Geissovelline, a New Alkaloid from *Geissospermum vellosii*

RICHARD E. MOORE*[1]

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

HENRY RAPOPORT

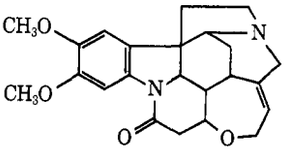
Department of Chemistry, University of California, Berkeley, California 94720

Received August 30, 1972

Geissovelline, $C_{23}H_{30}N_2O_4$, is a new dihydroindole alkaloid from the bark extract of Brazilian *Geissospermum vellosii*. Based on the chemistry of the unusual functional groups, *e.g.*, a tertiary nitrogen which interacts transannularly with an α,β-unsaturated ketone carbonyl, structure **3** is proposed for geissovelline and is supported by complete analyses of proton and carbon-13 nmr spectra of deacetylgeissovelline (**28**). The reactions of this alkaloid are unparalleled. Deacetylgeissovelline is readily pyrolyzed to 1-ethyl-6,7-dimethoxycarbazole. Lead tetraacetate oxidation of deacetylgeissovelline prior to pyrolysis, on the other hand, leads to compound **6**.

A detailed procedure for the separation of the alkaloid-rich bark extract of Brazilian *Geissospermum vellosii* into various fractions using liquid–liquid extraction at different pH's has been described.[2] Further purification of the weakly basic fraction B or fraction 1[3] by chromatography on alumina has resulted in the isolation of a new crystalline alkaloid, geissovelline, and the structure determination and chemistry of this new alkaloid is the subject of the present report.

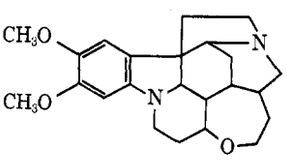
Structure Determination.—Geissovelline, a moderately basic alkaloid (pK_a = 6.7), has the molecular formula $C_{23}H_{30}N_2O_4$ and shows the presence of two OCH_3, one NCH_3, and two CCH_3 groups. The infrared spectrum of geissovelline shows no OH or NH absorption but exhibits a strong amide carbonyl band at 1659 cm^{-1}. Its ultraviolet spectrum is typical of an *N*-acyldialkoxyindoline and yet noticeably different from the spectrum of brucine (**1**) (Figure 1). However, when geissovelline is protonated, its ultraviolet absorption is comparable to that of **1** (which is unaffected



1

by acid), suggesting the presence of a second chromophore in geissovelline which is transparent in acid.

When geissovelline is treated with 1 *N* acid, acetic acid and deacetylgeissovelline, $C_{21}H_{28}N_2O_3$, are produced. The ultraviolet spectrum of deacetylgeissovelline resembles that of a 5,6-dialkoxyindoline but there are appreciable differences in the peak intensities when one compares it with the spectrum of a typical model compound such as dihydrobrucidine (**2**) (Figure 2). Both deacetylgeissovelline and **2**, however, show similar ultraviolet spectra in acid. In the infrared

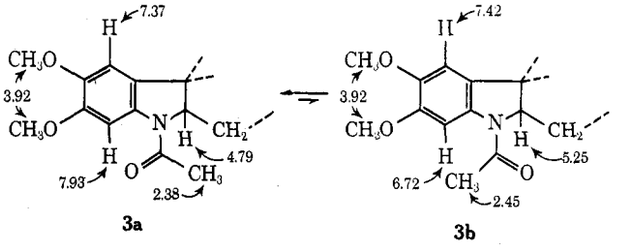


2

spectrum of deacetylgeissovelline a new band has appeared at 3338 cm^{-1} for the indoline NH and the amide carbonyl absorption has disappeared. Geissovelline is regenerated when deacetylgeissovelline is treated with acetic anhydride in pyridine.

Singlet peaks at δ 6.25 and 7.22 in the nmr spectrum of deacetylgeissovelline are ascribed to two aromatic protons which are para to each other and ortho and meta, respectively, to the indoline NH. The remaining two positions of the aromatic ring are occupied by the two methoxyl substituents as shown by nmr signals at δ 3.76 and 3.81.

In geissovelline the indoline NH is acetylated. The nmr spectrum of geissovelline (Figure 3), however, is complex owing to the presence of the *N*-acetyl group, as the rate of rotation for the amide *N*-carbonyl bond is slow enough at 25° that absorptions for two conformers are observed. The *N*-acetyl protons, for example, appear as 2:1 singlets at δ 2.38 and 2.45 for the cisoid and transoid conformers, respectively. At 100° the interconversion of the two conformers is faster and the *N*-acetyl peaks coalesce to a single peak at δ 2.38. A comparison of the nmr spectra of geissovelline and deacetylgeissovelline indicates that a proton is present on the α carbon of the indoline ring. This proton, which appears as doublets of doublets (J = 12 and 6.5 Hz) at δ 4.79 and 5.25 for the two geissovelline conformers (**3a** and **3b**) and as a single absorption at δ 4.26 for deacetylgeissovelline, is coupled with two protons on adjacent carbons. No β hydrogens are present on the indoline ring, as geissovelline is not oxidized to an *N*-acetyl-5,6-dimethoxyindole with lead tetraacetate and is recovered unchanged. It is therefore concluded that the two protons are on a methylene group that is also attached to the α position of the indoline ring.



3a **3b**

The singlet at δ 1.90 in the nmr spectrum of geissovelline (δ 1.86 for deacetylgeissovelline) is ascribed to an *N*-methyl group, as this signal is shifted paramagnetically about 1 ppm after protonation. One of the two

(1) National Institutes of Health Predoctoral Fellow, 1959–1962, University of California, Berkeley.

(2) H. Rapoport, T. P. Onak, N. A. Hughes, and M. G. Reinecke, *J. Amer. Chem. Soc.*, **80**, 1601 (1958).

(3) H. Rapoport and R. E. Moore, *J. Org. Chem.*, **27**, 2981 (1962).

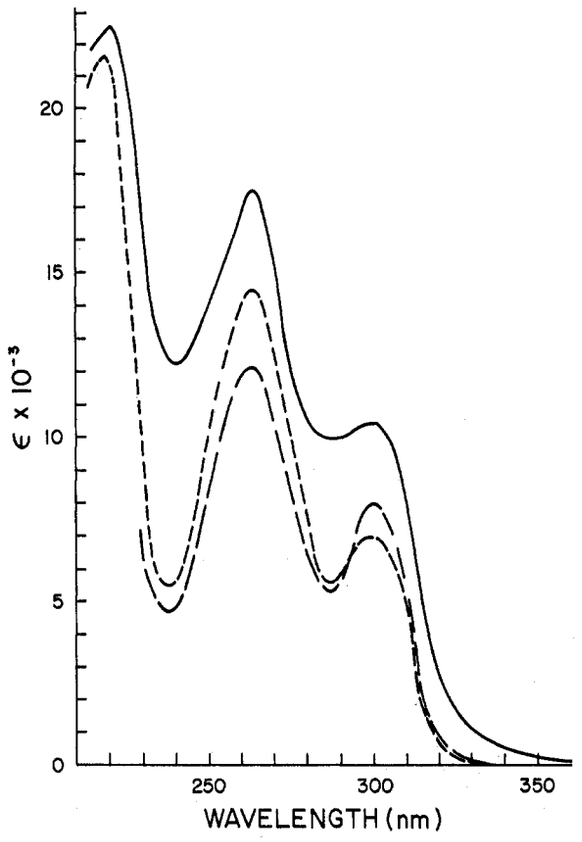


Figure 1.—Comparison of the ultraviolet spectra of geissovelline in ethanol (——) and 0.01 *N* ethanolic hydrochloric acid (– – – –) and brucine in ethanol (— —).

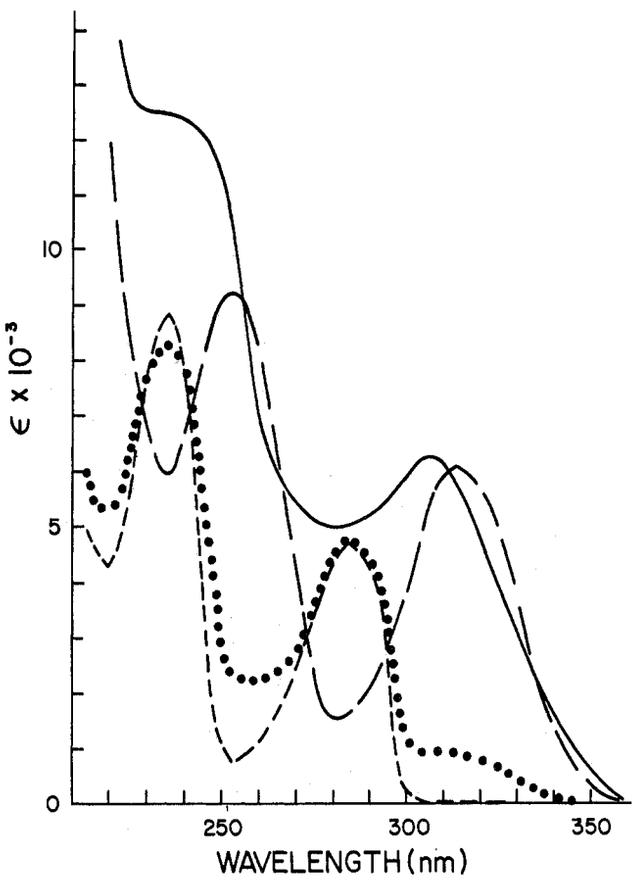
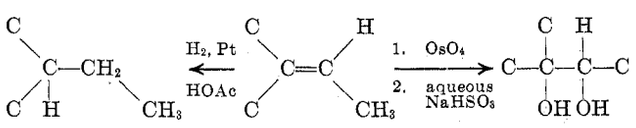


Figure 2.—Comparison of the ultraviolet spectra of deacetylgeissovelline in ethanol (——) and 0.1 *M* ethanolic hydrochloric acid (– – –), and dihydrobrucidine in ethanol (— —) and 0.1 *N* ethanolic hydrochloric acid (· · · ·). The shoulder at 310 nm in curve · · · · is due to incomplete protonation of the indoline nitrogen of dihydrobrucidine in 0.1 *N* ethanolic hydrochloric acid.

CCH_3 groups of geissovelline is the indoline *N*-acetyl group and the other an ethylidene group, as shown from a doublet at δ 1.71 (J = 7.7 Hz) for the methyl protons and two 1:3:3:1 quarters at δ 6.52 and 6.45 for the olefinic proton of the two geissovelline conformers **3a** and **3b**, respectively.

The presence of the olefinic double bond was demonstrated chemically when it was found that geissovelline catalytically absorbs 1 mol of hydrogen and reacts with 1 mol of osmium tetroxide. The dihydrogeissovelline obtained from catalytic hydrogenation exhibits its CCH_3 absorption as a perturbed triplet at δ 0.9 and apparently is a mixture of *C*-ethyl epimers as indicated by its melting point range. Kuhn–Roth oxidation of the dihydrogeissovelline now gave propionic acid, proving that the ethylidene group had been converted to an ethyl group. The dihydroxydihydrogeissovelline resulting from cis hydroxylation exhibits its methyl absorption as a doublet at δ 1.08 and also appears to be a mixture of epimers from its melting point range. No hydrogen is attached to the carbon bearing the ethylidene group, as no other olefinic proton signals are observed in the nmr spectrum of geissovelline. Furthermore, a nitrogen or oxygen cannot be attached to the ethylidene double bond, as the chemical shift of the olefinic proton in such an environment should resonate at higher field. Carbons must therefore be attached to the ethylidene double bond.



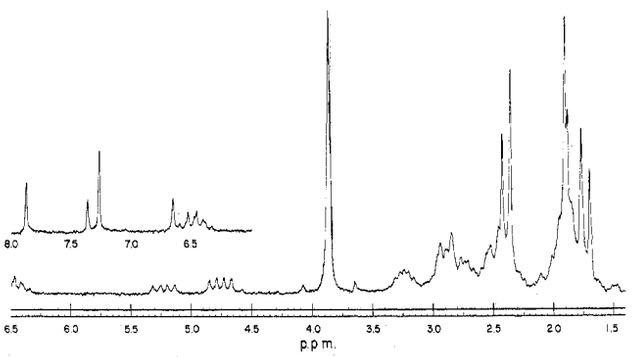
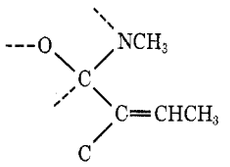


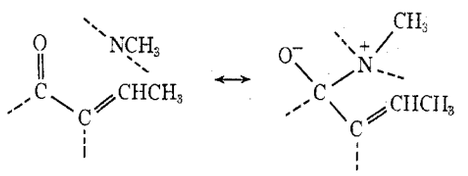
Figure 3.—The 100-MHz proton nmr spectrum of geissovelline in chloroform-*d*.

Treatment of geissovelline with sodium borohydride produces the same dihydrogeissovelline obtained by catalytic hydrogenation. Similarly, deacetylgeissovelline is reduced to a deacetyldihydrogeissovelline which is identical with the acid hydrolysis product of dihydrogeissovelline. Surprisingly, the CCH_3 protons of the ethylidene group could be exchanged for deuterium when geissovelline was treated with sodium ethoxide in ethanol-*O*-*d*. To account for both the reduction of the olefinic double bond by borohydride and the acidity of the methyl protons of the ethylidene group, a carbonyl group had to be in conjugation with the olefinic double bond. The ultraviolet spectrum of geissovelline

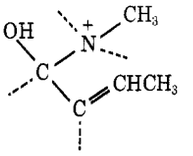
had already suggested the presence of a second chromophore, but, if this chromophore was due to an α,β-unsaturated ketone, it was not apparent why such a system should become transparent to uv on acidification. In addition the infrared spectrum of deacetylgeissovelline did not show an absorption band typical of an α,β-unsaturated ketone. Structures in which the ketone carbonyl was masked were considered but all were finally eliminated. A carbinolamine structure, for example, could be immediately ruled out, as geissovelline showed no OH absorption in the infrared. An azaketal structure could also be rejected, as it was not compatible with the ultraviolet spectral properties.



The masked carbonyl structures were completely rejected when the carbon-13 nmr spectrum of geissovelline revealed the presence of two carbonyl absorptions. The signal at δ 167.1 was clearly due to the amide carbonyl, but the signal at δ 184.3 could only be attributed to an α,β-unsaturated ketone. In the infrared spectrum of deacetylgeissovelline the absorption nearest the normal carbonyl region was a strong band at 1608 cm^{-1}. An absorption of such low frequency is shown only by carbonyls of relatively long bond length such as found in carboxylate anions where the nonbonding electrons interact with the carbonyl carbon. Perhaps the ketone carbonyl bond of geissovelline was longer for a similar reason, but it is the nonbonding pair of electrons on the nitrogen which interacts which the carbonyl carbon. Such a transannular nitrogen–carbonyl interaction has been observed before.[4,5] The transannular nitrogen–carbonyl structure[6] explains the weaker basicity of

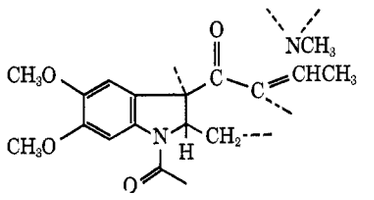


geissovelline (pK_a = 6.7)[7] and the disappearance of the ultraviolet absorption in acidic medium. The nitrogen is not available for protonation owing to its transannular interaction with the carbonyl. Instead the less basic carbonyl oxygen is protonated, resulting in loss of the α,β-unsaturated ketone chromophore. Also consistent with the unavailability of the electron pair on



the nitrogen is the nonreactivity of geissovelline with methyl iodide or cyanogen bromide in aprotic solvents.

