analyze mixtures of the two complexes. Equilibrium, K_{eq} = [20]/[19] = 14.2 ± 0.2, was approached from both complexes. Least-squares analysis as above afforded $k_{19\rightarrow20}$ = 5.32 ± 0.32 × 10^{-3} min^{-1} at 119.55 ± 0.05° in degassed toluene solution. The complexes could not be separated by chromatography.

Interconversion of the Isomeric 1-*p*-Methoxyphenyl-6-(3,4-dichlorophenyl)-1,3,5-hexatriene*tetrahaptoiron* Tricarbonyl Complexes (17) and (18). The isomerization was approached from both directions, using **17**-*4*-d_1 and **18**-*3*-d_1.[25] In the nmr spectra of each of these deuterated complexes, the ratio of the upfield olefinic hydrogen peaks to the methoxy hydrogen peak is 1:3, while in the spectra of their shift isomers **16**-*4*-d_1 and **12**-*3*-d_1, respectively, the ratio is 2:3. Therefore the ratio varies over the interval 0.333–0.667 on equilibrating **17**-*4*-d_1 and **18**-*4*-d_1, and **18**-*3*-d_1 and **17**-*3*-d_1. Integration of the two areas (20 integrals) after heating dilute degassed tetrahydrofuran solutions of the two complexes at 110° for 19 half-lives and isolation of the mixture of complexes by chromatography afforded K_{eq} = (**18**)/(**17**) = 55/45 = 1.26 ± 0.02. Analysis of the first-order equilibration rate at 100.08 ± 0.02° afforded $k_{17\rightarrow18}$ = 4.4 ± 0.3 × 10^{-3} min^{-1}.

Interconversion of the Two Isomers of 1-Phenyl-7-anisyl-1,3,5-hexatriene*tetrahaptoiron* Tricarbonyl. The ratio of **16** and **15** was determined by taking advantage of the small separation of the methoxy resonances in the nmr spectra of the two complexes. The peaks are separated by 1.3 Hz, in $CDCl_3$, that of **16** being at the lower field. Heating each of the isomers at 110° for *ca.* 20 half-lives and isolating the mixture by chromatography afforded K_{eq} = **16**/**15** = 1.21 ± 0.02. The kinetics of the interconversion of the two isomers was investigated using the same analytical techniques on the deuterated derivatives of **15** and **16** as was used above for the dichlorophenyl–anisyl complexes.

For interconversion of **15** and **16** $k_{15\rightarrow16}$ = 1.36 ± 0.6 × 10^{-3} min^{-1} at 99.37° in degassed tetrahydrofuran solution.

Isomerization of 3, 4, and 5. Infrared absorbances employed to analyze mixtures of these three complexes were the 962-cm^{-1} band of **4**, the 810-cm^{-1} band of **5**, and the 754-cm^{-1} band of **3**.

Kinetic runs were performed in dilute freeze–thaw degassed (10^{-5} mm) toluene solutions in the dark. For analysis, a tube was opened, solvent was removed by evaporation *in vacuo*, and the residue was dissolved in carbon disulfide and subjected to infrared analysis.[17] Samples consisted of 5.0 ± 0.5 mg in 0.04 ml of carbon disulfide. Two spectra were determined of each sample. A typical result of analysis of unknown mixtures of the three complexes, arising from 1-phenyl-8-tolyloctatetraene-5,6,7,8-*tetrahaptoiron* tricarbonyl, is shown in Table V. Time–concentration plots are presented in Figure 1.

Acknowledgment. Support of this work by the National Institutes of Health and the National Science Foundation is acknowledged. C. Reich was supported in part by an N.I.H. predoctoral fellowship.

(25) These deuterated complexes were prepared by the base-catalyzed hydrogen–deuterium exchange of the deuterium-free complex with ethanol-d_1 (C. Reich and R. Markezich, to be reported).

Stereospecific Syntheses of Uleine and Epiuleine

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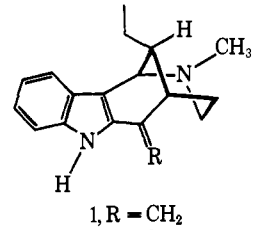
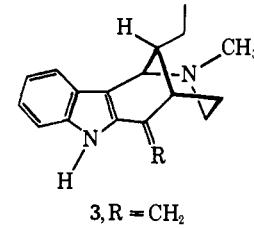
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. *Received September 12, 1970*

Abstract: 1-Aminohexan-3-one (**12**) prepared from the known 1-chlorohexan-3-one (**5**) *via* the phthalimide **11** on Mannich condensation with 3-formylindole gave the trans-disubstituted piperidone **13**. The stereochemistry of the corresponding formamide **15**, which exists preferentially as a diaxially substituted piperidone, was established by nuclear magnetic resonance spectroscopy. Condensation of the ketone **15** with acetylene to the carbinol **21** was followed by treatment with mercuric acetate furnishing the acetoxy ketone **23**. Reduction of the latter with lithium in liquid ammonia, cyclization of the resulting *trans,trans*-methyl ketone **24**, and reduction of the formamide **29** with lithium aluminum hydride completed the stereospecific synthesis of epiuleine (**3**). The tetrasubstituted α,β-unsaturated ketone **31**, available by pyrolysis of the acetate **23** on catalytic reduction, afforded mostly the *cis,cis*-methyl ketone **35** in addition to minor portions of the *cis,trans*-methyl ketone **37**. Cyclization of the former with boron trifluoride followed by hydride reduction gave uleine (**1**). A reversal of the usual conformational stability relationship was encountered in several of the intermediates and attributed to the vicinal alkyl amide effect.

Uleine, a secondary plant metabolite of *Aspidosperma ulei* Mgf., belongs to a small group of indole alkaloids whose structures lack the tryptamine unit. Work on the two-dimensional constitution of uleine was complete in 1959[2] but the configuration of the ethyl group remained to be established. The first evidence concerning this point was provided by the reaction of the alkaloid with methyl iodide. The high rate of quaternization observed suggested that the ethyl group is situated equatorially away from the basic nitrogen atom.[3] An examination of *Aspidosperma subincanum* carried out in the same year led to the isolation of a new alkaloid which proved to be epiuleine.[4] The C-methyl triplet in the nuclear magnetic resonance spectrum of epiuleine appears at δ 1.08 while it is shifted upfield to 0.88 in uleine. This difference was attributed to long-range shielding from the indole ring and uleine and epiuleine were assigned the configurations **1** and **3**, respectively.[4]



1, R = CH_2
2, R = O

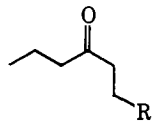


3, R = CH_2
4, R = O

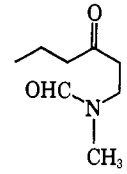
(1) National Institutes of Health Predoctoral Fellow, 1967–1970.
(2) G. Büchi and E. W. Warnhoff, *J. Amer. Chem. Soc.*, **81**, 4433 (1959).
(3) M. Shamma, J. A. Weiss, and R. J. Shine, *Tetrahedron Lett.*, 2489 (1967).
(4) A. J. Gaskell and J. A. Joule, *Chem. Ind. (London)*, 1089 (1967).

Synthetic studies in this area have led to nonstereoselective total syntheses of four natural products: dasycarpidone (**2**),[5,6] epidasycarpidone (**4**),[5,6] uleine (**1**),[5] and epiuleine (**3**).[5,6] There remained the task of a stereoselective synthesis of any of these alkaloids which would corroborate the stereochemical assignments, and in this paper we describe the achievement of this goal.

The known 1-chloro-3-hexanone (**5**)[7] was condensed with 2 equiv of *N*-methylbenzylamine and the resulting tertiary amine **6** converted to the secondary amine **7** by catalytic hydrogenation of the corresponding hydrochloride. Formylation of crude secondary amine **7** with formic acetic anhydride[8] gave the formamide **8**. Condensation of the latter with indole in tetrahydrofuran solution containing phosphoryl chloride led to an intermediate which based on its ultraviolet light absorption at 342 nm[9] was assigned structure **9**. Cyclization to the crystalline tricyclic ketone **10** was effected by treatment with base. Although a suitably substituted piperidine was now available for further transformation it was decided to replace it with the amide **15** because products derived from the amine **10** proved to be noncrystalline and sensitive to air.



5, R = Cl
6, R = $N(CH_3)CH_2C_6H_5$
7, R = $NHCH_3$



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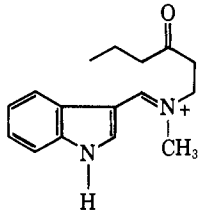

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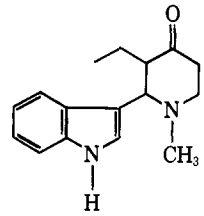
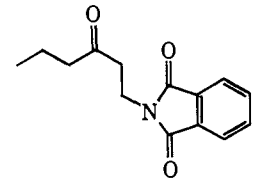
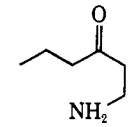


10

Condensation of the chloride **5** with potassium phthalimide[10] gave the substituted imide **11**. Hydrolysis to the primary amine **12** by means of hydrochloric acid[11] was followed by condensation with 3-formylindole giving mainly the tricyclic ketone **13**. The nuclear magnetic resonance spectrum featured a one-proton doublet at δ 4.1 caused by the hydrogen atom (to be called the methine proton henceforth) located on the carbon atom between indole ring and piperidine nitrogen. In agreement with the presence of two axially oriented, vicinal protons the coupling constant between H_A and H_B was 9 Hz in ketone **13**. The formation of a piperidone with two equatorial substituents can be rationalized if cyclization proceeds within a chair-like intermediate (**14**) with the large substituents on the two double bonds trans oriented.



