($CHCl_3$) OH 2.82 (w), 2.95 (w), C=O 5.81 (s), and C=C 6.05 (m) μ; pmr δ 1.5–3.0 (m, 14 H), 3.50 and 3.63 [s, each, 3 each, $(OMe)_2$], 4.02 (m, 1, OCH), 4.53 (t, 1, J = 3 Hz, olefinic H).

Anal. Calcd for $C_{15}H_{23}O_4N$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.25; H, 8.10; N, 4.95.

A 0.7 *M* heptane solution of diisobutylaluminum hydride, 13 ml, was added slowly to a solution of 530 mg of **24b** in 70 ml of dry toluene under nitrogen at −78° and the mixture kept at −78° for 6 hr. The excess hydride was destroyed by the addition of 5 ml of methanol, and the solution was poured into sodium citrate solution of *ca.* pH 8. It was extracted with chloroform and the extract dried and evaporated. Sublimation of the residual solid. 510 mg, at high vacuum and crystallization of the sublimate from hexane gave colorless crystals of **26b**: mp 102–104°; ir (Nujol) OH 2.88 (m), C=O 5.89 (s), C=C 6.06 (s), and 6.24 (w) μ; pmr δ 1.1–3.2 (m, 14 H), 3.49, 3.76 [s each, 3 each, $(OMe)_2$], 4.15 (dd, 1, J = 6, 4 Hz, OCH), 4.74 (d, 1, J = 4 Hz, olefinic H); *m/e* 281 (M^+), 222 (base), 204, 190, 188 (M, 222 → 204), 176, 152 (M, 204 → 176).

Anal. Calcd for $C_{15}H_{23}O_4N$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.21; H, 8.16; N, 4.98.

A 1.1 *M* heptane solution of diisobutylaluminum hydride, 6.5 ml, was added slowly to a solution of 503 mg of **24c** in 30 ml of dry toluene and 30 ml of dry ether under nitrogen at −78° and the mixture kept at this temperature for 6 hr. Work-up as for the reduction of **24b** (*vide supra*), high vacuum sublimation of the solid alcohol product, 445 mg, and crystallization from hexane yielded **26c**: mp 85–86°; ir ($CHCl_3$) OH 2.99 (w), C=O 5.78 (s), and C=C 5.97 (s) μ; pmr δ 1.2–3.3 (m, 14 H), 3.53 and 3.69 [s each, 3 each, $(OMe)_2$], 4.19 (dd, 1, J = 6, 4 Hz, OCH), 5.10 (dd, 1, J = 6, 2 Hz, olefinic H).

Anal. Calcd for $C_{15}H_{23}O_4N$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.04; H, 8.34; N, 4.85.

Methyl *trans,trans*-7a,8,10a,10b-Tetrahydro-8-julolidone-10b-carboxylate (27a) and Ketol 28. A solution of 105 mg of alcohol **26a** (mp 108–110°) in 10 ml of 5% sulfuric acid was kept at room temperature for 30 min and then poured into aqueous ammonia and extracted with chloroform. The extract was dried and evaporated leaving 70 mg of solid residue whose sublimation and crystallization from hexane yielded **27a**: mp 97–98°; ir ($CHCl_3$) C=O 5.81 (s), 5.95 (s), and C=C 6.20 (w) μ; uv (MeOH) λ_{max} 226 nm (log ϵ 3.89); pmr δ 1.2–3.3 (m, 14 H), 3.61 (s, 3, OMe), 5.98 (dd, 1, J = 10, 3 Hz, olefinic α-H), 6.50 (dd, 1, J = 10, 2 Hz, olefinic β-H).

Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.67; H, 7.73; N, 5.60.

While **27a** was inert to triethylamine at room temperature for 30 hr, it was converted to four uncharacterized products (by tlc analysis), none being any enone **27**, on refluxing with 0.2 equiv of sodium methoxide in methanol for 1 hr.

A solution of 375 mg of alcohol **26a** (mp 119–121°) in 2 ml of alcohol and 30 ml of 10% sulfuric acid was kept at room temperature under nitrogen for 1 hr and then poured into cold aqueous ammonia and extracted with chloroform. The extract was dried and evaporated. Chromatography of the residue on silica gel and elution with USP ether gave 100 mg of **27a**, identical in all respects with the above sample. Elution with 10:1 ether–methanol yielded 220 mg of tlc-pure ketol **28**: mp *ca.* 70°, 136–139°; ir ($CHCl_3$) OH 2.94 (w) and C=O 5.81 (s) μ; pmr δ 1.0–3.9 (m, 17 H), 3.64 (s, 3, OMe); *m/e* 267 (M^+), 208, 190, 174 (M, 208 → 190); *m/e* 267.1460 (calcd for $C_{14}H_{21}O_4N$, 267.1470).

Enones 27b and 27c. A solution of 295 mg of alcohol **26b** in 2 ml of dioxane and 20 ml of 10% sulfuric acid was kept at room temperature for 3 hr. Work-up as above gave 247 mg of product whose chromatography on silica gel and elution with ether yielded a solid. Sublimation of the latter and crystallization from hexane afforded colorless plates of **27b**: mp 125–126°; ir ($CHCl_3$) C=O 5.79 (s), 6.00 (s), and C=C 6.20 (w) μ; uv (MeOH) λ_{max} 233 nm (log ϵ 3.76); pmr δ 1.2–3.3 (m, 14 H), 3.70 (s, 3, OMe), 5.90 (dd, 1, J = 10, 3 Hz, olefinic α-H), 6.82 (dd, 1, J = 10, 2 Hz, olefinic β-H); *m/e* 249 (M^+), 190 (base).

Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.52; H, 7.56; N, 5.53.

Refluxing a methanol solution of **27b** and 0.2 equiv of sodium methoxide for 15 min leads t **27c** (*vide infra*).

A solution of 325 mg of alcohol **26c** in 2 ml of dioxane and 5 ml of 10% sulfuric acid in 50 ml of water was kept at room temperature under nitrogen for 1 hr. Work-up as above, chromatography of the crude product on alumina (activity III), and elution with benzene gave 195 mg of solid whose sublimation and crystallization from hexane yielded **27c**: mp 86–87°; ir ($CHCl_3$) C=O 5.79 (s) and 5.99 (s) μ; uv (MeOH) λ_{max} 225 nm (log ϵ 3.89); pmr δ 1.0–3.3 (m, 14 H), 3.75 (s, 3, OMe), 6.06 (dd, 1, J = 10, 3 Hz, olefinic α-H), 6.48 (dd, 1, J = 10, 2 Hz, olefinic β-H).

Anal. Calcd for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.45; H, 7.61; N, 5.52.

Attempts to isomerize **27c** in methanolic sodium methoxide (0.2 equiv) were unsuccessful. A reaction at room temperature for 1 hr left the substance unchanged, while reactions at the same temperature but for 20 hr or on refluxing for 1 hr yielded uncharacterized materials, none of which proved to be isomers **27**.

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