Reaction of geissovelline with lithium aluminum hydride in diethyl ether produced a mixture of epimers in which the *N*-acetyl had been reduced to an *N*-ethyl group and the olefinic double bond was hydrogenated. More vigorous treatment with lithium aluminum hydride in refluxing tetrahydrofuran led to reduction of the ketone carbonyl; the resulting mixture of epimeric alcohols was found to be readily oxidized by air, apparently forming indoles. To account for the possible formation of indoles the α,β-unsaturated ketone function was most likely attached to the β position of the indoline ring (**3c**).



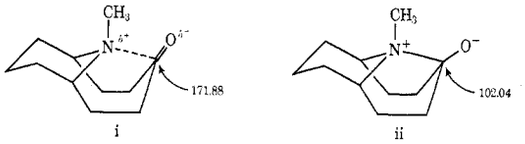
3c

Further evidence for its attachment to the β position of the indoline ring came from the following experiment. Oxidation of deacetylgeissovelline with lead tetraacetate did not lead to an indolenine but rather to a water-soluble product which had an ultraviolet spectrum characteristic of an indole. Pyrolysis of the water-soluble indole at 180° lead to a new compound, $C_{21}H_{26}N_2O_3$, which had lost only two hydrogens compared with deacetylgeissovelline over the course of the two reactions. Examination of the nmr spectrum of the pyrolysis product immediately revealed that the α,β-unsaturated ketone group had been expelled from the β position of the indoline ring[8] during the oxidation, as the indolic NH had become acylated during the pyrolysis. A sharp singlet at δ 8.00 showed that the aromatic proton ortho to the nitrogen was again experiencing the anisotropy of a carbonyl group attached to the nitrogen. A 1:3:3:1 quartet at δ 7.15 showed that the olefinic proton of the ethylidene group was cis to the amide carbonyl[9] in the pyrolysis product and therefore probably cis to the ketone group in geissovelline. Also shown in the nmr spectrum was a doublet of doublets at

(4) N. J. Leonard, *Rec. Chem. Progr.*, **17**, 243 (1956); N. J. Leonard and M. Oki, *J. Jap. Chem.*, **10**, 1003 (1956); N. J. Leonard, J. A. Adamcik, C. Djerassi, and O. Halpern, *J. Amer. Chem. Soc.*, **80**, 4858 (1958).

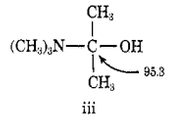
(5) Transannular nitrogen–carbonyl interactions are exhibited by the *Strychnos* alkaloids novacin and vomicin. For a review see H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademe-Verlag, Berlin, 1961.

(6) It has recently been reported [T. T. Nakashima and G. E. Maciel, *Org. Magn. Resonance*, **4**, 321 (1972)] that 11-methyl-11-azabicyclo[5.3.1]undecan-4-one is best represented by formula i in aprotic solvents such as cyclohexane and by ii in proton solvents such as 90% chloroform in cyclo-



i ii

hexane. The conclusion is based on the carbon-13 chemical shift (parts per million relative to cyclohexane) of C-4 in the two solvents. The chemical shift for C-4 of ii agrees with the one estimated from additivity considerations for a similar carbon in the model system iii.



iii

(7) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **32**, 1851 (1949).

(8) Indolenines having *Strychnos* and *Aspidosperma* structural skeletons are readily reduced and rearranged by a retro-Mannich reaction to indoles when treated with sodium or potassium borohydride: G. F. Smith and J. T. Wrobel, *J. Chem. Soc.*, 792 (1960); K. Biemann and G. Spiteller, *Tetrahedron Lett.*, 299 (1961).

(9) The appreciable difference in chemical shift of an olefinic proton cis to a carbonyl function compared with one trans is demonstrated by the geometrical isomers tiglic acid (δ 7.06) and angelic acid (δ 6.27).

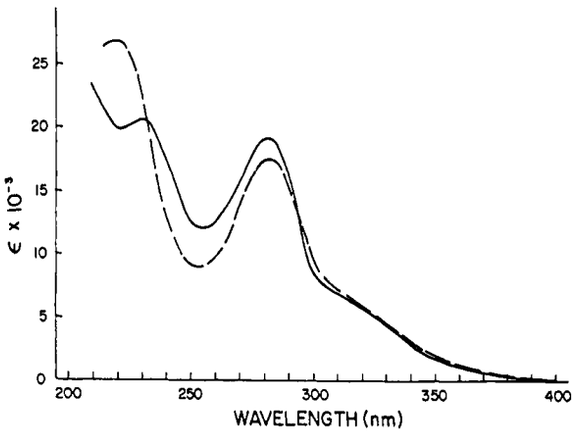
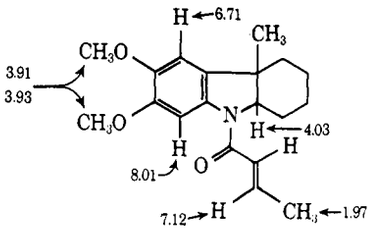


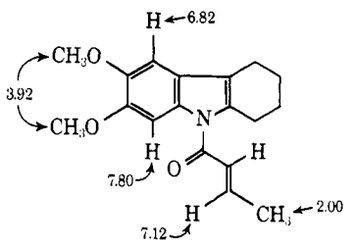
Figure 4.—Comparison of the ultraviolet spectra of compound **6** (—) and *N*-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (**5**) (– – –).

δ 4.53 which suggested that the pyrolysis product had regained a proton on the α carbon of an indoline ring. This possibility was quickly ruled out, as the ultraviolet spectrum of the pyrolysis product did not resemble that of *N*-crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (**4**). It made more sense mecha-

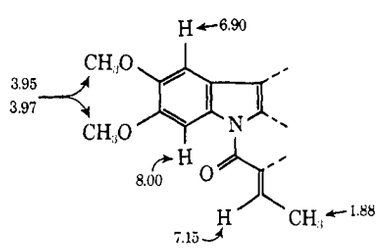


4

nistically that the pyrolysis product should possess an indole ring. Comparison of the ultraviolet spectra of the pyrolysis product and a suitable synthetic model compound, *N*-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (**5**) (Figure 4) showed indeed that the pyrolysis product had the partial structure **6a**.

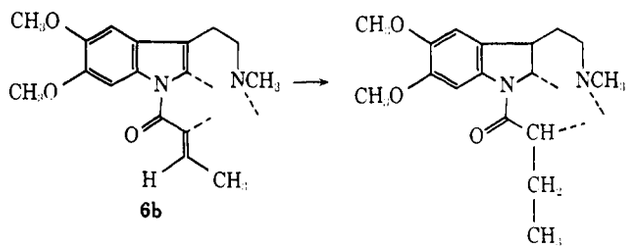


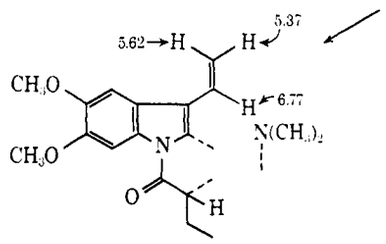
5



6a

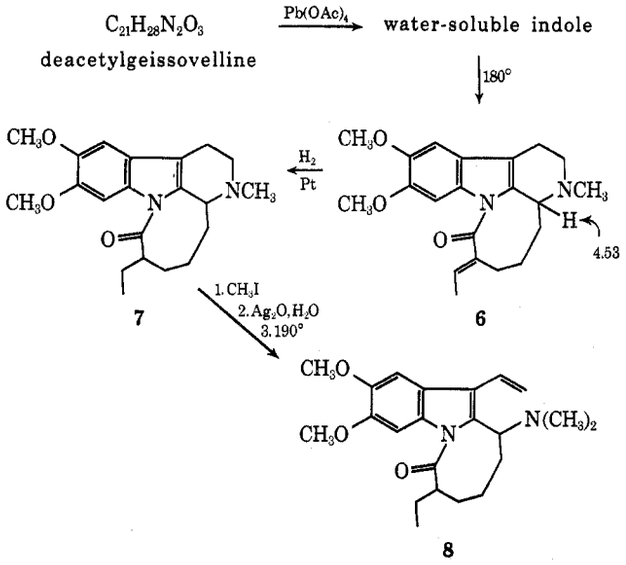
Assuming that geissovelline has the tryptamine structure, *i.e.*, the basic nitrogen is separated from the β carbon of the indoline ring by two carbon atoms, and that this structure is retained after pyrolysis of the lead tetraacetate oxidation product of deacetylgeissovelline, then Hofmann degradation of the pyrolysis product **6b** might lead to a compound having a vinyl group attached to the β position of the indole ring. The ethylidene double bond in **6b** was first catalytically hydrogenated so that isomerization and other side reactions would be minimized during the Hofmann elimination reaction. As predicted, Hofmann degradation of **7a** led to a β-vinyl indole **8a**. The nmr spectrum of the product



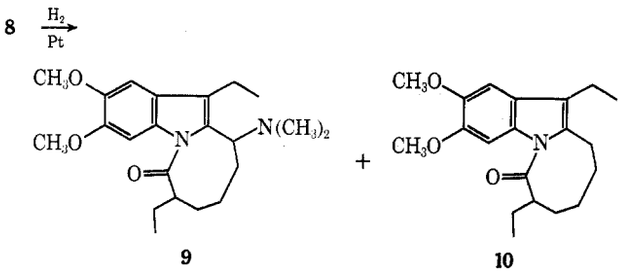


exhibited doublets of doublets at δ 5.37 (J = 12 and 2 Hz, 5.62 (J = 18 and 12 Hz), and 6.77 (J = 18 and 12 Hz) for the vinyl protons. Many of the signals in the spectrum were doubled either to cisoid and transoid vinyl conformers or to *C*-ethyl epimers. As the aromatic proton meta to the indole nitrogen appeared to be more strongly influenced by the anisotropy of the vinyl group (singlet peaks at δ 6.87 and 7.13) than the ortho aromatic proton (singlet peaks at δ 8.04 and 8.09), the vinyl group had to be attached to the β position on the indole ring in the Hofmann degradation product. The nmr signal for the *N*-methyl protons was also doubled (singlet peaks at δ 2.20 and 2.36) and this suggested that the dimethylamino group was very close to the vinyl group. The closest that one can place the dimethylamino group with respect to the vinyl substitutent is to attach it to a benzylic carbon at the α position of the indole ring. Only three carbons remain unassigned now for a complete structure and must be used to construct a ring. The three carbons, which can only be methylenes as the sole CCH_3 group has already been accounted for, connect the benzylic carbon at the α position of the indole ring and the carbon bearing the ethyl group (in **7a** and **8a**) or the ethylidene group (in **6b**). Structures **6b**, **7a**, and **8a** can now be expanded to **6**, **7**, and **8**.

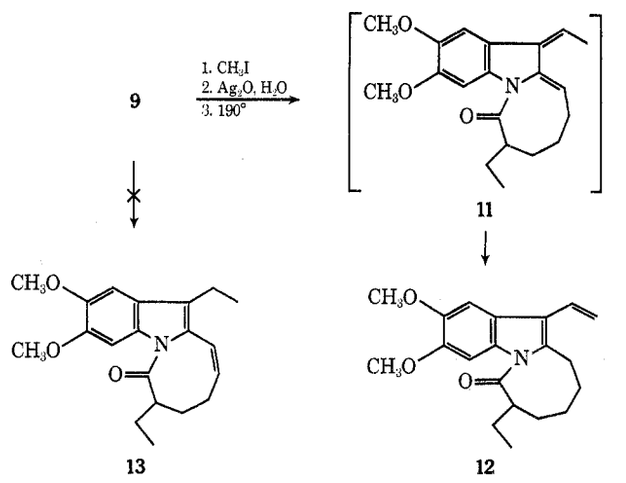
The doublet of doublets at δ 4.53 in the nmr spectrum of the pyrolysis product is readily explained by structure **6**. In deacetylgeissovelline a methylene had been attached at the α position of its indoline ring, but it appeared that the basic nitrogen had reacted with this carbon, most likely during the pyrolysis of the water-soluble indole when it was benzylic. Difficult to explain with structure **6** was the seemingly facile formation of a strained eight-membered ring by acylation of the indole nitrogen during the pyrolysis.



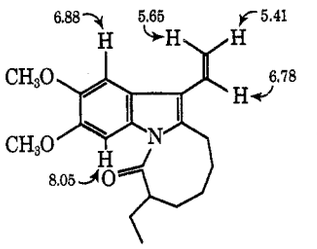
To secure structure **6** for the pyrolysis product, an exhaustive Hofmann degradation was carried out. Compound **8** was first catalytically hydrogenated to a mixture of a basic compound **9** and a nonbasic compound which exhibited no *N*-methyl absorption in its nmr spectrum. Loss of the dimethylamino group is rationalized only by hydrogenolysis from a benzylic position such as that present in **8**. The nonbasic compound must therefore have structure **10**.

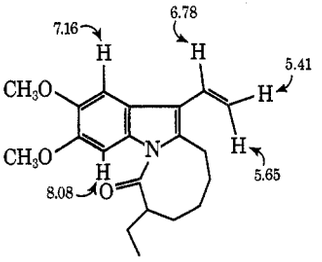


Hofmann degradation of **9** led to a product which nmr analysis showed to be the β-vinylindole **12**. Pyrolysis of the methohydroxide of **9** did not lead to **13**, as the hydroxide ion attacked the more acidic benzylic proton and eliminated trimethylamine to give the intermediate **11**. A 1,5-sigmatropic proton shift in **11** then leads to the more stable **12**. The nmr spectrum of **12** showed the identical pattern of peaks for the olefinic and aromatic protons as for **8**. The aromatic signals were



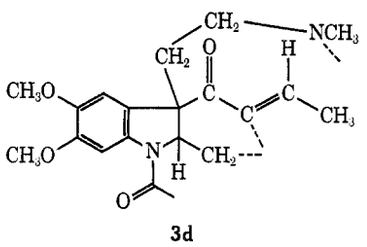
again doubled and this clearly had to be attributed to cisoid and transoid conformations of the vinyl group (**12a** and **12b**). In the nmr spectrum of **8** the doubling



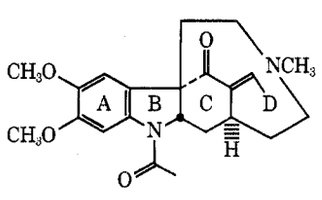


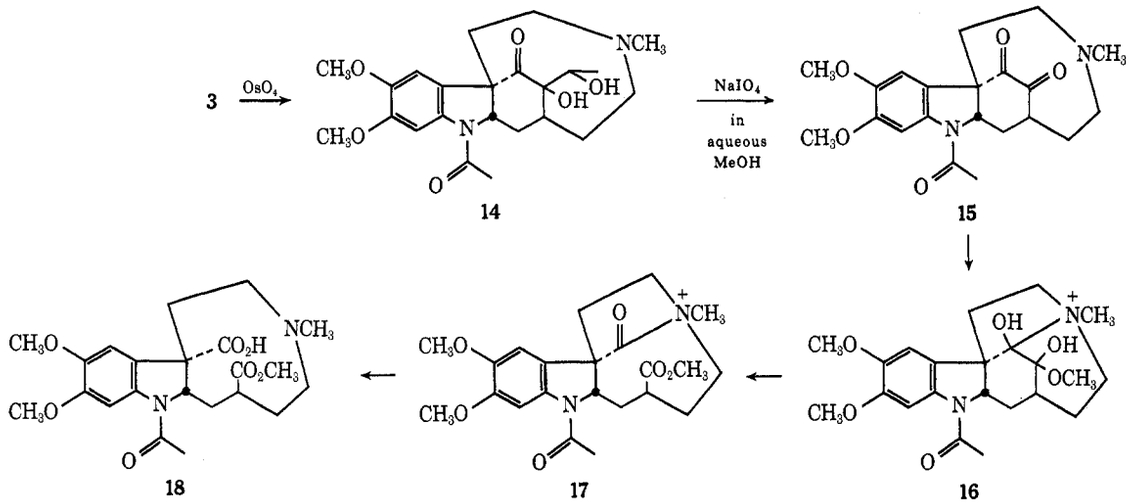
of the aromatic and dimethylamino signals must therefore have been due to vinyl conformers rather than to *C*-ethyl epimers.