11



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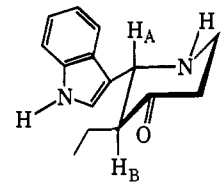
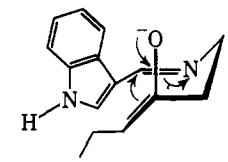


13



14

Treatment of the formamide **15** derived from the *trans*-amine **13** with sodium acetate in methanol solution[12] resulted in partial conversion to a new substance which proved to be the cis isomer **18**. The same equilibrium mixture containing 70% trans and 30% cis epimer could be obtained starting with pure cis epimer **18**. Examination of the nmr spectrum of the *trans*-*N*-formylpiperidone **15** revealed the presence of two discrete species due to restricted rotation about the carbon–nitrogen bond of the amide[13] and comparison of chemical shifts of methine protons in the two rotamers with those of 4-methylpiperidine (**16**) and the two *N*-acetylpiperidines **17a** and **17b**[14] allowed the structural assignments indicated in **15a** and **15b**. It is worthy of note that the *N*-formylpiperidones **15** and **18** in analogy to cyclohexane-1,4-diones might prefer a twist-boat conformation[15] but that such a conformational change would not affect our arguments. The appearance of the methine protons as singlets accords with the presence of axially oriented indole rings and to relieve steric crowding between equatorial indole substituent and amide carbonyl groups formylation was accompanied by conformational inversion. This vicinal alkyl amide effect is well documented[13] and represents a special case of $A^{(1,3)}$ strain.[16] Furthermore, it should be pointed out that the 2-alkyl ketone effect[16] and the two trigonal centers both increase the stability of conformers with axial substituents. The spectral assignments were confirmed by high-temperature studies in deuteriodimethylformamide and are presented in the Experimental Section.

A nuclear magnetic resonance spectrum of the *cis*-*N*-formylpiperidone **18** again revealed the presence of two rotamers at room temperature and relevant chemical shifts and multiplicities are given in structures **18a** and **18b**.

The next phase of the synthesis was concerned with the introduction of the remaining two carbon atoms. Treatment of the *N*-formyl-*trans*-piperidone **15** with lithium acetylide–ethylenediamine complex[17] in benzene

(5) N. D. V. Wilson, A. Jackson, A. J. Gaskell, and J. A. Joule, *Chem. Commun.*, 584 (1968); *J. Chem. Soc. C*, 2738 (1969).
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(7) K. Bowden, E. A. Braude, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 45 (1946).
(8) C. W. Huffman, *J. Org. Chem.*, 23, 727 (1958).
(9) A similar imminium salt is reported to have uv max 345 nm: G. F. Smith, *J. Chem. Soc.*, 3845 (1954).
(10) J. C. Sheehan and W. A. Bolhofer, *J. Amer. Chem. Soc.*, 72, 2786 (1950).
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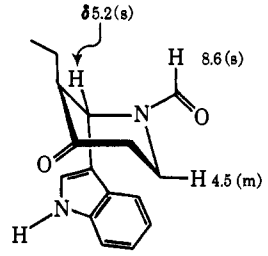
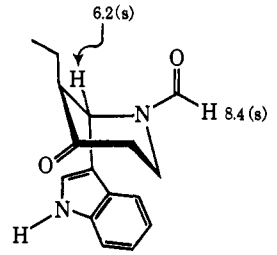
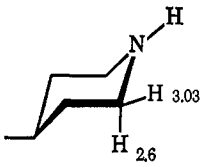
(13) H. Paulsen and K. Todt, *Chem. Ber.*, 100, 3385 (1967).
(14) A. M. Monro and M. J. Sewell, *Tetrahedron Lett.*, 595 (1969), and references cited therein.
(15) R. D. Stolow and C. B. Boyce, *J. Amer. Chem. Soc.*, 83, 3722 (1961); N. L. Allinger and L. A. Freiberg, *ibid.*, 83, 5028 (1961); A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Lett.*, 1247 (1963).
(16) F. Johnson, *Chem. Rev.*, 68, 375 (1968).



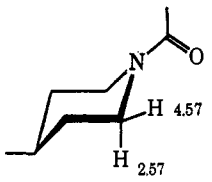
15a



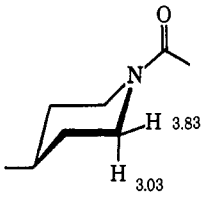
15b



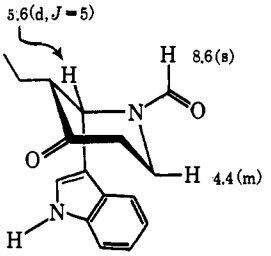
16



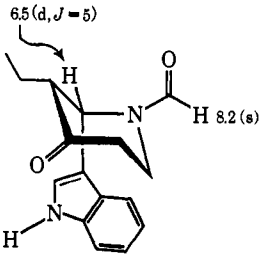
17a



17b

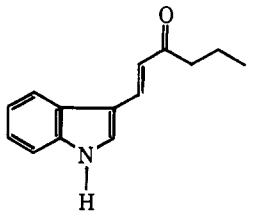


18a



18b

solution did not yield the desired ethynyl carbinol but a compound isomeric with starting material. Spectral comparison with the ketone **19**[18] revealed it to be the bicyclic formamide **20** resulting from β-elimination. Efforts to recyclize it to either of the tricyclic isomers **15** and/or **18** with either acid or base failed, excluding the intermediacy of the α,β-unsaturated ketone **20** in the equilibration of the two epimers **15** and **18**. After con-



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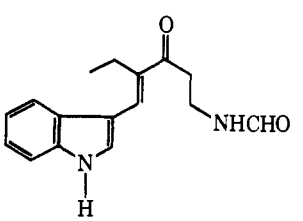
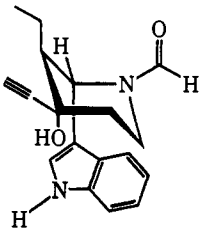
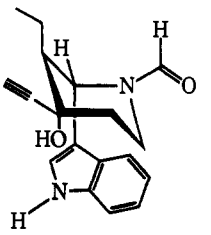


20

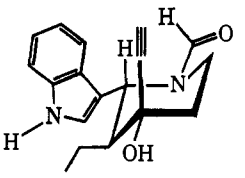
siderable experimentation it was found that ethynylation predominated when the ketone **15** was condensed with potassium acetylide in the protic solvent mixture *tert*-butyl alcohol–tetrahydrofuran.[19] A nucleophilic reagent should attack the ketone carbonyl group in **15** from the side opposite to the indole ring and the configuration of the acetylenic substituent was tentatively assigned on this basis. An argument to be mentioned in the sequel fully confirmed this. The spectroscopic properties of the ethynylcarbinol detailed in the Experimental Section agree with the presence of three conformers **21a–c**.



21a

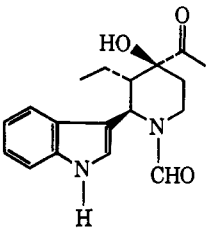


21b

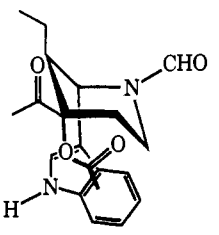


21c

Mercuric acetate in acetic acid brought about smooth conversion of the ethynylcarbinol **21** to a mixture of the acetoxy ketone **23** and minor amounts of the corresponding hydroxy ketone **22**.[20,21] Efforts to suppress the formation of the latter or to acetylate the alcohol **22** to the acetate **23** failed and the two products, unfortunately, had to be separated by chromatography. Singlets in the nmr spectrum of the acetate **23** at δ 5.1 and 6.1 demand the presence of two rotamers and coupled with the absence of a doublet at 4.5 pointed again to an axial orientation of the indole ring. In agreement with this postulate long-range shielding from the indole ring caused the three-proton singlet of the acetate methyl group to be shifted upfield by nearly 1 ppm to δ 1.2.



22



23

Contrary to the case of the ethynylcarbinol **21** conformers with equatorial indole substituents were not detected at room temperature and this is probably a manifestation of the larger size of the acetyl as compared to the ethynyl grouping. Earlier work[21] has shown that the configuration of the hydroxy group does not change in the ethynylcarbinol–acetoxy ketone conversion. Calcium, sodium, and lithium in liquid ammonia all served in the reductive elimination of the acetoxy group but in preparative runs lithium metal gave superior yields.[22,23] The appearance of the methine proton as a

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(18) J. C. Powers, Ph.D. Thesis, Massachusetts Institute of Technology, 1963.
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(21) H. B. Kagan, A. Marquet, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1079 (1960).
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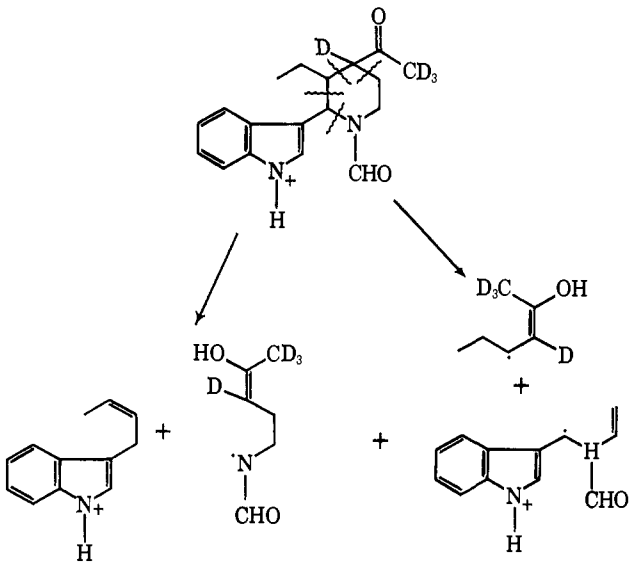
(23) E. S. Rothman and M. E. Wall, *J. Amer. Chem. Soc.*, **79**, 3228 (1957).

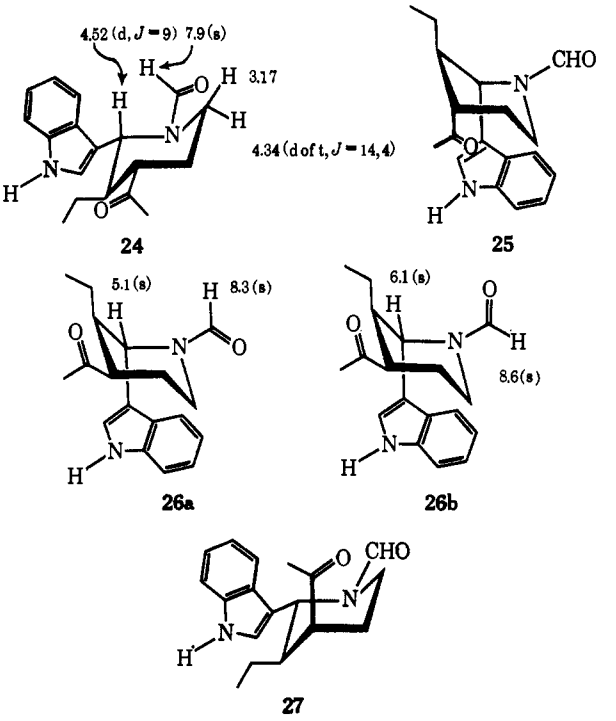
doublet (J = 9 Hz) confirmed the trans arrangement of indole and ethyl substituents in the reduction product and further nmr data given in the Experimental Section demand the presence of a single species with structure **24**. Prolonged exposure of the methyl ketone **24** to sodium acetate in hot methanol resulted in no change, yet hydrogen–deuterium exchange under the same conditions in methanol-d_1 led to incorporation of four deuterium atoms in addition to conversion of N–H to N–D. Absence of an acetyl methyl signal in the nmr spectrum and appearance of an $M^+ - 46$ ($COCD_3$) peak in the mass spectrum revealed the location of three of the four labels. Additional intense peaks at m/e 132 and 89 in the mass spectrum due to fragments produced as outlined in Scheme I strongly indicate that the fourth deuterium atom also is located next to the keto group.

Scheme I

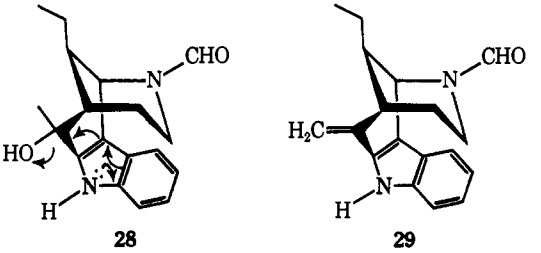


These findings suggest that the trans,trans-trisubstituted piperidine **24** should be thermodynamically more stable than the corresponding trans,cis epimer **26** to be described later. Whether the trans,trans isomer **24** was formed in the reduction directly or through the trans,cis isomer **26** as a rate-controlled intermediate is not known. Before discussing the transformation of the tricyclic ketone **24** to a tetracyclic intermediate we should emphasize that the greater stability of the conformer with three equatorial substituents came as no surprise because the indole–acetyl 1,3-diaxial interaction operating in the chair form **25** should be more severe than the equatorial alkyl group formamide repulsion in **24**. On the other hand the finding that the trans,trans isomer **24** is much more stable than the trans,cis epimer which turned out to exist in conformation **26** rather than **27** was not exactly anticipated and must be the result of a number of effects we cannot evaluate quantitatively.

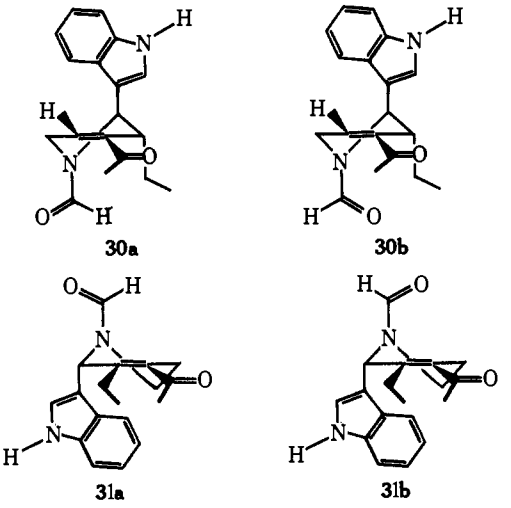
Cyclization of the methyl ketone **24** with boron trifluoride etherate in methylene chloride gave a product **29** with typical 2-vinylindole absorption in the ultraviolet. The overall change undoubtedly proceeds *via* the methylcarbinol **28** and it is to be noted that dehydration can proceed only in one direction (Bredt's rule) as symbolized by the arrows in **28**. Reduction of the formamide **29** with lithium aluminum hydride gave racemic epiuleine (**2**) identical with natural material as



judged by comparison of infrared, ultraviolet, mass, and nuclear magnetic resonance spectra.[24]



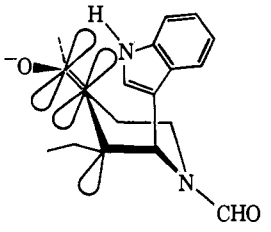
After having completed the stereospecific synthesis of epiuleine (**2**) we turned to the synthesis of uleine (**1**). Short contact time pyrolysis of the acetoxy ketone **23** yielded a mixture of tri- and tetrasubstituted α,β-unsaturated ketones whose structures were easily deduced from spectroscopic data. Nmr spectra measured at ambient temperature revealed the presence of the conformers **30a,b** and **31a,b**, respectively. The trisubstituted olefin



(24) We are deeply indebted to Dr. J. A. Joule, Manchester University, for this comparison.

30 was of no further use in the synthesis except that it did allow the preparation of the trans,cis-trisubstituted piperidine **26** which we have already alluded to while discussing the stereochemistry of its epimer **24** leading to epiuleine (**2**). Catalytic hydrogenation of the olefin **30** over a palladium catalyst furnished a mixture of the two saturated ketones **24** and **26** separable by chromatography. Treatment of the latter with sodium acetate in hot methanol-d_1 induced very slow epimerization only and we suspected that proton abstraction on the ring carbon atom is retarded by the indole substituent located on the same side of the molecule. Indeed a mass spectrum of a sample withdrawn after 5 days contained approximately 80% trideuterio- and only 20% tetradeuterio ketone. However, when the *trans,cis*-ketone **26** remained in contact with sodium methoxide in refluxing methanol solution for 1 day it was quantitatively converted to the trans,trans isomer **24**. Incidentally efforts to cyclize the former epimer to the tetracyclic olefin **29** with boron trifluoride failed indicating that the two epimers cannot be equilibrated with this catalyst.

Reduction of the tetracyclic olefin **31**, whose genesis by cis elimination of acetic acid within the acetate **23** lends further support for the configurational assignments already made, was first attempted by chemical means. When brought about by lithium in liquid ammonia a 2:1 mixture of dihydro ketones was obtained. The major product proved to be the hitherto unknown cis,cis isomer **35** while the minor product was the familiar *trans,trans*-ketone **24**. The ratio of products obtained has been postulated to reflect the relative stabilities of the two intermediate enolate anions.[25] In the case at hand epimer **32** with axial indole ring again seems to be more stable than the equatorially substituted epimer **33**. Since the cis,cis isomer **35** only was



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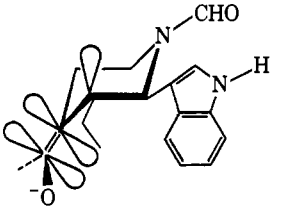
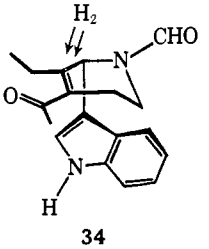


33

useful for further transformation to uleine (**1**) we investigated catalytic hydrogenations of olefin **31**. Our hope that the axially oriented indole group would direct hydrogen delivery from the catalyst surface to the top side of the molecule (arrows in **34**) was fully confirmed by experiment. Hydrogenation of **31** in methanol so-



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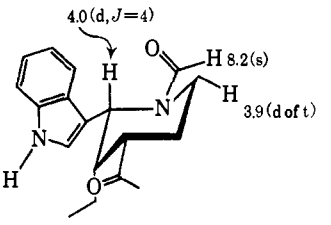
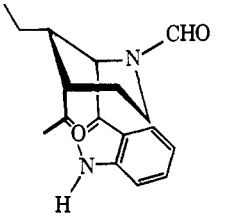
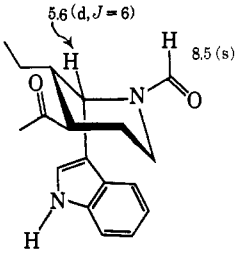
lution containing a trace of pyridine[26] over a palladium catalyst gave the *cis,cis*-ketone **35** and small amounts of the *cis,trans*-ketone **37**. The latter appeared to result from epimerization of the initially formed cis,cis isomer and complete epimerization was smoothly effected by sodium methoxide in methanol. The nmr spectra of



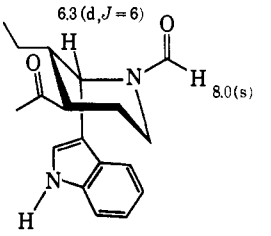
35



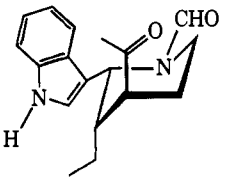
36



37a



37b



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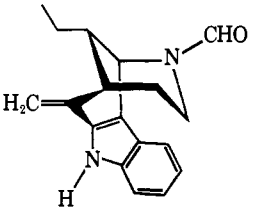
the epimers were distinctly different and allowed stereochemical assignments to be made. At room temperature the cis,cis epimer exists in single conformation **35** with indole ring and amide carbonyl cis-oriented. The cis,trans isomer is a mixture of the two rotamers **37a** and **b** while conformer **38**, not surprisingly, is undetectable. To avoid 1,3-diaxial indole–acetyl repulsion in conformer **36** the cis,cis isomer prefers conformation **35** in which these substituents occupy equatorial positions (*cf.* **24**). In analogy to the cis-disubstituted piperidone **18** the methine protons in the cis-disubstituted piperidines **35** and **37** appear as doublets. Finally, the steric disposition of the methyl group and the indole ring in the conformers **37a** and **37b** is approximately the same as it is in uleine (**1**) and indeed the spectrum of the cis,-trans isomer **37** exhibits a methyl triplet diamagnetically shifted to δ 0.71 from its normal position (at δ 1.22 in the case of the trans,cis epimer **26**) by the aromatic ring.