We were not able to rationalize a complete structure for geissovelline from **6** and therefore concluded that a rearrangement had occurred during the conversion of deacetylgeissovelline to **6**. What was learned about the structure of geissovelline was (1) the olefinic proton was cis to the ketone carbonyl group and (2) the tryptamine structure was present. The partial structure of geissovelline could now be expanded to **3d**.



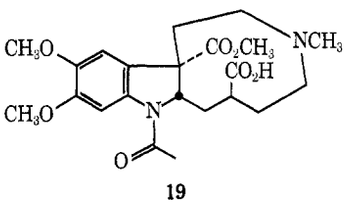
Two methylenes and one methine remained unassigned and had to be put together to construct two additional rings. Only six structures (nonionic) could be written for geissovelline. One of these structures was not considered further, as the transannular nitrogen–carbonyl interaction resulted in a strained four-membered ring. Four of the remaining five structures were eliminated when an oxidative degradation of geissovelline revealed that a methine is attached to the olefinic double bond and that the *N*-methyl group cannot be on a carbon β to the olefinic double bond. By this process of elimination geissovelline was proposed to have the remaining structure **3** and furthermore the stereo-



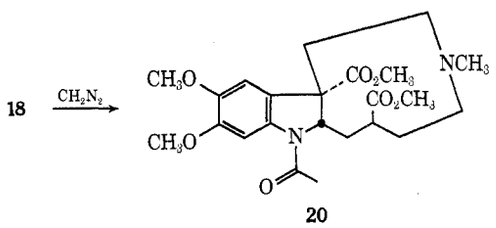


chemistry depicted from molecular model considerations.[10]

The oxidative degradation of geissovelline was carried out as follows. Hydroxylation of **3** with osmium tetroxide to the diol **14** followed by oxidation with sodium metaperiodate in aqueous methanol produced acetaldehyde and a product $C_{22}H_{30}N_2O_7$ which had incorporated a molecule of methanol during the oxidation as shown by nmr and Zeisel analyses. The α diketone was most likely formed first, but subsequent nucleophilic addition of methanol and protonation of **15** led to **16**, which underwent further oxidation to **17**. Hydrolysis of the labile quaternary amide **7** then resulted in the product **18**. It was possible that the periodate oxidation product had instead structure **19**, resulting from hydration and protonation of ketone **15**, oxidation to a quaternary amide, and reaction with

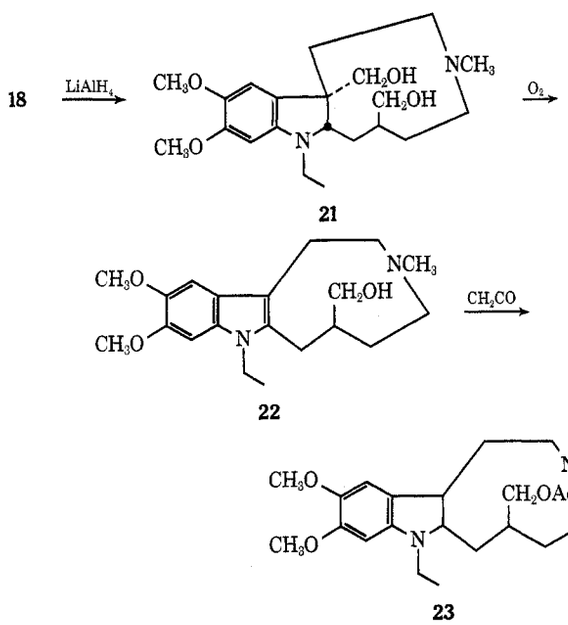


methanol. Evidence for ester, amide, and carboxyl carbonyls in **18** was shown by both the infrared and carbon-13 spectra. Compound **18** readily formed the dimethyl ester **20** on treatment with diazomethane.



Treatment of **18** with sodium ethoxide in ethanol-*O*-*d* resulted in exchange of the *N*-acetyl protons and the acidic proton, as shown by the disappearance of their nmr signals. It could not be determined whether a proton on the carbon α to the ester carbonyl had been exchanged, as the remainder of the nmr spectrum looked essentially the same before and after exchange. Compound **18** did appear to be fairly stable to the strong alkaline conditions, and this suggested that the *N*-methyl group was not on a carbon β to the carbomethoxy group.

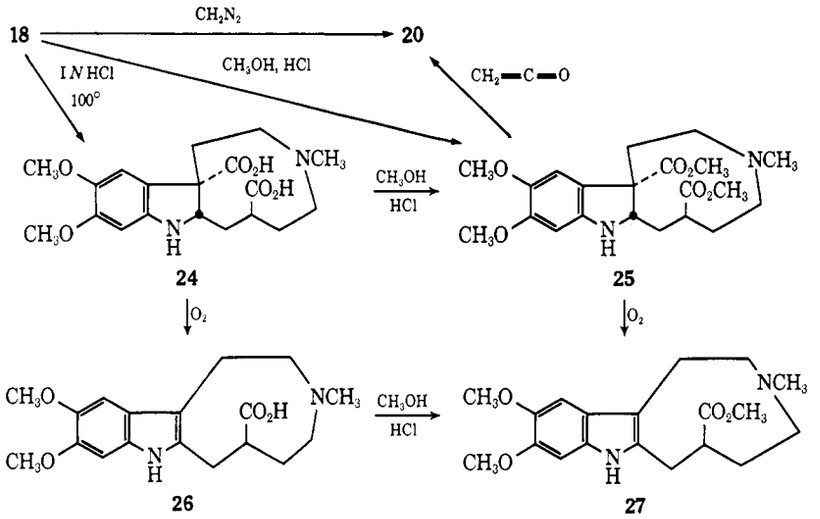
Reduction of **18** with lithium aluminum hydride gave the *N*-ethylindoline **21**, which was rapidly converted to the indole **22** by an oxidative decarbonylation.



The nmr spectrum of **22** showed a sharp doublet at δ 3.7 (J = 6 Hz) assigned to a methylene flanked by a methine and a hydroxy group which upon acetylation with ketene **23** showed the expected 0.5-ppm paramagnetic shift. The nmr evidence showed that a methine was adjacent to the ester carbonyl in **18** and therefore to the olefinic double bond in geissovelline (**3**).

Acid hydrolysis of the amide and ester of **18** gives an indoline which must have structure **24**, since it can be converted to **20** by Fischer esterification followed by acetylation with ketene. Fischer esterification of **18** or **24** yields the same indoline **25**. Compound **24** is readily

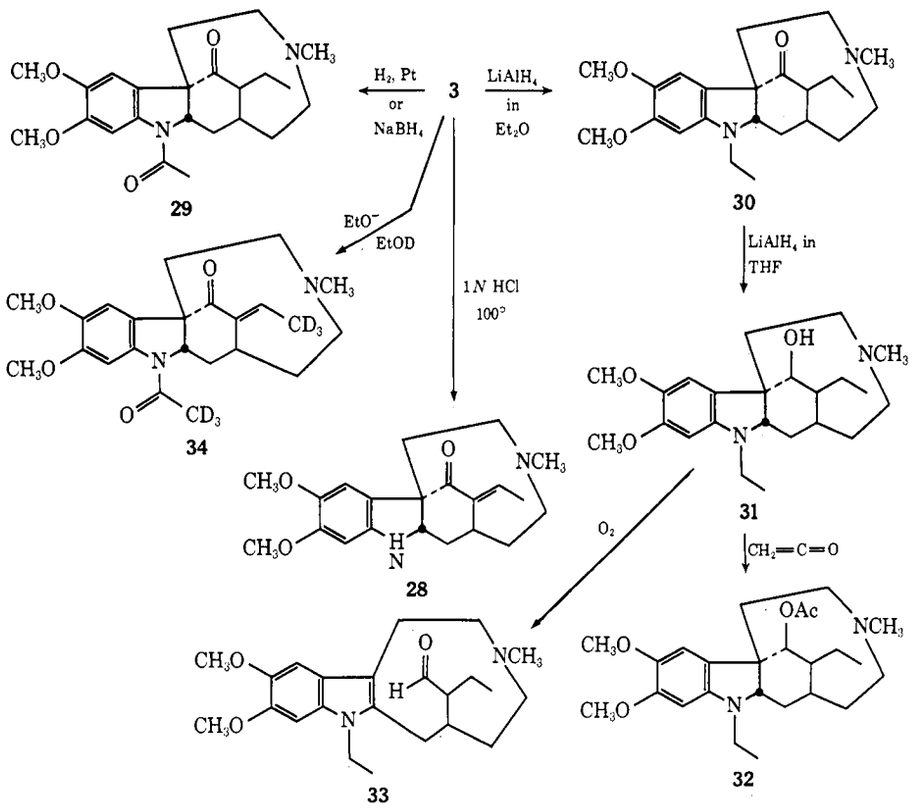
(10) Geissovelline appears to be related to the alkaloids condyfoline [D. Schumann and H. Schmid, *Helv. Chim. Acta*, **46**, 1966 (1963)] and condylocarpine [K. Biemann, A. L. Burlingame, and D. Stauffacher, *Tetrahedron Lett.*, 527 (1962); A. Sandoval, F. Walls, J. N. Schoolery, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, 409 (1962)].



oxidized by air to an indole, presumably by an oxidative decarboxylation to **26**. Compound **25** also undergoes a facile oxidation to indole **27**, which is identical with the Fischer esterification product of **26**. The carbomethoxy group at the β position of the indoline ring of **25** appears to be easily hydrolyzed, possibly owing to a transannular assistance by the nitrogen.

Structure **3** is consistent with all of the chemistry of geissovelline. Acid hydrolysis of **3** gives deacetylgeissovelline (**28**). Catalytic hydrogenation or sodium borohydride reduction of **3** leads readily to an epimeric mixture of dihydrogeissovellines (**29**). Reduction of the ketone group, however, is sluggish; geissovelline is rapidly reduced to **30** with lithium aluminum hydride and to **31** only with more vigorous conditions. Compound **31** forms a monoacetate **32** with ketone and is oxidized by air to an indole, possibly **33** as suggested by carbonyl absorption at 1725 cm^{-1}. Reaction of **3** with sodium ethoxide in ethanol-*O*-*d* results in geissovelline-d_6 (**34**).

The mass spectrum of geissovelline is also compatible with structure **3** for the alkaloid. The largest fragment ion produced upon electron impact of **3** corresponds to the loss of 71 mass units and the elements of C_4H_9N from the molecular ion. The transition is accompanied by a metastable ion at *m/e* 268.7. The M − 71 ion is shifted six mass units higher in the mass spectrum of geissovelline-d_6 (**34**), showing that both the ethylidene and *N*-acetyl methyl groups are retained. The mass spectrum of deacetylgeissovelline (**28**) also exhibits a prominent M − 71 ion which may be identical with the *m/e* 285 ion resulting from loss of ketene from the M − 71 ion of **3**. The M − 71 ion is conspicuously missing in the mass spectrum of dihydrogeissovelline (**29**), suggesting that fragmentation leading to the M − 71 ion is initiated by fission of the allylic C–C bond in ring D of **3**.



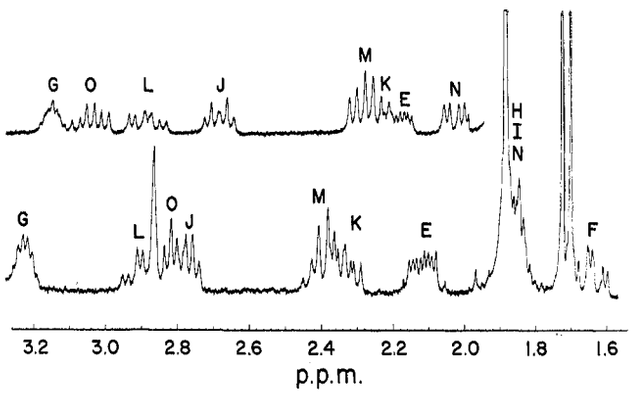
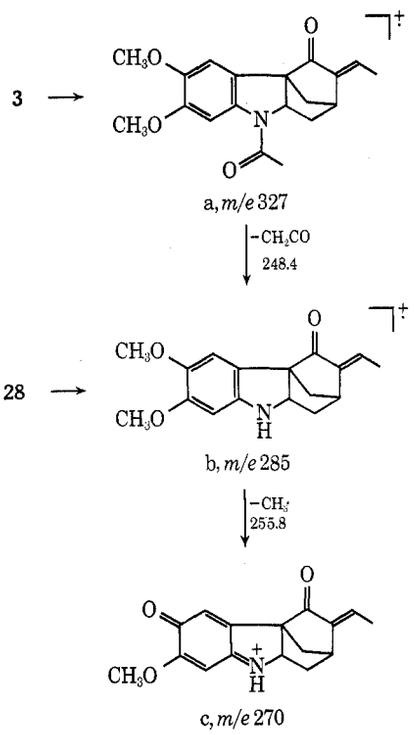
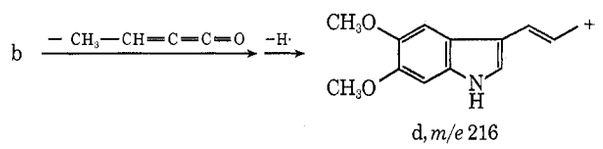


Figure 5.—High-field region of the 300-MHz proton nmr spectrum of deacetylgeissovelline in chloroform-*d* (lower trace) and pyridine-d_5 (upper trace).

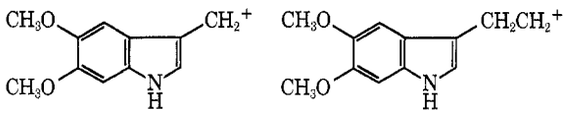
Two possible structures for the M − 71 ions of **3** and **28** are a and b, respectively.



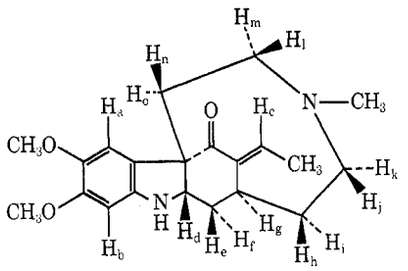
In the mass spectrum of **28** the largest fragment ion is found at *m/e* 216 and has the elemental composition $C_{13}H_{14}NO_2$. The *m/e* 216 ion is also present in the mass spectrum of **3**, is shifted to *m/e* 217 in the mass spectrum of **34**, and is missing in the mass spectrum of **29**. The *m/e* 216 ion has about the same relative intensity as the *m/e* 285 ion (b) in both the mass spectra of **3** and **28**, suggesting that the *m/e* 216 ion might be formed from b. No metastable ions could be found to account for the origin of the *m/e* 216 ion. The *m/e* 216 ion could be the results of a two-step degradation of ion b and have structure d.