In complete analogy to the situation encountered in the synthesis of epiuleine (**2**) only the isomer with cis-oriented acetyl and indole groupings was capable of cyclization. Treatment of the cis,cis epimer **35** with boron trifluoride etherate in methylene chloride afforded the tetracyclic amide **39**. Reduction with lithium



39

(25) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, 82, 1512 (1960).
(26) H. J. Ringold, *ibid.*, 82, 961 (1960).

aluminum hydride completed the stereoselective total synthesis of racemic uleine (**1**).

Experimental Section

General. All reactions were carried out under a dry nitrogen atmosphere. Anhydrous magnesium sulfate was employed as the drying agent. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ultraviolet (uv) spectra were recorded on a Cary 14 spectrophotometer. Infrared (ir) spectra were measured on a Perkin-Elmer Model 237 grating spectrometer and on an Hitachi Model 247 grating spectrometer. Only intense peaks are reported, and the abbreviation sh refers to shoulder. Nuclear magnetic resonance (nmr) spectra were measured on Varian Associates T-60 and HA-100 instruments and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. The abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Mass spectra (ms) were determined at 70 eV on Hitachi RMU6D and CEC 21-104 instruments using the direct inlet system; only the molecular ion is reported, except when another ion is of equal or greater intensity. The abbreviation M refers to molecular ion. High-resolution mass spectra were measured on a CEC 21-110B instrument. Thin layer chromatograms (tlc) were made with Merck silica gel PF_{254} and Merck alumina PF_{254}. Merck silica gel PF_{254}, neutral Woelm alumina (Activity II), and Fisher Florisil (100–200 mesh) were used for column chromatography. Vapor phase chromatographic (vpc) analysis was performed on an F & M 720 instrument employing a 2 ft, 10% silicon rubber column.

1-Benzylmethylamino-3-hexanone (6). Benzylmethylamine (500 g, 4.12 mol) was gradually added to a stirred ice-cooled solution of 276 g (2.06 mol) of 1-chloro-3-hexanone (**5**)[7] in 1 l. of dry ether. The cooling was removed and the mixture was stirred at 30°. During the first hour a white precipitate formed, which was filtered off after 18 hr and washed with ether. The combined ethereal solution was washed twice with 2 *N* NaOH and dried over K_2CO_3. After evaporation of the ether, the crude reaction product was distilled giving free amine **6** of sufficient purity for further reactions (368 g, 82%). A small sample was distilled for analysis: bp 105–107° (0.2 mm); ir (liquid) 3000, 1700, 1490, 1445, and 1355 cm^{-1}; nmr (CCl_4) δ 0.85 (3 H, t, J = 7 Hz), 1.1–1.9 (2 H, m), 2.05 (3 H, s), 2.2–2.7 (6 H, m), 3.35 (2 H, s), 7.06 (5 H, s).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.41; H, 9.60

The hydrochloride when recrystallized from ethyl acetate–ethanol had mp 127–132°.

1-Methylamino-3-hexanone (7). The hydrochloride of **6** (244.5 g, 0.59 mol) was dissolved in 1200 ml of absolute ethanol and 24.5 g of 10% Pd–C was added under protection of nitrogen. Hydrogenation was complete after 5 hr. The catalyst was filtered off and the clear solution evaporated to give 187 g (100%) of hygroscopic crystals, mp 93–98°. This hydrochloride was treated with concentrated aqueous K_2CO_3 and the free base was extracted with ether. The ether extract was dried over K_2CO_3 and evaporated to give 146 g (100%) of pale yellow oil. It decomposed partially upon distillation, bp 48° (0.6 mm).

1-Methylformamido-3-hexanone (8). Acetic anhydride (340 g, 3.33 mol) and 153.5 g (3.33 mol) of 100% formic acid were heated 2 hr at 55°. 1-Methylamino-3-hexanone (146 g, 1.13 mol) was treated with formic acetic anhydride reagent and the mixture was stirred overnight at 20° and then evaporated under reduced pressure at 30°. The residue was treated with concentrated Na_2CO_3 solution and extracted with ethyl acetate. Drying and evaporation of the solvent followed by distillation gave 112.2 g (64%) of **8**: bp 85° (0.02 mm), 100° (0.05 mm); ir (liquid) 1710, 1678 cm^{-1}; nmr (CCl_4) δ 0.9 (3 H, t, J = 6.5 Hz), 1.1–1.9 (2 H, m), 2.73, 2.95 (3 H, 2 s), 3.45, 3.49 (2 H, 2 t), 7.88, 7.94 (1 H, 2 s).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62. Found: C, 61.30; H, 9.43.

Tricyclic Ketone 10. Indole (5.85 g, 50 mmol) and 7.85 g (50 mmol) of 1-methylformamido-3-hexanone (**8**) were dissolved in 120 ml of dry tetrahydrofuran and 8.43 g (55 mmol) of $POCl_3$ was gradually added with stirring at 20° over a period of 2 hr. After the reaction mixture had been stirred for 18 hr a solution of 20% KOH in ethanol was added until the brown reaction mixture turned to light yellow and was alkaline. Stirring was continued for 2 hr and the reaction mixture was shaken with an excess of 2 *N* HCl and chloroform. The chloroform layer was separated and reextracted with 2 *N* HCl and the combined acidic phase was washed with chloroform. The acidic extract was made alkaline by addition of solid K_2CO_3 (ice cooling) and the free base was extracted with chloroform to give 8 g of crystals. Recrystallization from $CHCl_3$–cyclohexane gave 5.6 g (40%) of **10**: mp 144–145°; ir ($CHCl_3$) 3460, 2765, 1705, 1450, 1410, 1365, 1330 cm^{-1}; uv max (EtOH) 291 nm (ϵ 4900); nmr ($CDCl_3$) δ 0.73 (3 H, t, J = 6 Hz), 1.0–1.8 (2 H, m), 2.05 (3 H, s), 2.2–3.5 (6 H, m), 6.8–8.1 (6 H, m).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86. Found: C, 74.62; H, 7.99.

1-Phthalimidohexan-3-one (11). To a slurry of potassium phthalimide (100 g, 0.55 mol) in dimethylformamide (500 ml, dried over molecular sieves), 1-chlorohexan-3-one (**5**) (57 g, 0.46 mol) was added, and the vigorously stirred mixture was heated to 100°. After 8 hr the mixture was cooled to room temperature; the precipitate was filtered, and the filtrate diluted with chloroform (400 ml) and water (1.4 l.). The aqueous layer was extracted with additional chloroform, and the combined organic extracts were washed with 0.2 *N* sodium hydroxide, dried, filtered, and concentrated *in vacuo* to give a light brown crystalline mass. Recrystallization from cyclohexane gave 85 g (87%) of the ketophthalimide **11**: mp 72.5–73.0°; ir ($CHCl_3$) 3020, 1772, and 1715 cm^{-1}; uv max (95% EtOH) 220 (ϵ 39,700), 233 (ϵ 12,300), 242 (ϵ 8400), and 290 nm (ϵ 1800); nmr ($CDCl_3$) δ 0.9 (t, 3, J = 3.5 Hz), 1.6 (t of q, 2, J = 3.5, 3.5 Hz), 2.5 (t, 2, J = 3.5 Hz), 2.9 (t, 2, J = 4 Hz), 4.0 (t, 2, J = 4 Hz), and 7.8 (m, 4); mass spectrum (70 eV) *m/e* (relative intensity) 245 (M, 33) and 160 (100).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.90; H, 6.14; N, 5.85.

1-Aminohexan-3-one Hydrochloride (12). The phthalimide **11** (20 g, 80 mmol) and constant boiling aqueous hydrochloric acid (226 ml) were vigorously stirred at reflux overnight. After cooling to room temperature the mixture was filtered and the filtrate extracted with chloroform. Concentration *in vacuo* of the aqueous layer yielded a tan crystalline mass which was recrystallized from ethanol–ether to give 12 g (98%) of the hydrochloride of **12**: mp 133.5–135.0°; ir (Nujol) 3430, 3330, 2660, 2560, 2460, and 1706 cm^{-1}.

Anal. Calcd for $C_6H_{14}NOCl$: C, 47.53; H, 9.30; N, 9.24. Found: C, 47.45; H, 9.45; N, 9.28.

***trans*-Piperidone 13.** To a stirred solution of the hydrochloride of **12** (4.6 g, 30 mmol) and indole-3-carboxaldehyde (3.7 g, 25 mmol) in 95% ethanol (250 ml), 1 *N* sodium hydroxide (30.9 ml) was slowly added to give a slightly basic solution (pH 9) which was stirred overnight at room temperature. The solution was concentrated *in vacuo* to about 20 ml (bath temperature below 40°), diluted with ethyl acetate, and extracted with 1 *N* hydrochloric acid. Solid potassium carbonate was used to neutralize the ice-bath-cooled aqueous extracts and the resulting solution was extracted with chloroform. The chloroform extracts were dried, filtered, and concentrated *in vacuo* to yield 4 g (66%) of the piperidone **13** as a thick oil: ir ($CHCl_3$) 3480, 3300, and 1705 cm^{-1}; nmr ($CDCl_3$) δ 0.8 (t, 3, J = 7 Hz), 1.45 (d of q, 2, J = 7, 2 Hz), 2.3–3.3 (m, 6), 4.05 (d, 1, J = 9 Hz), 6.9–7.5 (m, 4), 7.7 (m, 1), and 9.9 (broad s, 1).

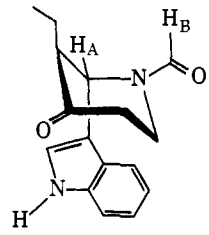
The hydrochloride showed mp 186–188°; ir (Nujol) 3230, 2800, 2640, 2550, and 1715 cm^{-1}; uv max (95% EtOH) 217 (ϵ 38,600), 273 (ϵ 6400), 281 (ϵ 6700), and 290 nm (ϵ 5700).

Anal. Calcd for $C_{15}H_{19}N_2OCl$: C, 64.62; H, 6.87; N, 10.05. Found: C, 64.44; H, 7.03; N, 10.15.

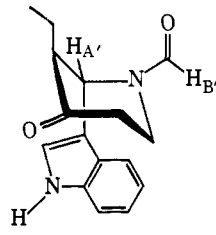
***N*-Formyl-*trans*-piperidone 15.** The piperidone **13** (13.5 g, 50 mmol) in tetrahydrofuran (20 ml, freshly distilled from $LiAlH_4$) was added to cold formic acetic anhydride, prepared from acetic anhydride (25.8 g, 0.28 mol) and 98% formic acid (11.6 g, 0.28 mmol), and the solution was stirred overnight at room temperature. After removal of the excess anhydride and acetic acid at reduced pressure, the residue was dissolved in saturated sodium bicarbonate and extracted with chloroform. The chloroform extracts were washed with 2 *N* hydrochloric acid, dried, and filtered. The filtrate was passed through a column of Florisil (50 g) which was eluted with additional chloroform. Concentration of the total eluent afforded a gum which crystallized upon trituration with toluene–cyclohexane. Recrystallization from ethyl acetate–cyclohexane gave 13 g (87%) of the *trans*-piperidone **15**: mp 148.5–150°; ir ($CHCl_3$) 3480, 1712, and 1665 cm^{-1}; ir (KBr) 3320, 1705 (sh), 1660, 1320, 1310, 965, and 945 cm^{-1}; uv max (95% EtOH) 216 (ϵ 38,000) 272 (ϵ 9600), 279 (ϵ 6600), and 289 nm (ϵ 5200); nmr (100 MHz) ($CDCl_3$) δ 1.02 (t, 3, J = 8 Hz), 1.8 (d of q, 2, J = 8, 3 Hz), 2.1–3.8 (m, 4.5), 4.5 (m, 0.5), 5.2 and 6.2 (2 s, 1), 7.0–7.7 (m, 5), 8.4 and 8.6 (2 s, 1), and 8.8 (broad d, 1); mass spectrum (80 eV) *m/e* (relative intensity) 270 (M, 100) and 227 (100).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.27; H, 6.75; N, 10.47.

Table I



15a



15b

Temp, °C	H_A	$H_{A'}$	H_B	$H_{B'}$
26	5.30	5.96	8.25	8.54
86	5.49	6.11	8.36	8.60
125	5.49 (broad)	6.11 (broad)	8.42 (broad)	
154	5.77 (broad)		8.40 (s)	
181	5.62 (s)		8.33 (s)	

Variable temperature spectra of the *N*-formyl-*trans*-piperidone **15** in DMF-d_7 are reported in Table I.

***N*-Formyl-*cis*-piperidone 18.** A portion (500 mg) of the crude reaction mixture resulting from the preparation of the *trans*-piperidone **15** was chromatographed on silica gel (40 g). Elution with 20% ether–methylene chloride first yielded 460 mg (93%) of the *trans*-piperidone **15** (mp 145–147.5°) followed by 35 mg (7%) of the *cis*-piperidone **18**: mp 196–198°; ir (KBr) 3160, 1705, 1645, 1260, and 865 cm^{-1}; nmr (100 MHz) ($CDCl_3$, DMSO-d_6) δ 1.0 (t, 3, J = 8 Hz), 1.5 (d of q, 2, J = 8, 2 Hz), 1.9–4.0 (m, 4.5), 4.5 (m, 0.5), 5.7 and 6.5 (2 d, 1, J = 5 Hz), 7.0–7.8 (m, 5), 8.2 and 8.6 (2 s, 1), and 10.6 (broad d, 1).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.92; H, 6.58; N, 10.19.

Epimerization of *trans*-Piperidone 15 to *cis*-Piperidone 18. A solution of pure *trans*-piperidone **15** (80 mg, 0.3 mmol) and anhydrous sodium acetate (60 mg, 0.74 mmol) in absolute methanol (20 ml) was allowed to reflux for 4 days. The solvent was removed *in vacuo;* the residue was dissolved in chloroform and filtered through a small pad of Florisil. Concentration of the eluent afforded 75 mg of a mixture of *trans*- and *cis*-piperidones: nmr (100 MHz) ($CDCl_3$) δ 1.0 (t, J = 7 Hz), 1.81 (d of q, J = 7, 3 Hz), 2.1–3.8 (m), 4.45 (m), 5.16 (s), 5.6 (d, J = 6 Hz), 6.21 (s), 6.52 (d, J = 6 Hz), 6.95–8.0 (m), 8.15 (s), 8.34 (s), 8.58 (s), and 8.94 (broad d). Integration of the singlets at 5.16 and 6.21 and the doublets at 5.6 and 6.52 indicated a 70:30 mixture of trans–cis.

The epimerization was repeated with this same material for an additional 4 days. Integration of the methine signals in the nmr spectrum (100 MHz) ($CDCl_3$) indicated a 69:31 mixture of trans–cis.

Separation on preparative tlc (silica gel PF_{254} eluting twice 10 cm with 20% ether–methylene chloride) followed by crystallization from ethyl acetate–cyclohexane afforded the *trans*-piperidone **15** (mp 147–149°) and the *cis*-piperidone **18** (mp 195–197°). Identity with authentic samples was confirmed by ir spectra (KBr).

Epimerization of *cis*-Piperidone 18 to *trans*-Piperidone 15. A solution of pure *cis*-piperidone **18** (45 mg, 0.17 mmol) and anhydrous sodium acetate (30 mg, 0.4 mmol) in absolute methanol (10 ml) was maintained at reflux for 7 days. Work-up as above and integration of the methine signals in the nmr spectrum indicated a 72:28 mixture of trans–cis. Separation by preparative tlc, followed by crystallization from ethyl acetate–cyclohexane, afforded the *trans*-piperidone **15** (mp 147–149°) and the *cis*-piperidone **18** (mp 195–198°), whose ir spectra (KBr) were identical with those of authentic samples.

Unsaturated Ketone 20. The *trans*-piperidone **15** (300 mg, 1.1 mmol) in tetrahydrofuran (9 ml, freshly distilled from $LiAlH_4$) was added to a suspension of lithium acetylide–ethylene diamine complex[17] (310 mg, 3 mmol) in tetrahydrofuran (6 ml, freshly distilled from $LiAlH_4$), and the mixture was stirred overnight at room temperature. The mixture was poured onto cold, saturated ammonium chloride and extracted with ethyl acetate. After being washed with saturated sodium chloride the organic extracts were dried, filtered, and concentrated *in vacuo* to give an oil which was chromatographed on silica gel (40 g). Elution with 20% ether–methylene chloride gave 170 mg (63%) of a mixture of *cis*- and *trans*-piperidones **18** and **15** and elution with 18% methanol–chloroform followed by crystallization from chloroform–cyclohexane afforded 84 mg (64% based on unrecovered starting material) of the unsaturated ketone **20**: mp 171.5–173.5 ; ir (Nujol) 3370, 3200, 1665, 1635, 1608, and 1235 cm^{-1}; uv max (95% EtOH) 223 (ε 26,600), 277 (ε 7600), and 351 nm (ε 8500); nmr (100 MHz) ($CDCl_3$, DMSO-d_6) δ 1.14 (t, 3, J = 7.5 Hz), 2.67 (q, 2, J = 7.5 Hz), 3.17 (t, 2, J = 6 Hz), 3.69 (d of t, 2, J = 6, 6 Hz), 6.82 (m, 1), 7.19–7.88 (m, 6), 8.16 (d, 1, J = 2 Hz), and 10.36 (broad s, 1); mass spectrum (80 eV) *m/e* 270 (M).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.87; H, 6.79; N, 10.36.

Ethynylcarbinol 21. *tert*-Butyl alcohol (100 ml, distilled from sodium hydride) and potassium *tert*-butoxide (20 g, 27 mmol) were added in three portions to tetrahydrofuran (300 ml, freshly distilled from $LiAlH_4$) maintained at −20° (Dry Ice–carbon tetrachloride bath) into which acetylene gas (purified by passing through concentrated sulfuric acid) had been bubbled for 1 hr. After 1 additional hr of stirring with continued addition of acetylene the *trans*-piperidone **51** (7.5 g, 26 mmol) in tetrahydrofuran (100 ml, freshly distilled from $LiAlH_4$) was added dropwise over 1.5 hr, whereupon the solution was warmed to 0° (ice–salt bath). Stirring and addition of acetylene were continued for 11 hr. The solution was warmed to 25° and carefully hydrolyzed with saturated ammonium chloride. After reducing the organic layer *in vacuo* to *ca.* 50 ml, it was recombined with the aqueous layer and extracted with chloroform. The chloroform extracts were dried, filtered, and concentrated *in vacuo* and the resulting oil dissolved in a few milliliters of chloroform. From this solution 3.3 g of pure ethynyl carbinol **21** crystallized. After filtration, 0.9 g of the unsaturated ketone **20** crystallized. The mother liquors were then chromatographed on silica gel (40 g). Elution with 12% methanol–chloroform consecutively afforded, after crystallization from chloroform–cyclohexane, 0.9 g of the unsaturated ketone **20** (total yield 1.8 g, 24%) and, after crystallization from ethyl acetate–cyclohexane, 0.8 g of the ethynyl carbinol **21** (total yield 4.1 g, 50%): mp 201–202.5°; ir (Nujol) 3295, 1670, and 1285 cm^{-1}; uv max (95% EtOH) 218 (ε 32,100), 273 (ε 4900), 281 (ε 5200), and 289 nm (ε 4800); nmr (100 MHz) (DMF-d_7) δ 0.64 and 0.70 (2 t, 3, J = 8 Hz), 1.30 (m, 2), 1.8–2.6 (m, 2), 3.18 (t of d, 1, J = 13, 3 Hz), 3.56 (s, 1), 3.72 (m, 1), 4.56 (d of t, 0.6, J = 13, 3 Hz), 4.64 (d, 1, J = 11 Hz), 5.65 and 6.02 (2 s, 0.4), 5.83 (broad s, 1, exchanges with D_2O), 7.1–7.9 (m, 6), 7.95 and 8.11 and 8.36 (3 s, 1, ratio 6:3:1); mass spectrum (70 eV) *m/e* 296 (M).