Formation of the ions at *m/e* 58, 70, 216, 270, 285, 312, 313, 327, and 339 in the mass spectrum of **3** appears to be initiated by cleavage of the allylic C–C bond in ring D, whereas ions at *m/e* 122, 124, and 138 may result from initial cleavage of the allylic C–C bond in ring C. All of these ions are absent in the mass spectrum of **29**. Formation of the ions at *m/e* 190 (e) and 204 (f) in the mass spectrum of **3** is independent of initial allylic C–C cleavage, as these ions are also found in the mass spectrum of **29**.



Nmr Studies of Deacetylgeissovelline.—To confirm the proposed structure for geissovelline, the 300-MHz proton nmr spectrum of deacetylgeissovelline (**28a**)



28a

(Figure 5) was determined and completely analyzed. In chloroform-*d* H_d is found at δ 4.26 as a doublet of doublets showing vicinal coupling to H_e and H_f. The coupling constants, J_{de} = 6.5 and J_{df} = 11.5 Hz, are consistent with the approximate dihedral angles of 60 and 180°, respectively, observed in a model of deacetylgeissovelline.

Irradiation of H_d removes the small splitting from an octet at δ 2.08, assigned to H_e, and the large splitting from the triplet of doublets at δ 1.61 for H_f. The resulting doublets of doublets now show only the geminal interaction of H_e and H_f (J_{ef} = 13 Hz) and the vicinal coupling of H_e and H_f to H_g ($J_{eg} = J_{fg}$ = 4 Hz). Again the coupling constants are compatible with the approximate dihedral angles of 60° in a model of **28a**.

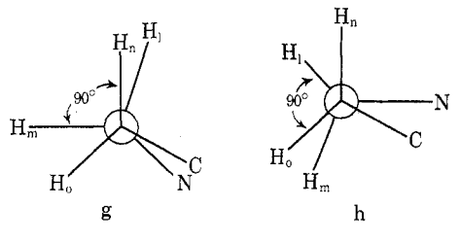
The sextet at δ 3.20 is attributed to H_g and irradiation of this proton also reduces the H_e signal to a doublet of doublets and the H_f signal to a triplet in which the geminal coupling of H_e and H_g and the vicinal interactions of H_e and H_f to H_d remain.

The H_h and H_i resonances are located in a complex three-proton multiplet at *ca.* δ 1.8 as shown by the appreciable change in its shape when H_g is irradiated. Conversely, irradiation of the multiplet at δ 1.8 causes the sextet for H_g to collapse to a 1:2:1 triplet ($J_{eg} = J_{fg}$ = 4 Hz). The sextet for H_g is a quartet of 1:2:1 triplets where the quartet is the X part of a typical ABX spectrum and the lines of the quartet are separated by about 4 Hz. Irradiation of the multiplet at δ 1.8 also causes a doublet of triplets at δ 2.74, assigned to H_j, and a multiplet at δ 2.31 for H_k to simplify, the resulting doublets showing only the geminal coupling of H_j and H_k (J_{jk} = 13.5 Hz). A reasonably close match between the experimental spectrum of H_g, H_h, H_i, H_j, and H_k and the calculated spectrum was achieved with the aid of generalized multispin programs LAOCOON I and II.

The parameters which agreed best with the experimentally observed line frequencies and intensities are $\nu_g = 962.47$, $\nu_h = 550.0$, $\nu_i = 568.0$, $\nu_j = 828.63$, and $\nu_k = 695.98$ for the chemical shifts and $J_{gh} = 8.46$, $J_{gi} = 3.56$, $J_{gj} = 0.0$, $J_{gk} = 0.0$, $J_{hi} = -13.0$, $J_{hj} = 5.46$, $J_{hk} = 8.93$, $J_{ij} = 5.54$, $J_{ik} = 6.03$, and $J_{jk} = -13.02$ Hz for the spin–spin coupling constants.

The *N*-methyl protons absorb at rather high field (δ 1.86), showing that the *N*-methyl group is located in the shielding region of the π-electron cloud of the α,β-unsaturated ketone system. In this conformation the nonbonding pair of electrons on the nitrogen is oriented toward the carbonyl carbon and this supports the existence of a transannular nitrogen–carbonyl interaction already indicated from infrared evidence.

The signals for H_l, H_m, H_n, and H_o appear as complex multiplets in the spectrum determined in chloroform-*d* but are seen very clearly in pyridine-d_5 (upper trace of Figure 6) as triplets of doublets at δ 2.84 and 3.03 and doublets of doublets at δ 1.99 and 2.24. Since two of the protons exhibit doublets of doublets, the vicinal coupling constant between these two protons must be zero and therefore the dihedral angle about 90°. Examining the many conformational possibilities for **28a**, only two (g and h) fulfill this requirement and show at the same time a transannular nitrogen–carbonyl interaction. In both g and h H_o is located near the



deshielding region of the aromatic ring while H_l interacts sterically with H_j. The two paramagnetically displaced triplets of doublets must therefore be attributed to H_o and H_l and the doublets of doublets at higher field to H_m and H_n. Hence protons H_l, H_m, H_n, and H_o in **28a** have the conformation depicted by g. The proton absorbing at highest field (δ 1.99) should be H_n, since it is in a methylene attached only to carbon. Proton H_n then shows a geminal coupling of −13 Hz to H_o and vicinal coupling of 6 Hz to H_l. The H_m proton should resonate at lower field (δ 2.24) as it is in a methylene attached to a nitrogen. A geminal coupling of −13 Hz is shown for H_m and H_l and a vicinal interaction of 7 Hz between H_m and H_o. After the coupling constants in the various multiplets were compared assuming that H_n absorbs at highest field, the triplets of doublets at δ 3.03 and 2.84 were assigned to H_o and H_l, respectively. A reasonable solution of the more complex experimental spectrum of protons H_l, H_m, H_n, and H_o in chloroform-*d* is obtained by calculating a spectrum with the parameters $\nu_l = 863.2$, $\nu_o = 845.9$, $\nu_m = 714.2$, and $\nu_n = 553.8$ Hz for the chemical shifts and $J_{mn} = 0$, $J_{no} = -14.8$, $J_{ln} = 6.6$, $J_{mo} = 7.0$, $J_{ml} = -14.5$, and $J_{lo} = 13.0$ Hz for the spin–spin coupling constants.

The H_o proton lies in the deshielding region of the aromatic ring and is the most paramagnetically displaced methylene proton, whereas H_f is shielded by the aromatic ring and is the most diamagnetically shifted

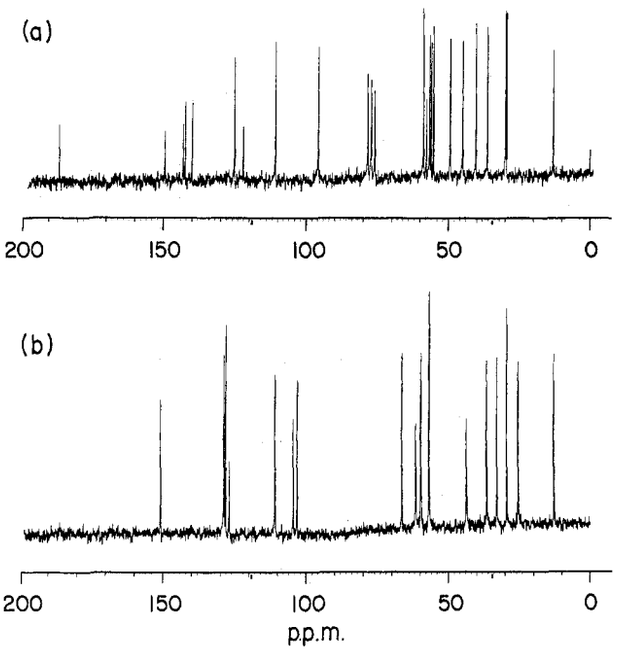
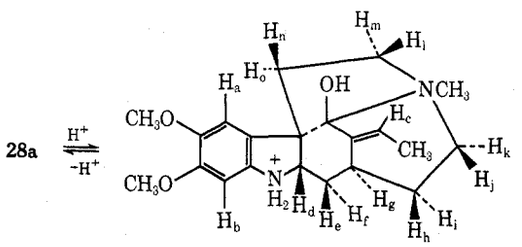


Figure 6.—The Fourier transform 25.2-MHz carbon-13 nmr spectrum of deacetylgeissovelline in (a) chloroform-*d* and (b) 0.1 *N* DCl in D_2O.

methylene proton. For the methylene groups attached to the basic nitrogen, H_l and H_j absorb at lower field than H_m and H_k owing to a nonbonded interaction between H_l and H_j. The H_g proton is found of fairly low field owing to van der Waals deshielding by the *C*-methyl group. Finally, the H_d proton is found at much lower field compared with other alkaloids owing probably to deshielding by the ketone carbonyl.

Since a transannular nitrogen–carbonyl interaction exists in deacetylgeissovelline, acidification results in protonation of the carbonyl oxygen rather than the tertiary nitrogen. The indoline nitrogen is also protonated at pH 0.



In 1 *N* DCl in D_2O the protons on carbons attached to the positively charged nitrogens are strongly deshielded. The *N*-methyl signal has shifted paramagnetically about 1 ppm (Table I), as have the signals for the four *N*-methylene protons H_j, H_k, H_l, and H_m which exhibit a very complex multiplet centered at about δ 3.65. The signal for H_d, however, is shifted only 0.54 ppm to lower field, as H_d no longer experiences deshielding by the ketone carbonyl. The aromatic proton ortho to the indoline nitrogen is strongly affected by the electron-withdrawing character of the positively charged nitrogen and is paramagnetically shifted 1.15 ppm. The aromatic proton meta to the indoline nitrogen, on the other hand, is more strongly affected by the removal of deshielding by the ketone carbonyl and is diamagnetically shifted 0.31

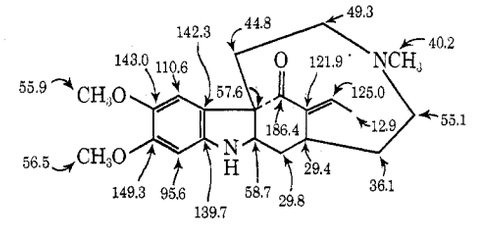
TABLE I
COMPARISON OF PROTON CHEMICAL SHIELDING PARAMETERS OF DEACETYLGEISSOVELLINE IN DIFFERENT SOLVENTS

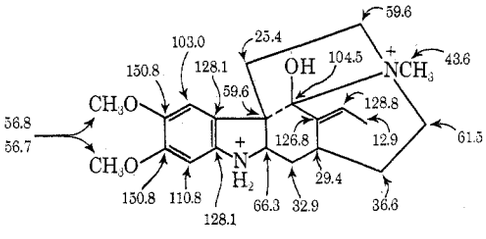
	Chemical shift, δ				
Protons	$CDCl_3$	C_5D_5N	C_6F_6	C_6D_6	0.1 *N* DCl in D_2O
OCH_3	3.76	3.65	3.64	3.68	3.66
	3.81	3.72	3.70	3.76	3.70
NCH_3	1.86	1.88	1.80	1.81	2.83
CCH_3	1.68	1.62	1.73	1.61	1.44
NH[a]	3.27	5.36	*b*	*c*	4.62[d]
H_a	7.22	7.71	*b*	7.26	6.91
H_b	6.25	6.47	*b*	6.14	7.40
H_c	6.43	6.68	*b*	6.47	5.88
H_d	4.26	4.52	4.25	4.12	4.80
H_e	2.08	2.13	2.13	1.91	2.46[e]
H_f	1.61	1.71	1.58	1.52	1.86
H_g	3.21	3.11	3.25	3.07	3.23
H_h	1.83	1.71	1.93	1.70	1.64[e]
H_i	1.89	1.71	1.93	1.70	1.98[e]
H_j	2.76	2.64	2.77	2.60	3.65[f]
H_k	2.32	2.20	2.35	2.18	3.65[f]
H_l	2.88	2.84	2.91	2.72	3.65[f]
H_m	2.38	2.24	2.33	2.25	3.65[f]
H_n	1.85	1.99	1.70	1.70	2.39[e]
H_o	2.82	3.03	2.69	2.82	2.61[e]

[a] Concentration dependent. [b] Not determined. [c] Not observed. [d] HDO peak. [e] Tentative assignment. [f] Center of complex 4 H multiplet.

ppm. The quartet for H_c and the doublet for the CCH_3 group are found at higher field, as these protons no longer feel the anisotropic and electron-withdrawing effects of the ketone carbonyl.

The 25.15-MHz proton-noise decoupled Fourier transform carbon-13 nmr spectrum of deacetylgeissovelline is shown in Figure 6. All 21 carbon signals of deacetylgeissovelline are resolved in $CDCl_3$, whereas only 18 lines are visible in 0.1 *N* DCl in D_2O. In $CDCl_3$ the off-resonance continuous-wave (cw) decoupled spectrum shows seven singlets, five doublets, five 1:2:1 triplets, and four 1:3:3:1 quartets, confirming the presence of seven quaternary, five methylene, five methine, and four methyl carbons, respectively, in the structure of deacetylgeissovelline. In acid the peaks for the two aromatic quaternary carbons attached to methoxyl, the two aromatic quaternary carbons at the indoline ring junction, and a methylene and a quaternary carbon at the β position of the indoline ring accidentally overlap, resulting in three lines instead of six. All of the methyl and methine carbon signals could be readily assigned,





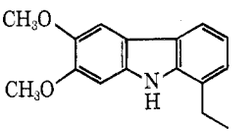
but most of the methylene and quaternary carbon assignments must remain tentative.

In the cw spectrum of deacetylgeissovelline the three doublets at 125.0, 110.6, and 95.6 ppm with residual splittings (J_r) of 26.6, 24.9, and 27.5 Hz are assigned to the olefinic methine carbon and the aromatic methine carbons meta and ortho to the indoline NH, respectively, as the separations of the corresponding methine proton signals from the applied decoupling frequency (δ 14) are 7.57, 6.78, and 7.75 ppm.[11] In 0.1 *N* DCl in D_2O these methine carbons are found at 128.8, 103.0, and 110.8 ppm, respectively, as shown from comparison of the magnitudes of J_r and the proton shift separations.

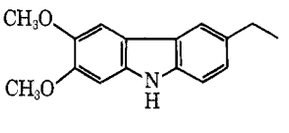
The most important feature of the carbon-13 spectrum in $CDCl_3$ is the peak at δ 186.4 attributed to the α,β-unsaturated carbonyl carbon. In 0.1 *N* DCl in D_2O the carbonyl signal disappears and a new signal is produced at higher field (δ 104.5) for $HOCN^+$.[6]

The CH_2 signals at lowest field (δ 49.3 and 55.1 in $CDCl_3$ and 59.6 and 61.5 in 0.1 *N* DCl) most likely are assigned to the methylene carbons attached to the tertiary nitrogen. All of the carbons attached to the deuterated nitrogens have shifted paramagnetically. The aromatic carbons ortho and para to the deuterated indoline nitrogen shift downfield to a greater extent than the meta carbons. Finally the methylene carbon attached to the β carbon of the indoline ring is influenced by the anisotropy of the carbonyl group and shifts diamagnetically upon deuteronation.