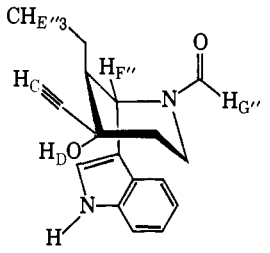
Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.73; H, 6.94; N, 9.61.

Variable temperature nmr spectra of ethynylcarbinol **21** in DMF-d_7 are reported in Table II.

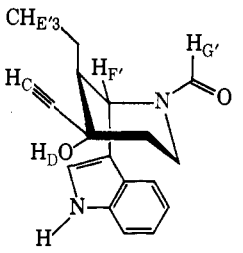
Both possible rotational isomers for the conformer with an axial indole are present; the singlets at 5.65 and 6.02 are due to the methine proton ($H_{F'}$ and $H_{F''}$, respectively) and the singlets at 8.11 and 8.36 are due to the amide proton ($H_{G''}$ and $H_{G'}$, respectively). The major geometrical form present, however, is the conformer with an equatorial indole, and only the rotational isomer with the amide carbonyl trans to the indole is present. The amide proton (H_G) appears as a singlet at 7.95, while the the methine proton (H_F) appears at 4.64 as a doublet (J_{aa} = 11 Hz) reminiscent of the Mannich product **21**. The methylene protons H_A and H_B—both deshielded by the amide carbonyl—appear at 3.8 (t of d. $J_{aa} = J_{geminal}$) and at 4.56 (d of t, $J_{ae} = J_{ee}$), respectively.

It is noted from the temperature study that the chemical shifts and couplings of $H_{F''-F}$, $H_{G''-G}$, H_A, H_B, the acetylenic proton, and the hydroxyl proton were temperature dependent. The signals due to the methyl protons of the ethyl group appeared as two overlapping triplets at room temperature, and these coalesced to one triplet upon heating. The first important change, appearing by 51°, was the collapse of the rotational barrier about the amide bond in forms **21a** and **21b** resulting in a singlet at 8.10 for the amide proton. Following a general broadening of all pertinent signals from 60 to 100°, coalescence was apparent by 106° as the interconversion of the three forms became more rapid than the nmr time scale. Finally, at 152°, the averaged spectrum of the rapidly equilibrating isomers was clearly defined (the hydroxyl proton was now under the doublet at 4.90). The most important signals were the singlet at 8.04 (amide proton), the doublet at 4.90 (methine proton $H_{F''-F}$), and the septet at 3.36 (methylene proton H_A). If a 60:40 mixture for **21c**:**21a** + **21b** is assumed and a limiting value of 1 Hz for the coupling of the diequatorial protons in **21a** and **21b** is used, one could predict a coupling of 7 Hz for proton $H_{F''-F}$ under rapidly equilibrating conditions. The observed coupling of 8 Hz is in excellent agreement. The septet would be due to protons which, time averaged, are 60% axial and

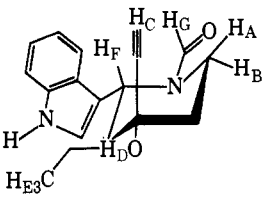
Table II



21a



21b



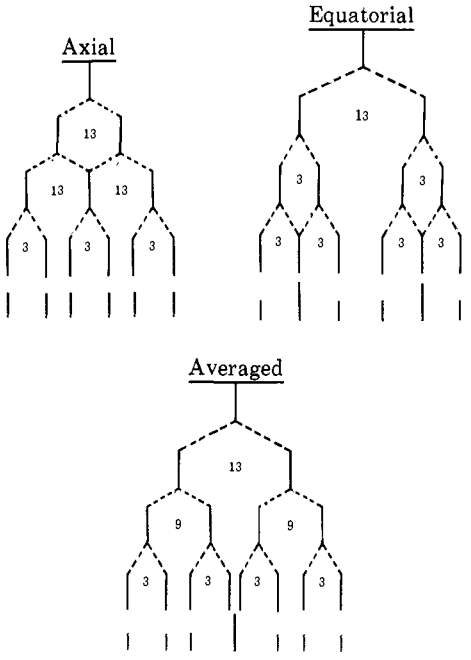
21c

T, °C	H_A	H_B	H_C	H_D	H_E	$H_{E'}$	H_F	$H_{F'}$	$H_{F''}$	H_G	$H_{G'}$	$H_{G''}$
25	t of d, 3.18 (J = 13, 3 Hz)	d of t, 4.56 (J = 13, 3 Hz)	3.56	5.83	0.64 (t)	0.70 (t)	4.64 (d, J = 11 Hz)	5.65	6.02	7.95	8.36	8.11
44	t of d, 3.18 (J = 13, 3 Hz)	d of t 4.56 (J = 13, 3 Hz)	3.48	5.70	0.69		4.58 (d, J = 11 Hz)	5.63	6.01	7.97	8.32 (broad)	8.10
51	t of d, 3.18 (J = 13, 3 Hz)	d of t 4.56 (J = 13, 3 Hz	3.46	5.65	0.69	0.77	4.58 (d, J = 11 Hz)	6.00		7.97	8.10	
60	3.23 (broad m)	4.52 (broad d)	3.43	5.60	0.71		4.58 (d, J = 11 Hz)	5.98		7.98	8.09	
73	3.25 (broad m)	4.48 (broad d)	3.36	5.49	0.73 (broad)		4.65 (broad d)			8.00	8.08	
84	3.30 (broad m)	4.4 (broad s)	3.30	5.40	0.73 (broad)		4.68 (broad s)			8.02	8.07	
106	3.31 (t of d)	4.38 (broad d)	3.24	5.24	0.81 (t)		4.88 (broad s)			8.04	8.05	
126	3.36 (t of d)	4.32 (d of t)	3.19	5.10	0.81 (t)		4.88 (broad d)				8.04	
152	7 lines 3.36 (J = 13, 9, 3 Hz)	4.30 (d of t)	3.11	4.90	0.81 (t)		4.90 (d, J = 8 Hz)				8.04	

$$\frac{0.6(11\text{ Hz}) + 0.4(1\text{ Hz})}{1.0} = 7\text{ Hz}$$

40% equatorial. Chart I shows the splitting pattern for each case, as well as the averaged pattern. If 1 Hz is considered the limiting value for resolution, one would predict an evenly spaced, seven-line pattern with the center line twice the magnitude of the other six. These data confirm the original hypothesis.

Chart I



Acetoxy Ketone 23 and Hydroxy Ketone 22. A solution of the ethynylcarbinol **21** (1.0 g, 3.4 mmol) and mercuric acetate (1.5 g, 4.9 mmol) in glacial acetic acid (60 ml) was stirred at room temperature for 2 days. After addition of ethyl acetate, hydrogen sulfide was bubbled into the solution, and the precipitated mercurous sulfide was then removed by filtration through a pad of Celite. The precipitate was washed with additional ethyl acetate and the combined filtrates were concentrated *in vacuo*. The crude product, dissolved in chloroform, was filtered through Florisil (18 g) eluted with 40% ethyl acetate–chloroform. After the eluent was concentrated *in vacuo* it was chromatographed on alumina (50 g). Elution with 70% chloroform–benzene afforded 0.8 g (67%) of the amorphous α-acetoxy ketone **23**: ir ($CHCl_3$) 3480, 1735, 1718, 1670, and 1240 cm^{-1}; uv max (95% EtOH) 221 (ϵ 34,900), 275 (ϵ 5300), 282 (ϵ 5800) and 290 nm (ϵ 5100); nmr (100 MHz) ($CDCl_3$) δ 1.2 (s, 3), 1.4 (t, 3, J = 10 Hz), 1.8–2.3 (m, 3), 2.1 (s, 3), 2.6–2.9 (m, 2), 3.4–3.8 (m, 1.5), 4.5 (m, 0.5), 5.1 and 6.1 (2 s, 1), 6.9–7.8 (m, 5), 8.2 and 8.4 (2 s, 1), and 8.5 (broad d, 1); high-resolution mass spectrum 356.17073 (M).

Continued elution with the same solvent afforded, after crystallization from ethyl acetate–cyclohexane, 120 mg (11%) of the α-hydroxy ketone **22** (as the cyclohexane solvate): mp 105–107°; ir (Nujol) 3360, 1715, and 1650 cm^{-1}; uv max (95% EtOH) 219 (ϵ 35,700), 273 (ϵ 5900) 282 (ϵ 6400), and 289 nm (ϵ 5100); nmr (acetone-d_6) δ 0.9 (t, 3, J = 7 Hz), 1.1–1.7 (m, 3), 2.1 (s, 3), 3.0 (m, 2), 3.6 (m, 2.5), 4.5 (m, 0.5), 5.1 and 6.0 (2 s, 1), 6.9–7.8 (m, 6), 8.1 and 8.2 (2 s, 1).

Anal. Calcd for $C_{18}H_{22}N_2O_3 \cdot C_6H_{12}$: C, 72.33; H, 8.60; N, 7.03. Found: C, 71.94; H, 8.66; N, 6.88.