Pyrolysis of Deacetylgeissovelline and Derivatives.—Structure **3** suggested that it might be possible to degrade geissovelline to a 3-ethyl-6,7-dimethoxycarbazole. Dehydrogenation or pyrolysis of **3** produced a mixture of uncharacterized *N*-acetylindolines, but no carbazole or *N*-acetylcarbazole. Pyrolysis of **28**, on the other hand, produced a 20% yield of 1-ethyl-6,7-dimethoxycarbazole (**35**), but not the expected 3-ethyl isomer (**36**) as shown by synthesis.[12]



35

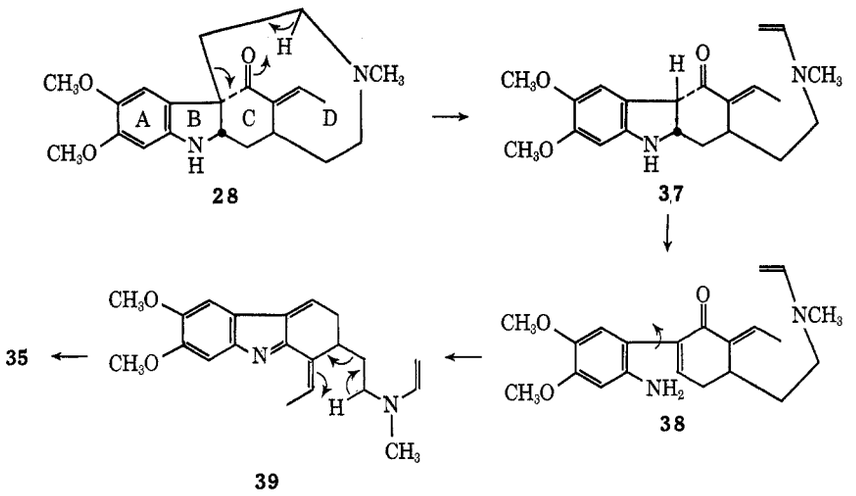


36

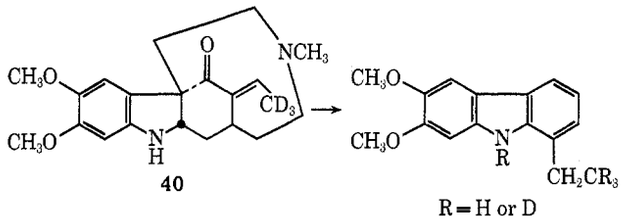
The degradation of **28** is probably initiated by cleavage of ring D at the β position of the indoline ring, abstraction of a *N*-methylene proton, and enolization of the ketone. Subsequent tautomerization to ketone **37** and β-elimination of the indoline nitrogen gives the α,β-unsaturated ketone **38**. Regeneration of the indoline ring from condensation of the amine and ketone groups to **39**[13] followed by tautomerism and elimination of divinylmethylamine results in **35**.

Pyrolysis of deacetylgeissovelline-d_3 (**40**) resulted in a mixture of 17% **35**, 19% mono-, 23% di-, 33% tri-, and 8% tetradeuterated 1-ethyl-6,7-dimethoxycarbazoles and mass spectrometry showed that the deuterium was predominately in the ethyl side chain. If one consid-

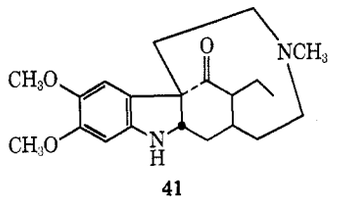
(11) R. R. Ernst, *J. Chem. Phys.*, **45**, 3845 (1966); M. Tanabe, T. Hamasaki, D. Thomas, and L. Johnson, *J. Amer. Chem. Soc.*, **93**, 273 (1971).
(12) R. E. Moore and H. Rapoport, *J. Org. Chem.*, **32**, 3335 (1967).
(13) This β elimination followed by amine–ketone condensation is similar to the rearrangement observed with certain β-amino acids: M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 3877 (1972).



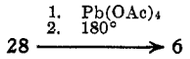
ers the acidity of the olefinic methyl group of **28**, it is not too surprising that scrambling of the deuterium occurs during the pyrolysis, for example by exchange



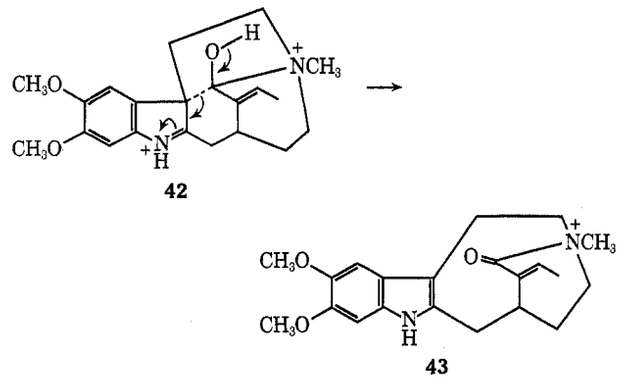
with the indoline NH. The presence of deuterium in the ethyl side chain of the carbazole shows that the ethyl group has originated from the ethylidene group. Dehydrogenation of deacetyldihydrogeissovelline (**41**) with 30% palladium on charcoal at 275° also resulted in the formation of **35**.



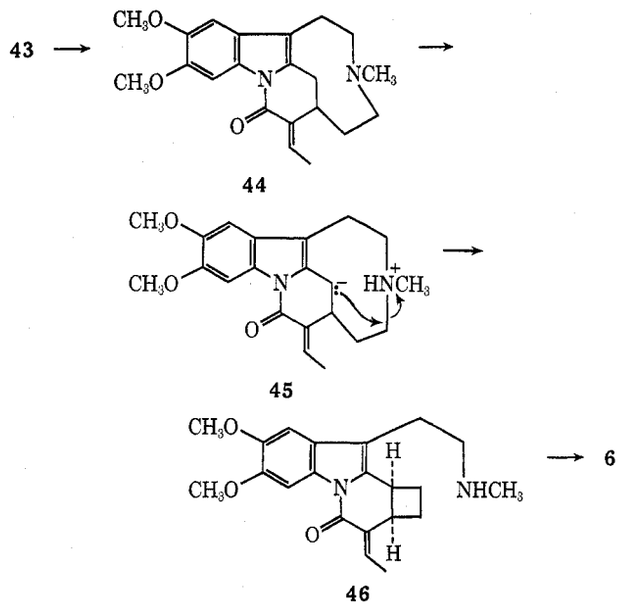
As shown above, when **28** is oxidized first with lead tetraacetate and then pyrolyzed at 180°, a 40% yield of **6** is obtained. The intermediate water-soluble product



of the lead tetraacetate oxidation, which exhibits an ultraviolet spectrum typical of an indole, may have structure **43**, arising presumably from a retroaldol type



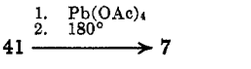
reaction of the bis-protonated indolenine **42**. Pyrolysis of the resulting unstable quaternary amide leads to internal acylation of the indole nitrogen and the product **44**.[14] Examination of a model of **44** in the conformation appearing to have the least torsional and ring strain and steric interaction of groups shows that one of the protons on the methylene attached to the α carbon of the indole ring is very close to the nonbonding pair of electrons of the basic nitrogen. This hydrogen is benzylic and therefore acidic enough to be abstracted by the nitrogen during the pyrolysis. The resulting carbanion **45** would then be in a position to nucleophilically attack the nearby *N*-methylene carbon to displace a secondary amino group and form the cyclobutane compound **46**. A model of **44** indicates that the two reacting carbons are close enough to each other for such a reaction, although unprecedented, to conceivably take place. Rupture of the cyclobutane ring and its subsequent reaction with the secondary amino group finally leads to **6**.



The ethylidene group of **28** appears to have no effect on the course of the reaction, as lead tetraacetate oxidation

(14) J. Harley-Mason and C. G. Taylor, *Chem. Commun.*, 1384 (1969).

of **41** followed by pyrolysis of the oxidation product leads similarly to a 45% yield of **7**.



Experimental Section[15]

Isolation of Geissovelline (3).—The chloroform-soluble portion of 65 g of fraction B[2] was applied to an alumina (Woelm, neutral, 600 g) column. Elution with 6 l. of chloroform removed 4.5 g of yellow oil followed by 5 g of red oil. The yellow oil was dissolved in 50% hexane–benzene and rechromatographed on alumina (Woelm, neutral, 120 g), developing the chromatogram with 250 ml of 50% benzene–hexane, 1-l. portions of 75 and 90% benzene–hexane, 500 ml of benzene, and 500 ml of 25% chloroform–benzene. Elution was continued with 2 l. of 50% chloroform–benzene and evaporation of the solvent gave 2.5 g of a gum which produced 1.45 g of crystalline geissovelline on trituration with ether. From a similar chromatography of 73 g of fraction 1,[3] obtained from further separation of the pH 7 ether extract as previously described, on alumina (Woelm, neutral, 2.2 kg) was obtained 8 g of crystalline geissovelline.

The crude geissovelline was crystallized once from chloroform–ether and twice from ethanol and sublimed at 155° (0.01 mm) to give a white, crystalline powder: mp 189–190°; $[\alpha]^{25}D$ −125° (*c* 1.15, $CHCl_3$); pK_a (50% EtOH–H_2O) = 6.7; uv max (95% EtOH) 217 nm (ε 22,600), 262 (17,500), 299 (10,500); uv max (0.01 *N* ethanolic HCl) 216 nm (ε 21,600), 262 (14,500), 297 (7000); ir (KBr) 1614 (C=O), 1659 cm^- (amide C=O); proton nmr ($CDCl_3$) δ 1.71 (d, 3, *J* = 7.7 Hz, C=CH**CH**$_3$), 1.90 (s, 3, NCH_3), 2.38 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **3a** and **3b**, respectively), 3.22 (m, 1, C=C**H**), 3.92 (s, 6, aromatic OCH_3), 4.79 and 5.25 (two dd, 1, *J* = 12 and 6.5 Hz, NCH for conformers **3a** and **3b**, respectively), 6.45 and 6.52 (quartet, 1, *J* = 7.7 Hz, C=C**H**CH_3 for conformers **3b** and **3a**, respectively), 6.72 and 7.93 (two singlets, 1, aromatic proton ortho to indoline N for conformers **3b** and **3a**, respectively), 7.37 and 7.42 (two singlets, 1, aromatic proton meta to indoline N for conformers **3a** and **3b**, respectively); proton nmr (HI salt in SO_2) δ 1.77 (d, 3, *J* = 7 Hz, C=CH–CH_3), 2.47 (s, 3, $NCOCH_3$), 3.12 (s, 3, $^+NCH_3$), 3.81 (s, 6, aromatic OCH_3), 5.59 (m, 1), 6.19 (q, 1, *J* = 7 Hz, C=C**H**CH_3), 7.54 (s, 1, aromatic proton meta to indoline N), 7.81 (s, 1, aromatic proton ortho to indoline N); carbon-13 nmr ($CDCl_3$) δ 12.8 (olefinic CH_3), 15.1, 22.9 ($NCOCH_3$), 24.0, 29.0, 29.2, 29.4 29.6, 29.9, 30.9, 31.6, 33.4, 40.0 (NCH_3), 40.4, 44.9, 50.0, 55.5, 55.8, 56.0, 56.2, 61.7, 62.2, 100.4, 102.1, 108.7, 110.2, 124.3, 125.5, 126.1, 127.1, 132.8, 134.0, 138.7, 145.9, 148.3, 167.1 (amide C=O), 184.3 (ketone C=O); low-resolution mass spectrum (70 eV) *m/e* (rel intensity) 398 (100), 383 (8), 370 (14), 355 (27), 339 (9), 327 (89), 313 (12), 312 (15), 285 (14), 270 (14), 216 (13), 204 (17), 190 (20), 166 (6), 146 (8), 138 (12), 124 (14), 122 (10), 70 (22), 58 (34), 57 (24), 44 (73), 43 (41), 42 (25); high-resolution mass spectrum (70 eV) *m/e* 398.2202 ($C_{23}H_{30}N_2O_4$), 370.2241 ($C_{22}H_{30}N_2O_3$), 355.2020 ($C_{21}H_{27}N_2O_3$), 339.1464 ($C_{20}H_{21}NO_4$), 327.1473 ($C_{19}H_{21}NO_4$), 312.1227 ($C_{18}H_{18}NO_4$), 285.1354 ($C_{17}H_{19}NO_3$), 270.1127 ($C_{16}H_{16}NO_3$), 216.1017 ($C_{13}H_{14}NO_2$), 204.1017 ($C_{12}H_{14}NO_2$), 190.0862 ($C_{11}H_{12}NO_2$), 146.0602 (C_9H_8NO), 138.1279 ($C_9H_{16}N$), 124.1125 ($C_8H_{14}N$), 122.0970 ($C_8H_{12}N$).

Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.3; H, 7.6; N, 7.0; (2) OCH_3, 15.5; (1) NCH_3, 3.8; (2) CCH_3, 7.5. Found: C, 69.5; H, 7.6; N, 6.9; OCH_3, 15.7; NCH_3, 3.5; CCH_3, 6.6.

Deacetylgeissovelline (28).—A solution of 1 g of geissovelline in 30 ml of 1 *N* hydrochloric acid was heated on the steam bath in a nitrogen atmosphere for 4 hr. The solution was neutralized with sodium bicarbonate and extracted with chloroform under nitrogen. The chloroform was dried and evaporated to give a gum which readily crystallized from ether. Sublimation at 145–150° (0.01 mm) produced 0.82 g (92%) of deacetylgeissovelline as a pale yellow crystalline powder: mp 158–159.5°; $[\alpha]^{28}D$ −6° (*c* 1.07, chloroform); pK_a (50% EtOH–H_2O) = 7.0; uv max (95% EtOH) 230 nm (ε 12,500), 305 (6260); uv max (0.1 *N* ethanolic HCl) 234 nm (ε 8770), 283 (4710); ir (KBr) 1608 (C=O), 1659 (C=C), 3338 cm^{-1} (NH); proton nmr ($CDCl_3$) δ 1.68 (d, 3, *J* = 7.7 Hz, C=CH**CH**$_3$), 1.86 (s, 3, NCH_3), 3.27 (b, 1, NH), 3.76 (s, 3, aromatic OCH_3), 3.81 (s, 3, aromatic OCH_3), 4.26 (dd, 1, *J* = 6.5 and 11.5 Hz, NCH), 6.25 (s, 1, aromatic H ortho to indoline N), 6.43 (q, 1, *J* = 7.7 Hz, C=C**H**–CH_3), 7.22 (s, 1, aromatic H meta to indoline N); carbon-13 nmr ($CDCl_3$) δ 12.9 (CCH_3), 29.4 (CH), 29.8 (CH_2), 36.1 (CH_2), 40.2 (NCH_3), 44.8 (CH_2), 49.3 (NCH_2), 55.1 (NCH_2), 55.9 (OCH_3), 56.5 (OCH_3), 57.6 (quaternary C), 58.7 (NCH), 95.6 (aromatic CH β to indoline N), 110.6 (aromatic CH γ to indoline N), 121.9 (olefinic C), 125.0 (olefinic CH), 139.7 (aromatic CN), 142.3 (aromatic C), 143.0 (aromatic CO), 149.3 (aromatic CO), 186.4 (C=O); carbon-13 nmr (1 *N* DCl in D_2O) δ 12.9 (CCH_3), 25.4 (CH_2), 29.4 (CH), 32.9 (CH_2), 36.6 (CH_2), 43.6 (^+NCH), 56.7 (OCH_3), 56.8(OCH_3), 59.6 (CH_2 and quaternary C), 61.5 (CH_2), 66.3 (^+NCH), 103.0 (CH), 104.5 (^+NCOH), 110.8 (aromatic CH), 126.8 (olefinic C), 128.1 (two aromatic C), 128.8 (CH), 150.8 (two aromatic CO); mass spectrum (70 eV) *m/e* (rel intensity) 356 (100), 341 (10), 328 (8), 327 (10), 313 (19), 285 (70), 270 (42), 256 (17), 216 (82), 204 (34), 190 (32), 146 (16), 124 (22), 110 (17), 58 (17), 57 (16), 44 (32).

Anal. Calcd for $C_{21}H_{28}N_2O_3$: C, 70.8; H, 7.9; N, 7.9; (1) CCH_3, 4.2. Found: C, 70.6; H, 7.8; N, 8.0; CCH_3, 4.1.

To regenerate geissovelline a solution of 15 mg of deacetylgeissovelline in 0.2 ml of pyridine and 0.1 ml of acetic anhydride was heated on the steam bath for 1 hr. The solution was made slightly basic with dilute ammonium hydroxide and extracted with chloroform. The giessovelline crystallized from ether and was sublimed at 155° (0.01 mm): mp and mmp 189–191°; $[\alpha]^{24}D$ −123° (*c* 1.19 chloroform).

Dihydrogeissovelline (29). A. Catalytic Hydrogenation of Geissovelline.—A solution of 125 mg of geissovelline in 5 ml of glacial or 5% ethanolic acetic acid was hydrogenated at atmospheric pressure using 50 mg of platinum oxide catalyst. Fresh catalyst was added periodically until absorption of hydrogen ceased. The acetic acid was removed *in vacuo* and the residual oil was shaken with aqueous sodium bicarbonate solution and chloroform. Evaporation of the chloroform and sublimation of the residual oil gave a white, crystalline solid, mp 50–70°. The melting point of the dihydrogeissovelline was not improved after several recrystallizations from carbon disulfide. The same product was obtained when geissovelline was catalytically hydrogenated in 0.5 *M* methanolic NaOH. Dihydrogeissovelline had the following properties: pK_a (50% EtOH–H_2O) = 8.4; uv max (95% EtOH) 260 nm (ε 14,100), 300 (8500); uv max (0.01 *N* ethanolic HCl) 262 nm (ε 15,600), 298 (7350); uv max (0.1 *N* ethanolic KOH) 262 nm (ε 14,800), 302 (16,000); proton nmr ($CDCl_3$) δ 0.9 (m, 3, CH_2**CH**$_3$), 2.04 (s, 3, NCH_3), 2.38 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **29a** and **29b**, respectively), 3.84 and 3.90 (two singlets, 6, aromatic OCH_3 for conformers **29b** and **29a**, respectively), 4.68 and 5.12 (two triplets, 1, NCH for conformers **29a** and **29b**, respectively), 6.72 and 7.92 (two singlets, 1, aromatic proton ortho to indoline N for conformers **29b** and **29a**, respectively), 7.00 and 7.12 (two singlets, 1, aromatic proton meta to indoline N for conformers **29a** and **29b**, respectively); mass spectrum (70 eV) *m/e* (rel intensity) 400 (54), 385 (11), 372 (11), 357 (11), 343 (11), 314 (11), 313 (35), 290 (21), 204 (11), 190 (14), 126 (22), 59 (100), 44 (25), 43 (20).

Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 69.0; H, 8.1. Found: C, 68.6; H, 7.9.

B. Sodium Borohydride Reduction of Geissovelline.—Sodium borohydride (250 mg) was added in five portions over 10 hr to a solution of 100 mg of geissovelline in 20 ml of 0.05 *N* ethanolic sodium hydroxide. After standing overnight dilute aqueous hydroxide was added, the ethanol was removed *in vacuo*, and the mixture was extracted with chloroform. The chloroform was evaporated to give dihydrogeissovelline, identical with the product produced by catalytic hydrogenation.

Deacetyldihydrogeissovelline (41). A. From Deacetylgeissovelline.—Deacetylgeissovelline (200 mg) in 6 ml of glacial acetic acid was hydrogenated at atmospheric pressure using 60 mg of platinum oxide. The mixture was filtered and evaporated *in vacuo* and the residual oil was distributed between dilute ammonium hydroxide and chloroform. The chloroform layer was separated and evaporated and the residue was sublimed at

(15) All melting points were determined on a Kofler hot stage and are uncorrected; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley; pK_a measurements were determined in 50% ethanol–water. Proton nmr spectra were determined on Varian A-60, HA-100, HR 220, and HR 300 spectrometers; carbon-13 nmr spectra were recorded on a XL-100 spectrometer equipped with Fourier transform; all chemical shifts are reported as δ units relative to TMS (δ 0) as an internal standard in organic solutions or an external standard in aqueous solutions. Low-resolution mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D spectrometer; high-resolution mass measurements were made on a CEC-21-110B instrument.

150° (0.01 mm) to give deacetylhydrogeissovelline: mp 50–60°; uv max (EtOH) 303 nm (ε 4980), sh 235 (11,100); uv max (0.1 *N* ethanolic HCl) 280 nm (ε 4730), 230 (8700); proton nmr ($CDCl_3$) δ 0.9 (m, 3, CCH_3), 2.00 (s, 3, NCH_3), 3.70 (b, 1, NH), 3.79 (s, 6, OCH_3), 4.18 (t, 1, NCH), 6.28 (s, 1, aromatic H ortho to indoline N), 6.93 (s, 1, aromatic H meta to indoline N).

Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.4; H, 8.4; (1) CCH_3, 4.2. Found: C, 70.7; H, 8.6; (1) CCH_3, 2.6.

The volatile acids from the Kuhn–Roth oxidation showed the presence of acetic and propionic acids by paper chromatography.

B. From Dihydrogeissovelline.—A solution of 35 mg of dihydrogeissovelline in 2 ml of 1 *N* hydrochloric acid was heated on the steam bath in a nitrogen atmosphere for 5 hr. The solution was made basic with sodium bicarbonate and extracted with chloroform under nitrogen. The chloroform was evaporated and the residual gum was sublimed at 150° (0.01 mm) to give deacetyldihydrogeissovelline, mp 60–80°.

Dihydroxydihydrogeissovelline (14).—Osmium tetroxide (100 mg) was added to a solution of 100 mg of geissovelline in 1.5 ml of pyridine and 1.5 ml of benzene. After standing overnight at room temperature the dark brown mixture was shaken with 7.5 ml of benzene, 10 ml of methanol, 1.8 g of sodium sulfite, 1.5 g of sodium bicarbonate, and 20 ml of water for 24 hr to decompose the osmate ester. The mixture was filtered through Celite and the Celite was washed with benzene and then with benzene–methanol. The combined filtrate and washings were concentrated *in vacuo* and extracted several times with benzene. Evaporation of the benzene gave 93 mg (86%) of dihydroxydihydrogeissovelline as a white, crystalline solid: mp 100–110°; $[\alpha]^{20}D$ −120° (*c* 0.69, chloroform); pK_a (50% EtOH–H_2O) = 6.7; uv max (95% EtOH) 258 nm (ε 13,750), 229 (8620); uv max (0.01 *N* ethanolic HCl) 262 nm (ε 14,100), 301 (7150); ir (KBr) 1655 (amide C=O), 3300–3600 cm^{-1} (OH); proton nmr ($CDCl_3$), δ 1.08 (d, 3, *J* = 6.1 Hz, $CH(OH)CH_3$), 2.13 (s, 3, NCH_3), 2.33 and 2.45 (two singlets, 3, $NCOCH_3$ for conformers **14a** and **14b**, respectively), 3.84 and 3.88 (two singlets, 6, aromatic OCH_3 for conformers **14b** and **14a**, respectively), 4.32 (quartet, 1, *J* = 6.1 Hz, $CH(OH)CH_3$), 4.64 and 5.07 (two triplets, 1, NCH for conformers **14a** and **14b**, respectively), 6.72 and 7.92 (two singlets, 1, aromatic proton ortho to indoline N for conformers **14b** and **14a**, respectively), 7.00 and 7.12 (two singlets, 1, aromatic proton meta to indoline N for conformers **14a** and **14b**); mass spectrum (70 eV) *m/e* (rel intensity) 432 (46), 415 (71), 404 (8), 387 (20), 373 (8), 359 (10), 341 (12), 331 (19), 328 (21), 327 (17), 325 (21), 303 (22), 289 (14), 204 (24), 190 (27), 158 (14), 155 (14), 149 (14), 142 (19), 141 (24), 85 (72), 83 (100), 81 (33), 71 (31), 69 (67), 57 (57), 55 (53), 45 (29), 43 (64), 41 (93).

Anal. Calcd for $C_{23}H_{32}N_2O_6$: C, 63.9; H, 7.5; N, 6.5. Found: C, 64.0; H, 7.5; N, 6.8.

The diol could be recrystallized twice from chloroform to give a small quantity of white needles, mp 170–176°. The bulk of the material, mp 110–130°, which remained in the mother liquors could not be improved in melting point by recrystallization.

Geissovelline-d_6 (34).—Sodium (100 mg) was dissolved in 5 ml of absolute deuterium ethoxide (90 atom %) and 100 mg of geissovelline was added. After standing at room temperature for 4 hr, the yellow solution was concentrated and distributed between deuterium oxide and chloroform. The chloroform was separated and evaporated to give a gum which readily crystallized in ether. Electronic integration of the nmr spectrum of the geissovelline-d_6 indicated the presence of 5.1 deuterons (95% exchange); mass spectrum (70 eV) *m/e* (elemental composition) 404 ($C_{23}H_{24}D_6N_2O_4$), 386 ($C_{22}H_{24}D_3N_2O_4$), 376 ($C_{22}H_{24}D_6N_2O_3$), 358 ($C_{21}H_{24}D_3N_2O_3$), 345 ($C_{20}H_{15}D_6NO_4$), 333 ($C_{19}H_{15}D_6NO_4$), 319 ($C_{18}H_{13}D_6NO_4$), 318 ($C_{18}H_{12}D_6NO_4$), 289 ($C_{17}H_{15}D_4NO_3$), 274 ($C_{16}H_{12}D_4NO_3$), 217 ($C_{13}H_{13}DNO_2$), 205 ($C_{12}H_{13}DNO_2$), 191 ($C_{11}H_{11}DNO_2$), 169 ($C_{10}H_{13}D_3NO$), 147 (C_9H_7DNO), 141 ($C_9H_{13}D_3N$), 127 ($C_8H_{11}D_3N$), 125 ($C_8H_9D_3N$), 70 (C_4H_8N), 58 (C_3H_8N), 57 (C_3H_7N), 46 (C_2D_3O), 44 (C_2H_6N), 43 (C_2H_5N), 42 (C_2H_4N).

Deacetylgeissovelline-d_3 (40).—Geissovelline-d_6 (100 mg) was hydrolyzed to **40** using the procedure described above for the preparation of **28**. Electronic integration of the nmr spectrum of **40** showed the presence of 2.5 deuterons (93% exchange).

***N*-Ethyldeacetyldihydrogeissovelline (30).**—A solution of 100 mg of geissovelline in 5 ml of chloroform was added to a solution of 100 mg of lithium aluminum hydride in 50 ml of ether. After standing at room temperature for 3 hr, the mixture was treated with ethyl acetate to decompose the excess hydride and then shaken with 25 ml of 10% sodium hydroxide solution. The ether was separated, dried (Na_2SO_4), and evaporated and the residue was sublimed at 150° (0.01 mm) to give *N*-ethyldeacetylhydrigeissovelline as a yellow gum which could not be induced to crystallize: uv max (95% EtOH) 251 nm (ε 9800), 328 (5220); uv max (0.5 *N* ethanolic HCl) 235 nm (9850), 282 (4900); proton nmr ($CDCl_3$) δ 0.88 (t, 3, *J* = 7.5 Hz, CCH_2CH_3), 1.21 and 1.24 (two triplets, 3, *J* = 7 Hz, NCH_2CH_3 for conformers **30a** and **30b**, respectively), 2.01 (s, 3, NCH_3), 3.24 (quartet, 2, *J* = 7 Hz, NCH_2CH_3), 3.78 and 3.84 (two singlets, 6, aromatic OCH_3 for conformers **30b** and **30a**, respectively), 4.06 (dd, 1, *J* = 7.5 and 9 Hz, NCH), 6.02 and 6.03 (two partially resolved singlets, 1, aromatic H ortho to indoline N for conformers **30b** and **30a**, respectively), 6.83 and 6.94 (two singlets, 1, aromatic H meta to indoline N).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.5; H, 8.9; N, 7.3; (2) CCH_3, 7.8. Found: C, 71.3; H, 8.6; N, 7.3; CCH_3, 3.8.[16]

The volatile acids from the Kuhn–Roth oxidation showed the presence of acetic acid and propionic acids by paper chromatography.

Reduction of *N*-Ethyldeacetyldihydrogeissovelline with Lithium Aluminum Hydride in Tetrahydrofuran.—A mixture of 50 mg of *N*-ethyldeacetyldihydrogeissovelline and 200 mg of lithium aluminum hydride in 10 ml of freshly distilled tetrahydrofuran was refluxed in a dry nitrogen atmosphere for 24 hr. The excess hydride was decomposed with ethyl acetate, the solvent was removed under reduced pressure, and the residue was distributed between 10% sodium hydroxide solution and chloroform. Evaporation of the chloroform gave a mixture, probably *C*-ethyl epimers of **31**, **33**, and unreduced **30**, as a yellow gum which darkened on exposure to air: ir (KBr) 1725, 3400–3600 cm^{-1} (OH); nmr ($CDCl_3$) δ 2.01 (NCH_3 for unreacted *N*-ethyldeacetyldihydrogeissovelline), 2.28 (NCH_3), 2.45 (NCH_3).

Treatment of the crude reduction product with ketene in benzene for 5 min gave a gum which was distributed between benzene and dilute hydrochloric acid. The aqueous layer was shaken with air, neutralized with sodium bicarbonate, and extracted with benzene and the benzene was evaporated to give a mixture of **30** and **32** as a gum: nmr (CS_2) δ 1.92 (NCH_3 for unreduced *N*-ethyldeacetyldihydrogeissovelline), 2.02 ($OCOCH_3$), 2.27 (NCH_3), 5.23 (d, 1, *J* = 6 Hz, CHCHOAC).

Lead Tetraacetate Oxidation of Deacetylgeissovelline. Isolation of Compound 6.—A solution of 100 mg (0.28 mmol) of deacetylgeissovelline in 0.1 ml of glacial acetic acid and 10 ml of benzene was shaken with 135 mg (0.30 mmol) of lead tetraacetate for 1 min. The mixture was filtered through $MgSO_4$, the dark yellow filtrate (and $CHCl_3$ wash of the $MgSO_4$) was evaporated *in vacuo* at room temperature, and the residue was sublimed rapidly at 180–200° (0.1 mm) to give 30–40 mg of compound **6** as a light yellow, waxy solid: uv max (95% EtOH) 230 nm (ε 20,600), 281 (19,200), sh 320 (5710); ir (KBr) 1625, 1637 (conjugated C=C), 1690 cm^{-1} (amide C=O); proton nmr ($CDCl_3$) δ 1.88 (d, 3, *J* = 7.5 Hz, $COC{=}CHCH_3$), 2.41 (s, 3, NCH_3), 3.95 (s, 3, aromatic OCH_3), 3.97 (s, 3, aromatic OCH_3), 4.53 (dd, 1, *J* = 13 and 3 Hz, NCCHN), 6.90 (s, 1, aromatic H meta to indole N), 7.15 (quartet, 1, *J* = 7.5 Hz, $CO{-}C{=}CHCH_3$), 8.00 (s, 1, aromatic H ortho to indole N); mass spectrum (70 eV) *m/e* 354.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4. Found: C, 71.3; H, 7.6.