***trans,trans*-Methyl Ketone 24 from the Acetoxy Ketone 23.** The acetoxy ketone **23** (300 mg, 0.84 mmol) in tetrahydrofuran (4 ml, freshly distilled from $LiAlH_4$) was added in 0.5 min to a stirred solution of lithium (100 mg, 14 mg-atom) in liquid ammonia (100 ml). After an additional 1.5 min the reaction was quenched with a solution of bromobenzene in toluene. After addition of unsaturated ammonium chloride, the ammonia was removed by evaporation. The residue was diluted with water, extracted with ethyl acetate, and the extracts were dried, filtered, and concentrated *in vacuo* to give a glass. This was dissolved in chloroform and filtered through Florisil (4 g). Elution with 20% ethyl acetate–chloroform and concentration of the eluent afforded a glass which crystallized from ether to give 180 mg (72%) of the ketone **24**. An analytical sample was recrystallized from ethyl acetate–cyclohexane: mp 157.5–158.5°; ir ($CHCl_3$) 3480, 1712, 1660, and 1245 cm^{-1}; uv max (95% EtOH) 218 (ϵ 42,400), 273 (ϵ 6400), 282 (ϵ 6800), and 289 nm (ϵ 6200); nmr (100 MHz) ($CDCl_3$) δ 0.8 (t, 3, J = 6 Hz), 1.35–1.8 (m, 5), 2.06 (s, 3), 2.64 (m, 1), 3.17 (d of d of d, 1, J = 14, 10, 4 Hz),

4.34 (d of t, 1, J = 14, 4 Hz), 4.52 (d, 1, J = 9 Hz), 7.0–7.6 (m, 5), 7.91 (s, 1) and 8.84 (broad s, 1); mass spectrum (70 eV) m/e 298 (M).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.14; H, 7.47; N, 9.37.

Deuterium Exchange with Methyl Ketone 24. A solution of ketone **24** (12 mg, 0.04 mmol) and anhydrous sodium acetate (8 mg) in methanol-d_1 (12 ml) was maintained at reflux for 4 days. The cooled solution was concentrated *in vacuo* and the residue was taken up in chloroform. Filtration through a pad of Celite and concentration of the filtrate afforded an oil which crystallized from ether to give 10 mg of the tetradeuterioketone: mp 150–153°; ir ($CHCl_3$) 3480, 1710, 1670 and 1210 cm^{-1}; mass spectrum (70 eV) m/e 302 (M), 256, 213, 199, and 170.

***trans,trans*-Methyl Ketone 24 from the Hydroxy Ketone 22.** The hydroxy ketone **22** (40 mg, 0.13 mmol) in toluene (2 ml) was added in 0.5 min to a solution of calcium (25 mg, 0.62 mmol) in liquid ammonia (15 ml). After an additional 1.5 min a solution of bromobenzene in toluene was added to quench the reaction, producing a yellow-brown solution. After evaporation of the ammonia the residue was diluted with water, extracted with chloroform and the extracts were dried, filtered, and concentrated *in vacuo* to give an oil. Purification by preparative tlc (silica gel PF_{254}, eluted with 5% methanol–chloroform) yielded 7 mg (18%) of the ketone **24**, mp 156–158°, whose ir spectrum was identical with that of an authentic sample.

Tetracyclic Formamide 29. To an ice-cold solution of the ketone **24** (100 mg, 0.33 mmol) in methylene chloride (25 ml), boron trifluoride ethereate (0.7 ml) was slowly added, and the mixture was stirred at room temperature for 15 hr. The solution was poured onto cold, saturated ammonium chloride, neutralized with solid potassium carbonate, and extracted with methylene chloride. The extracts were dried, filtered, and concentrated *in vacuo* to give a glass which was dissolved in 50% benzene–chloroform and filtered through Florisil (2.5 g). Concentration of the filtrate followed by crystallization from ether gave 66 mg (70%) of the amide **29**. An analytical sample was recrystallized from ethyl acetate: mp 240–242°; ir ($CHCl_3$) 3490, 1665, 1620, and 880 cm^{-1}; uv max (95% EtOH) 209 (ϵ 23,300), 241 (ϵ 10,700), and 308 nm (ϵ 16,300); nmr (100 MHz) ($CDCl_3$, DMSO-d_6) δ 1.05 (t, 3, J = 7 Hz), 1.4–3.2 (m, 7.5), 4.05 (m, 0.5), 4.78 and 5.80 (2 s, 1), 5.02 (d, 1, J = 2 Hz), 5.55 (d, 1, J = 2 Hz), 7.0–7.6 (m, 4), 8.02 and 8.25 (2 s, 1), and 10.40 (broad d, 1); mass spectrum (70 eV) m/e 290 (M).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.65; H, 7.24; N, 9.80.

Racemic Epiuleine (3). A solution of lithium aluminum hydride in glyme (2.0 ml, 2% $LiAlH_4$) was added to the amide **29** (50 mg, 0.18 mmol) in glyme (10 ml, freshly distilled from $LiAlH_4$) and the solution was stirred 1.5 hr at room temperature. Careful addition of methanol was followed by addition of water (2 ml) to precipitate the inorganic salts. After stirring 10 min the mixture was filtered through a pad of Celite and the precipitate was washed with chloroform. The organic layer was dried, filtered, and concentrated *in vacuo* to give a glass which was dissolved in 5% chloroform–benzene and chromatographed on alumina (1.5 g). Elution with the same solvent mixture and concentration of the eluent afforded 40 mg (84%) of crystalline racemic epiuleine (**3**): mp 122–129° (lit. 125–132°)[6]; ir ($CHCl_3$) 3480, 3070, 3010, 2970, 1635, 1615, 1460, 1265, 870, and 815 cm^{-1}; uv max (95% EtOH) 210 (ϵ 22,200), 241 (ϵ 11,300), 308 (ϵ 17,400), and 315 nm (ϵ 17,400); nmr ($CDCl_3$) δ 1.05 (t, 3, J = 7 Hz), 1.25–3.2 (m, 7), 2.36 (s, 3), 3.7 (m, 1), 4.2 (s, 1), 5.0 (s, 1), 5.3 (s, 1), 7.1–7.7 (m, 4), and 8.55 (broad s, 1); mass spectrum (70 eV) m/e 266 (M).

Unsaturated Ketones 30 and 31. A solution of the acetoxy ketone **23** (100 mg, 0.28 mmol) in toluene (30 ml) was passed through a Pyrex column 10 cm in diameter packed with 7-cm glass beads, 7-cm glass helices, and another 7-cm glass beads (all previously washed with dilute ammonium hydroxide and then with water) heated to 470° as a slow stream of nitrogen was passed through the system from above. The product was collected at the bottom in a flask cooled by an isopropyl alcohol–Dry Ice bath. After washing the column with additional toluene (30 ml), the solvent was removed *in vacuo*. The crude product (650 mg) from eight runs was chromatographed on silica gel (55 g). Elution with 20% ether–methylene chloride yielded an oil which was crystallized from ether to give 180 mg (26%) of the trisubstituted unsaturated ketone **30**. An analytical sample was recrystallized from ethyl acetate–cyclohexane: mp 160–162°; ir ($CHCl_3$) 3480, 1670, 1640, and 1205 cm^{-1}; uv max (95% EtOH) 219 (ϵ 51,100), 273 (ϵ 6100), 281 (ϵ 6400), and 289 nm (ϵ 5400); nmr (100 MHz) ($CDCl_3$) δ (t, 3, J = 8 Hz) 1.15–1.9 (m, 2), 2.35 (s, 3), 3.2–3.8 (m, 2), 4.0 (d of d, 0.4, J = 18, 4 Hz), 4.82 (d of d, 0.6, J = 18, 4 Hz), 5.2 and 6.25 (2 s, 1), 6.78 (m, 1), 7.0 (m, 1), 7.2–7.9 (m, 4), 8.6 and 8.8 (2 s, 1, and 8.85 (broad s, 1); mass spectrum (70 eV) (relative intensity) 296 (M, 100), 172 (49).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.63; H, 6.88; N, 9.43.

Further elution with the same solvent mixture yielded 300 mg (43%) of the amorphous tetrasubstituted unsaturated ketone **31** (sublimed to a glass at 130° (0.05 mm)): ir ($CHCl_3$) 3480, 1685 (sh) and 1670 cm^{-1}; uv max (95% EtOH) 217 (ϵ 29,300), 242 (ϵ 7300), 272 (ϵ 5900), 278 (ϵ 5700), 282 (ϵ 5600), and 289 nm (ϵ 4900); nmr (100 MHz) ($CDCl_3$) δ 1.0 (t, 3, J = 7 Hz), 1.7–2.8 (m, 4), 2.33 (s, 3), 3.5 (m, 2), 5.5 and 6.45 (2 s, 1), 7.2–8.8 (m, 5), 8.27 and 8.82 (2 s, 1) and 8.95 (broad s, 1): mass spectrum (70 eV) m/e (relative intensity) 296 (M, 100) and 253 (100); high resolution ms 296.15268 (M).

***trans,trans*-Methyl Ketone 24 and *trans,cis*-Methyl Ketone 26 by Catalytic Reduction of 30.** The unsaturated ketone **30** (150 mg, 0.5 mmol) and 10% Pd–C (50 mg) in methanol (25 ml) were stirred under hydrogen (1 atm) for 15 hr. The catalyst was filtered and concentration of the filtrate afforded a mixture of saturated ketones. Chromatography on silica gel (12 g) allowed their separation. Elution with 25% ether–methylene chloride gave 60 mg (40%) of the amorphous ketone **26**: ir ($CHCl_3$) 3490, 1710, 1668, 1435, 1165, and 1045 cm^{-1}; uv max (95% EtOH) 219 (ϵ 33,200), 273 (ϵ 5100), 281 (ϵ 5400), and 290 nm (ϵ 4800); nmr ($CDCl_3$) δ 1.22 (t, 3, J = 7 Hz), 1.5–2.1 (m, 4), 2.2 (s, 3), 2.6–3.6 (m, 3.5), 4.4 (m, 0.5), 5.1 and 6.1 (2 s, 1), 7.0–7.8 (m, 5), 8.35 and 8.7 (2 s, 1), and 9.2 (broad d, 1); high-resolution mass spectrum 298.16721 (M).