Lead Tetraacetate Oxidation of Deacetyldihydrogeissovelline. Isolation of Compound 7.—A mixture of 170 mg of deacetyldihydrogeissovelline in benzene, 0.2 ml of acetic acid, and 210 mg of lead tetraacetate was shaken for 1 min. The mixture was filtered through magnesium sulfate and the filtrate and $CHCl_3$ wash of the $MgSO_4$ were evaporated *in vacuo*. The foamy residue was rapidly heated at 180° (0.1 mm) in a sublimation apparatus and compound **7** was collected on the cold finger as a yellow, waxy solid. The unsublimed portion was redissolved in chloroform, the chloroform was evaporated, and the residue again heated in the sublimation apparatus for an additional yield of compound **7**. The total yield of compound **7** was 75 mg (45%): uv max (95% EtOH) 261 nm (ε 17,000), 295 (7400); proton nmr ($CDCl_3$) δ 1.0 (m, 3, CH_2CH_3), 2.41 (s, 3, NCH_3), 3.93 (s, 3, aromatic OCH_3), 3.95 (s, 3, aromatic OCH_3), 6.88 (s, 1, aromatic H meta to indole N), 7.94 (s, 3, aromatic H ortho to indole N); mass spectrum (70 eV) *m/e* 356.

Compound **7** could also be obtained by catalytic hydrogenation

(16) The yield of acetic acid from Kuhn–Roth oxidation of an *N*-ethyl group is generally very low.

of 6 with 1 molar equiv of hydrogen in ethanol using a platinum catalyst.

1,2,3,4-Tetrahydro-11-methyl-6,7-dimethoxycarbazolenine.—A solution of 2.05 g (0.01 mol) of 3,4-dimethoxyphenylhydrazine hydrochloride and 1.11 g (0.01 mol) of 2-methylcyclohexanone in 100 ml of 50% methanol–benzene was heated to reflux in a nitrogen atmosphere, 2 ml of pyridine was added, and the mixture was refluxed for 15 min and then evaporated *in vacuo*. The residue was dissolved in 50 ml of glacial acetic acid, the mixture was heated for 10 min on the steam bath and then evaporated, and the residue was distributed between ether and dilute hydrochloric acid. The aqueous layer was neutralized with ammonium hydroxide and extracted with ether, the ethereal layer was evaporated, and the residual oil was treated with picric acid. The precipitated picrate was washed thoroughly with warm ethanol and then distributed between ether and aqueous ethanolamine. After the ethereal layer was washed free of ethanolamine picrate, it was dried (Na_2SO_4) and evaporated to give a gum which crystallized readily from *n*-hexane. After repeated vacuum sublimation and recrystallization from *n*-hexane, 0.71 g (28%) of the pure carbazolenine as pale yellow crystals was obtained: mp 72.5–73.5°; uv max (95% EtOH) 219 nm (ϵ 21,400), 290 (6800); uv max (0.1 *N* ethanolic HCl) 223 nm (ϵ 24,400) sh 245 (15,400), 330 (5190); proton nmr ($CDCl_3$) δ 1.28 (s, 3, C-11 methyl), 3.91 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 6.88 (s, 1, aromatic H on C-8), 7.23 (s, 1, aromatic H on C-5).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.8. Found: C, 73.1; H, 7.7.

9-Crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (4).—A solution of 250 mg of 1,2,3,4-tetrahydro-11-methyl-6,7-dimethoxycarbazolenine in ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of platinum oxide catalyst. When hydrogen was no longer absorbed, the mixture was filtered and the filtrate was evaporated to give 1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole as a colorless gum which was air sensitive and could not be induced to crystallize.

A stirred solution of 90 mg (1.05 mmol) of crotonic acid in 10 ml of acetone and 0.1 ml of water was cooled to 0° and 0.15 ml of triethylamine and 100 mg (0.92 mmol) of ethyl chloroformate in 5 ml of acetone was added. Stirring was continued at 0° for 1 hr, 200 mg (0.81 mmol) of 1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole in acetone was then added all at once, and the mixture was stirred at room temperature for an additional 3 hr. The acetone was evaporated and the residue was distributed between 1 *N* potassium hydroxide solution and ether. Evaporation of the ether gave a gum that slowly crystallized from *n*-hexane. After two recrystallizations from *n*-hexane and sublimation at 130° (0.1 mm), light yellow crystals of 9-crotonyl-1,2,3,4,10,11-hexahydro-11-methyl-6,7-dimethoxycarbazole (**4**) were obtained: mp 143–145°; uv max (95% EtOH) 212 nm (ϵ, 22,400), 295 (10,400), 316 (12,500); ir (KBr) 1658 cm^{-1} (amide C=O); proton nmr ($CDCl_3$) δ 1.13 (s, 3, C-11 methyl), 1.97 (dd, 3, J = 7.5 and 1.5 Hz, $COCH{=}CHCH_3$), 3.91 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 4.03 (m, 1, C-10 proton), 6.33 (doublet of quartets, 1, J = 15 and 1.5 Hz, $CO\text{-}CH{=}CHCH_3$), 6.71 (s, 1, aromatic H on C-5), 7.12 (doublet of quartets, 1, J = 15 and 7.5 Hz, $COCH{=}CHCH_3$), 8.01 (b, 1, aromatic H on C-8).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.4; H, 8.0. Found: C, 72.2; H, 7.9.

1,2,3,4-Tetrahydro-6,7-dimethoxycarbazole.—A mixture of 3.8 g of 4-aminoveratrole, 3.4 g of 2-chlorocyclohexanone, and 2.5 g of anhydrous sodium acetate in 100 ml of absolute ethanol was refluxed for 6 hr in a nitrogen atmosphere. Sodium chloride precipitated during the first hour of reflux. The mixture was evaporated *in vacuo*, the residue was distributed between water and ether, and the ethereal layer was washed with 0.5 *M* hydrochloric acid and water, dried ($MgSO_4$), and evaporated slowly under a stream of nitrogen to give 1.7 g (30%) of indole which was sublimed at 90° (0.1 mm): mp 108–110° (lit.[17] mp 105–106°); uv max (95% EtOH) 229 nm (ϵ 28,100), sh 280 (5200), 303 (8850); proton nmr ($CDCl_3$) δ 1.85 (m, 4, C-2 and C-3 CH_2), 2.63 (m, 4, C-1 and C-4 CH_2), 3.80 (s, 3, aromatic OCH_3), 3.89 (s, 3, aromatic OCH_3), 6.68 (s, 1, aromatic H on C-5), 6.94 (s, 1, aromatic H on C-8), 7.66 (b, 1, indole NH).

9-Crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (5).—A solution of 500 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole in 18 ml of 50% sulfuric acid was placed in a porous cup and reduced electrolytically for 48 hr using a 6-V battery and lead electrodes (1 × 10 cm separated by 3 cm). After 48 hr an aliquot remained clear on dilution with water. The solution was diluted with water, washed with ether, made basic with sodium bicarbonate and sodium sulfite, and extracted again with ether to remove the product. The ether was evaporated and the residue, which darkened on exposure to air, was distilled (short-path) at 110° (0.3 mm.) to give 280 mg of 1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole as a light yellow oil.

A solution of 130 mg of crotonic acid in 10 ml of acetone and 0.1 ml of water was cooled to 0° and 0.2 ml of triethylamine was added followed by 150 mg of ethyl chloroformate in acetone. Triethylamine hydrochloride precipitated and the mixture was stirred at 0° for 1 hr. The 280 mg of 1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole in acetone was added all at once and the mixture was stirred for 3 hr at room temperature, concentrated *in vacuo*, and distributed between 1 *N* potassium hydroxide solution and ether. The ethereal layer was washed with dilute hydrochloric acid and then with aqueous sodium sulfite, dried (Na_2SO_4), and evaporated to give 312 mg of 9-crotonyl-1,2,3,4-10,11-hexahydro-6,7-dimethoxycarbazole as a yellow gum.

A mixture of 177 mg of 9-crotonyl-1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 10 ml of benzene, 0.1 ml of acetic acid, and 300 mg of lead tetraacetate was stirred for 5 min. The benzene solution was decanted and washed with aqueous sodium sulfite solution, dried (Na_2SO_4), and evaporated. The product, which crystallized from chloroform–ether, was sublimed at 155° (0.4 mm) and recrystallized several times from chloroform–ether to give 100 mg of 9-crotonyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole (**5**) as light yellow crystals: mp 128–130°; uv max (95% EtOH) 220 nm (ϵ 26,800), 281 (17,500), sh 320 (5800); proton nmr ($CDCl_3$) δ 1.85 (m, 4, C-2 and C-3 CH_2), 2.00 (dd, 3, J = 7.5 and 1.5 Hz, $COCH{=}CH{-}CH_3$), 2.62 (m, 2, C-4 CH_2), 2.86 (m, 2, C-1 CH_2), 3.92 (s, 6, aromatic OCH_3), 6.57 (doublet of quartets, 1, J = 15 and 1.5 Hz, $COCH{=}CHCH_3$), 6.82 (s, 1, aromatic H on C-5), 7.12 (doublet of quartets, 1, 15 and 7.5 Hz, $COCH{=}CHCH_3$), 7.80 (s, 1, aromatic H on C-8).

Anal. Calcd. for $C_{18}H_{21}NO_3$: C, 72.2; N, 4.7. Found: C, 72.1; N, 4.5.

Hofmann Degradation of Compound 7.—A solution of 75 mg of compound **7** in 2.5 ml of methanol and 2.5 ml of methyl iodide was refluxed under argon for 2 hr. Evaporation of the solvent gave the methiodide of compound **7** as a brown resin which was dissolved in 5 ml of water and shaken with 70 mg of freshly prepared silver oxide for 30 min. The mixture was filtered, the filtrate was washed with chloroform and evaporated, and the methohydroxide of compound **7** was pyrolyzed in a sublimation apparatus at 190° (0.1 mm). Compound **8** was deposited on the cold finger as a yellow gum (55 mg) which could not be induced to crystallize: uv max (95% EtOH) 224, 261, 295 nm; proton nmr ($CDCl_3$) δ 1.08 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.20 and 2.36 (two singlets, 3, NCH_3 for conformers **8b** and **8a**, respectively), 3.93 (s, 6, aromatic OCH_3), 5.37 (dd, 1, J = 12 and 2 Hz, vinyl methylene H trans to indole ring), 5.62 (dd, 1, J = 18 and 2 Hz, vinyl methylene H cis to indole ring), 6.77 (dd, 1, J = 12 and 18 Hz, vinyl methine H), 6.87 and 7.13 (two singlets, 1, aromatic H meta to indole N for conformers **8a** and **8b**, respectively), 8.04 and 8.09 (two singlets, 1, aromatic H ortho to indole N for conformers **8a** and **8b**, respectively).

A solution of 55 mg of compound **8** in ethanol was hydrogenated at atmospheric pressure using 5 mg of platinum oxide catalyst. When absorption of hydrogen had ceased, the mixture was filtered, the filtrate was evaporated, and the residue was distributed between dilute phosphoric acid and chloroform. Evaporation of the chloroform left 10 mg of a brown gum, compound **10**, which could not be induced to crystallize: proton nmr (CS_2) δ 1.0 (m, 3, $CHCH_2CH_3$), 1.22 (m, 3, $=CCH_2CH_3$), 3.71 (s, 6, aromatic OCH_3), 6.64 (s, 1, aromatic H meta to indole N), 7.77 (s, 1, aromatic H ortho to indole N); mass spectrum (70 eV) m/e 329. The aqueous portion was made basic with ammonium hydroxide and extracted with chloroform. Evaporation of the chloroform and sublimation of the residual gum gave 40 mg of compound **9** as a light, yellow solid: mass spectrum (70 eV) m/e 372.

A solution of 40 mg of compound **9** in 1 ml of methanol and 1 ml of methyl iodide was refluxed under argon in the presence of a small amount of anhydrous potassium carbonate for 2 hr. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residual glass, the methiodide of compound **9**, was dissolved

(17) R. J. S. Beer, L. McGrath, A. Robertson, A. B. Woodier, and J. S. E. Holker, *J. Chem. Soc.*, 2061 (1949).

in water and the solution was shaken with 4 mg of freshly prepared silver oxide for 30 min. Filtration of the mixture and evaporation of the chloroform-washed filtrate gave the methohydroxide of **9** as a brown glass. Pyrolysis in a sublimation apparatus at 190° (0.1 mm) led to an orange-brown solid which was distributed between dilute phosphoric acid and chloroform. Evaporation of the chloroform gave 12 mg of compound **12** as a light brown gum: proton nmr ($CDCl_3$) δ 5.41 (dd, 1, J = 12 and 2 Hz, vinyl methylene H trans to indole ring), 5.65 (dd, 1, J = 18 and 2 Hz, vinyl methylene H cis to indole ring), 6.78 (dd, 1, J = 12 and 18 Hz, vinyl methine H), 6.88 and 7.16 (two singlets, 1, aromatic H meta to indole N for conformers **12a** and **12b**), 8.05 and 8.08 (two singlets, 1, aromatic H ortho to indole N for conformers **12a** and **12b**; mass spectrum (70 eV) m/e 327.

Periodate Oxidation of Dihydrodihydrogeissovelline. Isolation of Compound 18.—A solution of 259 mg (0.60 mmol) of dihydroxydihydrogeissovelline (**14**) in 2 ml of methanol and 4 ml of water was treated with a solution of 256 mg (1.20 mmol) of sodium metaperiodate in 8 ml of water over a period of 24 hr at 0–5°. After standing for an additional 24 hr at 0–5°, the mixture was extracted with chloroform. Evaporation of the chloroform gave 105 mg (40%) of a colorless gum which slowly crystallized. Recrystallization from chloroform–ether (seeding) gave pure compound **18**: mp 175–177° after drying at 90° (0.2 mm); uv max (95% EtOH) 269 mm (ϵ 11,300), 303 (7600); ir (KBr) 1615 (carboxylic acid C=O), 1653 (amide C=O), 1725 (ester C=O), 2400–3600 cm^{-1} (carboxylic acid OH); proton nmr ($CDCl_3$) δ 2.27 (s, 3, NCH_3), 2.57 (s, 3, $NCOCH_3$), 3.60 (s, 3, CO_2CH_3), 3.87 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 5.62 (m, 1, NCH), 6.62 (s, 1, aromatic H meta to indoline N), 6.95 (b, 1, aromatic H ortho to indoline N), 9.92 (b, 1, CO_2H); carbon-13 nmr ($CDCl_3$) δ 25.8 ($NCOCH_3$), 32.0, 33.6, 41.4, 44.0 (NCH_3), 45.6 (CH), 49.6, 52.1 (CO_2CH_3), 56.3 (CH_2 and two aromatic OCH_3), 58.2 (quaternary C), 75.7 (NCH), 100.2 (aromatic CH), 106.4 (aromatic CH), 126.8 (aromatic quaternary C), 134.7 (aromatic quaternary C), 146.2 (aromatic $COCH_3$), 149.2 (aromatic $COCH_3$), 169.8 (C=O), 173.5 (C=O), 177.8 (C=O); mass spectrum (70 eV) m/e (rel intensity) 434 (17), 419 (6), 415 (4), 406 (7), 391 (14), 375 (100), 303 (12), 290 (22), 204 (25), 190 (13), 144 (15), 142 (18), 141 (11), 138 (15), 87 (10), 85 (55), 83 (82), 58 (20), 57 (40), 44 (20), 43 (18).

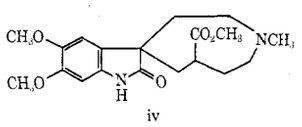
Anal. Calcd for $C_{22}H_{30}N_2O_7$: C, 60.8; H, 7.0; N, 6.5; (3) OCH_3, 21.3; (1) NCH_3, 3.5. Found: C, 60.9; H, 7.2; N, 6.5; OCH_3, 19.6; NCH_3, 3.1.

To a solution of 100 mg of sodium in 2.5 ml of absolute deuterium ethoxide (90%) was added a solution of 50 mg of **18** in 2.5 ml of absolute deuterium ethoxide. The mixture was allowed to stand at room temperature under nitrogen for 1.5 hr, diluted with 5 ml of deuterium oxide (99.5%), and extracted with chloroform. The chloroform extract was washed with a small amount of D_2O, dried over anhydrous magnesium sulfate, and evaporated to dryness to give tetradeuterated **18** which showed no signals at δ 2.57 ($NCOCH_3$) or 9.92 (CO_2H) in the proton nmr spectrum ($CDCl_3$).

Hydrolysis and Oxidation of Compound 18.—A solution of 100 mg of **18** in 5 ml of 2 N hydrochloric acid was heated on the steam bath under a nitrogen atmosphere for 1 hr. Evaporation *in vacuo* gave compound **24** as a water-soluble glass: uv max (0.01 N ethanolic HCl) 239 nm (ϵ 5200), 282 (4500); ir (KBr) 1620, 1725 (carboxylic acid C=O), 2600–3600 cm^{-1}.

A solution of compound **24** in 10 ml of 0.01 N ethanolic HCl was shaken periodically for 1 hr with air. The oxidation was monitored by ultraviolet spectroscopy and after 20 min the spectrum had changed from an indoline to that of an indole. Evaporation *in vacuo* gave **26** as a water-soluble glass [uv max (95% EtOH) 302 nm (ϵ 8800)] which was dissolved in methanol saturated with dry hydrogen chloride and allowed to stand in a stoppered flask at room temperature for 24 hr. The methanolic HCl was evaporated *in vacuo* and the residue was distributed between aqueous sodium bicarbonate and chloroform. Evaporation of the chloroform gave **27** as a yellow gum which darkened rapidly on contact with air: uv max (95% EtOH) sh 260, 302 nm; proton nmr[18] ($CDCl_3$) δ 1.92 (NCH_3), 2.53 (NCH_3), 3.61 (OCH_3), 3.75 (OCH_3), 3.81 (OCH_3), 3.84 (OCH_3), 3.89 (OCH_3), 6.71 (aromatic H), 6.81 (aromatic H), 7.01 (aromatic H). Compound **27** was also obtained by a similar air oxidation of **25** (see below).

(18) It was not determined whether the complexity (*i.e.*, doubling) of the nmr spectrum was due to a slow interconversion of conformers or to a mixture of oxidation products such as the indole **27** and oxindole iv.



iv

Compound 20. A. From Compound 18.—A solution of 17 mg of compound **18** in ether was treated with excess diazomethane at 0° for 1 hr. Evaporation of the ether gave compound **20** as a colorless gum: uv max (95% EtOH) 266, 302 nm; ir ($CHCl_3$) 1650 (amide C=O), 1730 cm^{-1} (ester C=O); proton nmr ($CDCl_3$) δ 2.34 (s, 3, NCH_3), 2.42 (s, 3, $NCOCH_3$), 3.63 (s, 3, CO_2CH_3), 3.74 (s, 3, CO_2CH_3), 3.87 (s, 3, aromatic OCH_3), 3.93 (s, 3, aromatic OCH_3), 5.55 (m, 1, NCH), 6.60 (s, 1, aromatic H meta to indoline N), 7.30 (b, 1, aromatic H ortho to indoline N); mass spectrum (70 eV) m/e 448.

B. From Compound 24. A solution of compound **24** in absolute methanol saturated with dry hydrogen chloride was allowed to stand for 24 hr under nitrogen. Evaporation of the methanolic HCl gave compound **25** [uv max (95% EtOH) 282 nm] as a light yellow air-sensitive gum. Compound **25** was also obtained when **18** was treated similarly.

A solution of compound **25** in benzene was treated with ketene and allowed to stand for 5 min. The mixture was introduced onto a short alumina column. The column was washed thoroughly with benzene and the product was eluted with 50% chloroform–benzene and chloroform. The resulting gum was distributed between benzene and 0.5 M sodium dihydrogen phosphate solution and the aqueous layer was neutralized with dilute ammonium hydroxide and extracted with benzene. Evaporation of the benzene gave compound **20**.

Compound 22.—A solution of 50 mg of compound **18** in ether–chloroform was added to a solution of 100 mg of lithium aluminum hydride in ether and the mixture was allowed to stand at room temperature for 3 hr. The excess hydride was decomposed with ethyl acetate, the mixture was shaken with 10% sodium hydroxide solution, and the ethereal layer was separated, dried, and evaporated. The yellow gum, a mixture of **21** and **22**, was distributed between benzene and dilute hydrochloric acid and the aqueous layer was separated, allowed to stand in contact with air for 20 min, neutralized with aqueous sodium bicarbonate, and extracted with benzene. Evaporation of the benzene gave compound **22** as a yellow gum: uv max (95% EtOH) 231, sh 280, 304 nm; proton nmr (CS_2) δ 1.3 (t, 3, J = 7.5 Hz, NCH_2CH_3), 2.4 (s, 3, NCH_3), 3.7 (d, 2, J = 6 Hz, CH_2OH), 3.9 (s, 6, aromatic OCH_3), 4.1 (quartet, 2, J = 7.5 Hz, NCH_2CH_3), 6.8 (s, 1, aromatic H meta to indole N), 7.0 (s, 1, aromatic H ortho to indole N).

Compound 23.—A solution of compound **22** in benzene was treated with ketene. The product was washed into dilute hydrochloric acid and the aqueous layer was neutralized with sodium bicarbonate and extracted with benzene. Evaporation of the benzene and sublimation of the residue gave compound **23** as a light yellow gum: uv max (95% EtOH) 231, sh 280, 304 nm; proton nmr (CS_2) δ 1.30 (t, 3, J = 7.5 Hz, NCH_2CH_3), 2.11 (s, 3, $OCOCH_3$), 2.39 (s, 3, NCH_3), 3.93 (s, 6, aromatic OCH_3), 4.10 (quartet, 2, J = 7.5 Hz, NCH_2CH_3), 4.19 (d, 2, J = 7 Hz, $CHCH_2OAc$), 6.80 (s, 1, aromatic H meta to indole N), 6.96 (s, 1, aromatic H ortho to indole N).

Pyrolysis of Deacetylgeissovelline to 1-Ethyl-6,7-dimethoxycarbazole (35).—Deacetylgeissovelline (100 mg) was pyrolyzed at 280° in a nitrogen atmosphere for 0.5 r. The product was sublimed at 0.01 mm, the yellow solid was distributed between ether and 1 N hydrochloric acid, the ether was dried and evaporated, and the residue was sublimed at 140° (0.2 mm) to give 15 mg (21%) of crude 1-ethyl-6,7-dimethoxycarbazole. After several recrystallizations from absolute ethanol, the carbazole (prisms) melted at 136–138° with resolidification to needles: mp and mmp 159–160° (lit.[12] mp 157.5–158°); uv max (95% EtOH) 210 nm (ϵ 28,000), 235 (44,300), sh 250 (19,400), 262 (15,600), 303 (17,500), 335 (5190), 340 (5280); ir (KBr) 3477 cm^{-1} (NH); proton nmr ($CDCl_3$) δ 1.38 (t, 3, J = 7.5 Hz, CH_2CH_3), 2.88 (quartet, 2, J = 7.5 Hz, CH_2CH_3), 3.90 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 6.92 (s, 1, aromatic H on C-8), 7.19 (m, 2, aromatic protons on C-2 and C-3), 7.51 (s, 1, aromatic H on C-5), 7.81 (t, 1, aromatic H on C-4), 7.94 (b, 1, NH); mass spectrum (70 eV) m/e (rel intensity) 255 (100), 240 (64), 212 (10), 197 (18), 184 (13), 183 (25), 182 (19).

Under the same conditions 25 mg of deacetylgeissovelline-d_3 (**40**) was pyrolyzed to 2 mg of a mixture of un-, mono-, di-, tri-, and tetrasubstituted 1-ethyl-6,7-dimethoxycarbazoles: mass

spectrum (20 eV) *m/e* (rel intensity) 260 (7), 259 (38), 258 (100), 257 (80), 256 (62), 255 (54).

Pyrolysis of geissovelline at 280° produced a white solid which had a uv spectrum corresponding to that of geissovelline and not a carbazole or a *N*-acetylcarbazole.

9-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole.—A mixture of 300 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, 0.5 g of anhydrous sodium acetate, and 3 ml of acetic anhydride was refluxed for 3 hr under nitrogen. The solvent was evaporated and the residue was distributed between chloroform and water. Evaporation of the chloroform gave 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, which was crystallized from ether and sublimed (0.1 mm): mp (136–137° (lit.[19] mp 136°); uv max (95% EtOH) 260 nm (ε 23,500), 285 (9380); proton nmr ($CDCl_3$) δ 1.80 (m, 4, C-2 and C-3 CH_2), 2.48 (s, 3, $NCOCH_3$), 2.52 (m, 2, C-1 or C-4 CH_2), 2.77 (m, 2, C-1 or C-4 CH_2), 3.89 (s, 6, aromatic OCH_3), 6.76 (s, 1, aromatic H on C-5), 7.91 (s, 1, aromatic H on C-8).

9-Acetyl-6,7-dimethoxycarbazole.—A mixture of 200 mg of 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole and 300 mg of 30% palladium/charcoal in 5 ml of *n*-hexyl ether was refluxed and stirred for 3 hr under nitrogen. The mixture was filtered hot and the cooled filtrate was diluted with petroleum ether (bp 30–60°). The product crystallized slowly. Three recrystallizations from ethanol gave colorless needles of 9-acetyl-6,7-dimethoxycarbazole: mp 123–124° after drying at 80° (0.1 mm); uv max (95% EtOH) 224 nm (ε 44,200), sh 240 (25,200), 295 (15,600), sh 303 (14,400), 324 (11,600).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6. Found: C, 71.3; H, 5.5.

(19) G. K. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. W.*, **71**, 428 (1938).

Dehydrogenation of Deacetyldihydrogeissovelline (41).—An intimate mixture of 225 mg of deacetyldihydrogeissovelline and 225 mg of 30% palladium/charcoal was heated at 275° in a nitrogen atmosphere for 0.5 hr. The cooled mixture was extracted with methanol, the methanol was evaporated, the residue was distributed between ether and 1 *N* hydrochloric acid, the dried ethereal layer was evaporated, and the residual gum was sublimed at 140° (0.3 mm) to give 27 mg of crude 1-ethyl-6,7-dimethoxycarbazole (**35**).

Registry No.—**3**, 36954-68-4; **4**, 36950-24-0; **5**, 36954-69-5; **6**, 36950-25-1; **7**, 36950-26-2; **8**, 36950-27-3; **9**, 36950-28-4; **10**, 36950-29-5; **12**, 36950-30-8; **14**, 36950-31-9; **18**, 36954-70-8; **20**, 36954-71-9; **22**, 36954-72-0; **23**, 36950-32-0; **27**, 36954-73-1; **28**, 36954-74-2; **29**, 36954-75-3; **30**, 36954-76-4; **34**, 36994-22-6; **41**, 36994-23-7; 1,2,3,4-tetrahydro-11-methyl-6,7-dimethoxycarbazolenine, 36950-33-1; 1,2,-3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-34-2; 9-crotonyl-1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-35-3; 9-acetyl-6,7-dimethoxycarbazole, 36950-36-4.

Acknowledgment.—The authors are indebted to Mr. LeRoy F. Johnson, Varian Associates, for determining and interpreting the carbon-13 nmr spectra. The technical assistance of Mr. Lewis W. Cary, Varian Associates, in obtaining the 300-MHz proton nmr spectra is also gratefully acknowledged.

6-Alkyl Penicillins and 7-Alkyl Cephalosporins

EKKEHARD H. W. BOHME, HAROLD E. APPLEGATE, JACQUELINE B. EWING, PHILIP T. FUNKE, MOHINDAR S. PUAR, AND JOSEPH E. DOLFINI*

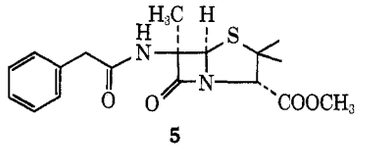
The Squibb Institute for Medical Research, New Brunswick, New Jersey 08903

Received July 18, 1972

Several 6-alkyl penicillins and 7-alkyl cephalosporins have been prepared. The syntheses of two unique cephalosporins are also discussed.

Although a 6-substituted penicillin has been known for some time,[1] the first generally useful synthetic method for the preparation of 6-substituted penicillins and 7-substituted cephalosporins was published only recently.[2] Since this publication, several papers[3] have appeared describing the synthesis of other 6-alkyl penicillins[4] and 7-alkyl cephalosporins as well as of 6-methoxypenicillins and 7-methoxycephalosporins. These interesting results prompt us to describe some further work we have carried out in this area.

6α-Methylpenicillin V *p*-methoxybenzyl ester (**3**) has been synthesized by the method previously reported (Scheme I). A convenient base for generating the anion of **1** was sublimed potassium *tert*-butoxide. Hydrogenolysis of ester **3** in dioxane–water using 10% palladium on calcium carbonate liberated the free acid, **4**. The stereochemical course of this alkylation has been discussed earlier.[2] Methylation occurs from the sterically less hindered α face of the 6 anion to give the thermodynamically less favored product. The stereochemistry has already been proven by X-ray diffraction analysis on 6-amino-6-α-methylpenicillanic acid methyl ester,[2] and has been corroborated by single-crystal X-ray diffraction analysis[5] on 6α-methyl-6-phenylacetamidopenicillanic acid methyl ester (**5**).



5

In agreement with the assigned stereochemistry is the finding that double irradiation of the C_6 methyl group[6] produces a 24% nuclear Overhauser effect on the C_5 proton.

(1) R. Reiner and R. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968).

(2) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

(3) (a) D. Cama, W. J. Leanza, T. R. Beatti, and B. G. Christensen, *ibid.*, **94**, 1408 (1972); (b) S. Karaday, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *ibid.*, **94**, 1410 (1972); (c) R. A. Firestone, N. Scheleshovv, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(4) The stereospecific alkylation of a penicillin at C-6 using a nitrogen ylide has been published previously: G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971).

(5) We wish to thank Professor Jack Z. Gougoutas and Mrs. B. Toeplitz for providing us with this data: Crystallization of **5** from dichloromethane–hexane solvent mixtures gave orthorhombic crystals of space group $P2_12_12_1$ which were used for the analysis (a = 9.75, b = 20.53, c = 9.52 Å, Z = 4, D_0 = 1.277 g/cm³). The R factor before refinement is 0.23 for the 1173 observed reflections. A full account of the refined structure will be published in a separate report.

(6) This technique has been used by Firestone, *et al.*,[3c] to determine stereochemistry in a similar series of compounds.