Continued elution with the same solvent mixture gave 63 mg (42%) of the ketone **24**, mp 156–158°, whose ir spectrum was identical with that of an authentic sample.

Epimerization of Ketone 26 to Ketone 24. A solution (5 ml) of sodium methoxide in methanol, prepared from sodium (125 mg) and methanol (50 ml), was added to a stirred solution of the ketone **26** (12 mg, 0.04 mmol) in methanol (5 ml) and the resulting solution was heated at reflux for 1.5 days. The cooled solution was concentrated *in vacuo* and the residue taken up in chloroform. Filtration through a pad of Celite followed by concentration of the filtrate afforded an oil which crystallized from ether to give 9 mg of the ketone **24**, mp 155–158°, identical as judged by its ir spectrum with authentic material.

***cis,cis*-Methyl Ketone 35 and *cis,trans*-Methyl Ketone 37 from Catalytic Reduction of 31.** The unsaturated ketone **31** (250 mg, 0.8 mmol) and 10% Pd–C (70 mg) in a solution of methanol (25 ml) and pyridine (5 drops) were stirred under hydrogen (1 atm) for 35 hr. The catalyst was filtered and concentration of the filtrate afforded a mixture of the saturated ketones **35** and **37** which was separated by chromatography on silica gel (20 g). Elution with 10% benzene–ethyl acetate gave 95 mg (38%) of the amorphous ketone **35**: ir ($CHCl_3$) 3500, 1710, 1650, and 1180 cm^{-1}; uv max (95% EtOH) 218 (ϵ 37,900), 273 (ϵ 5900), 280 (ϵ 6200), and 289 nm (ϵ 5500); nmr ($CDCl_3$) δ 1.0 (t, 3, J = 7 Hz), 1.5–2.8 (m, 6), 2.4 (s, 3), 3.7 (m, 1), 3.9 (d of t, 1, J = 17, 5 Hz), 4.0 (d, 1, J = 5 Hz), 7.1–7.7 (m, 5), 8.18 (s, 1), and 9.3 (broad s, 1); high-resolution mass spectrum 298.16951 (M).

Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.17; H, 7.53; N, 9.31.

Continued elution with the same solvent mixture yielded 105 mg (42%) of the amorphous ketone **37**: ir ($CHCl_3$) 3500, 1712, 1660, 1460, and 1440 cm^{-1}; uv max (95% EtOH) 218 (ϵ 32,200), 273 (ϵ 5200), 281 (ϵ 5500), and 289 nm (ϵ 5000); nmr ($CDCl_3$) δ 0.71 (t, 3, J = 7 Hz), 1.1–1.6 (m, 4), 1.6–1.9 (m, 1), 2.2 (s, 3), 2.6–3.4 (m, 2.6), 4.2 (m, 0.4), 5.6 and 6.3 (2 d, 1, J = 6 Hz), 7.0–7.9 (m, 5), 8.0 and 8.5 (s 2, 1), and 9.2 (broad d, 1); high-resolution mass spectrum 298.16867.

Epimerization of Ketone 35 to Ketone 37. A solution (5 ml) of sodium methoxide in methanol, prepared from sodium (125 mg) and methanol (50 ml), was added to a stirred solution of the ketone **35** (10 mg, 0.04 mmol) in methanol (5 ml), and the resulting solution was heated at reflux overnight. The cooled solution was concentrated *in vacuo* and the residue taken up in chloroform. Filtration through a pad of Celite followed by concentration of the filtrate afforded 8 mg of the ketone **37**, identical by ir and tlc behavior with authentic material.

***trans,trans*-Methyl Ketone 24 and *cis,cis*-Methyl Ketone 35 from Reduction of the Tetrasubstituted Unsaturated Ketone 31.** The unsaturated ketone **31** (50 mg, 0.16 mmol) in tetrahydrofuran (3 ml, freshly distilled from $LiAlH_4$) was added to a solution of lithium (25 mg, 4 mmol) in liquid ammonia (50 ml). After 2 min the reac-

tion was quenched with a solution of bromobenzene in toluene, giving a deep-red solution. After addition of saturated aqueous ammonium chloride the ammonia was removed by evaporation. The residue was diluted with water, extracted with ethyl acetate, and the extracts were dried, filtered, and concentrated *in vacuo* to give an oil. This was dissolved in chloroform and filtered through Florisil (2 g). Elution with chloroform removed less polar impurities and elution with 25% ethyl acetate–chloroform yielded 40 mg of a 2:1 mixture of ketones **24** and **35**. Separation by preparative tlc (silica gel PF_{254}) developed twice, 10 cm with 20% ether–methylene chloride) afforded 10 mg (25%) of ketone **35**, whose ir was identical with that of authentic material, and 18 mg (47%) of ketone **24**, mp 156–158°, identical by its ir spectrum with an authentic sample.

Tetracyclic Formamide 39. To an ice-bath-cooled solution of the ketone **35** (30 mg, 0.1 mmol) in methylene chloride (40 ml), boron trifluoride etherate (0.35 ml) was slowly added and the resulting red solution was stirred 11 hr at room temperature. The solution was poured onto cold, saturated ammonium chloride, neutralized with solid potassium carbonate, and extracted with methylene chloride. The extracts were dried, filtered, and concentrated *in vacuo* to give a glass which was dissolved in 50% benzene–chloroform and filtered through Florisil (0.5 g). Elution with additional solvent and concentration of the filtrate yielded a glass which crystallized from ether to give 20 mg (72%) of the amide **39**. An analytical sample was recrystallized from ethyl acetate–cyclohexane: mp 264–266°; ir ($CHCl_3$) 3480, 1660, 1620, 1455, 1435, and 880 cm^{-1}; uv max (95% EtOH) 209 (ϵ 24,800), 240 (sh) (ϵ 13,100), and 308 nm (ϵ 19,200); nmr (100 MHz) ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz), 1.2–1.58 (m, 2), 1.6–2.2 (m, 4), 2.9–3.4 (m, 1.6), 3.9 (m, 0.4), 4.88 and 5.88 (2 d, 1, J = 4 Hz), 5.12 (d, 1, J = 2 Hz), 5.42 (d, 1, J = 2 Hz), 7.1–7.8 (m, 4), 8.02 and 8.40 (2 s, 1), and 8.40 (broad s, 1).

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.16; H, 7.13; N, 9.83.

Racemic Uleine. A solution of lithium aluminum hydride in glyme (3.5 ml, ~2% $LiAlH_4$) was added to the amide **39** (35 mg, 0.13 mmol) in glyme (20 ml, freshly distilled from $LiAlH_4$) and the mixture was stirred at room temperature for 2.5 hr. Careful addition of methanol was followed by addition of water (2 ml) to precipitate the inorganic salts. After stirring 10 min the mixture was filtered through a pad of Celite and the precipitate was washed with chloroform. The organic layer was dried, filtered, and concentrated *in vacuo* to give a glass which was chromatographed on alumina (1 g). Elution with 10% chloroform–benzene followed by concentration of the eluent yielded 24 mg (73%) of crystalline racemic uleine (**1**) which was recrystallized from methanol: mp 62–74° (methanol solvate) and 140–148° (lit.[5] mp 61–92°); ir ($CHCl_3$) 3480, 3080, 3005, 1635, 1615, 1460, 1450, 1255, 880, and 845 cm^{-1}; uv max (95% EtOH) 209 (ϵ 24,100), 240 (sh) (ϵ 12,100), 308 (ϵ 18,200), and 315 nm (ϵ 18,000); nmr ($CDCl_3$) δ 0.88 (m, 3,) 1.1–3.0 (m, 8), 2.28 (s, 3), 4.07 (d, 1, J = 2 Hz), 4.95 (s, 1), 5.15 (s, 1), 7.0–7.8 (m, 4), and 8.25 (broad s, 1); mass spectrum (70 eV) *m/e* 266 (M).

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The Polonovski Transformation of (+)-Nupharidine. A Study of the Stereochemistry and Utility in Synthesis[1,2]

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Abstract: (+)-Nupharidine has been converted by the Polonovski reaction to Δ^6-dehydrodeoxynupharidine. The latter in turn was transformed to (−)-deoxynupharidine, (−)-7-epideoxynupharidine, and (−)-nupharamine. Treatment of nupharidine-6β,7β-d_2 under Polonovski conditions produced Δ^6-dehydrodeoxynupharidine-6-d_1, thus illustrating that the 6α-hydrogen is eliminated. Since an X-ray diffraction study of nupharidine hydrobromide had demonstrated the presence of a cis-fused quinolizidine *N*-oxide, the Polonovski elimination had occurred trans in the labeled nupharidine.

The selective conversion of a quinolizidine type *Nuphar* alkaloid, such as deoxynupharidine, **1a**, or one of its derivatives, to the Δ^6-dehydrodeoxynupharidine, **2a**, was of interest for a number of reasons. Foremost was the potential of using this enamine as an intermediate in the preparation of isotopically labeled deoxynupharidine which would be employed in biogenetic and mass spectral studies. Second, the enamine **2a** offered the potential for converting the quinolizidine type to the less abundant piperidine type *Nuphar* alkaloids,[4] **3**, through cleavage of the enamine double bond.

The abundant, naturally occurring *N*-oxide nupharidine was regarded as a possible starting point to achieve the selective introduction of a double bond into ring B at the C-6 position. Should nupharidine possess a trans-fused, quinolizidine *N*-oxide system as in **4**, a point which was uncertain at the outset, there would be only a single hydrogen cis to the *N*-oxide oxygen atom.

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(2) A preliminary account of a portion of this work has been disclosed: E. Auer and R. T. LaLonde, Abstracts of Papers, 157th Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, ORGN 150.

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(4) In earlier correlations piperidine alkaloids have been converted to the quinolizidine type, *cf.* nupharamine[5] and nuphamine[6] to deoxynupharidine and 7-epideoxynupharidine.

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