# Lythraceae Alkaloids. VII. The Structure and Stereochemistry of the Biphenyl Alkaloids of *Decodon* and *Hemia*[1,2]

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**Abstract:** A group of alkaloids isolated from the Lythraceae family have been shown to be biphenylquinolizidine lactones (*cf.* I). One group of these alkaloids has oxygen substituents at the 4'' and 5'' positions of the biphenyl nucleus (A and B series) and another group has oxygen substituents at the 5'' and 6'' positions (C and D series). Each of these groups is further subdivided on the basis of the relative configuration at C-10 of the quinolizidine ring. The A and C series have the same configuration at C-10 with a trans ring juncture and the B and D series have the same C-10 configuration but opposite to the A and C series with a cis ring juncture.

The first crystalline alkaloids from the Lythraceae plant family were described in 1962.[4] Since that time over 20 new alkaloids have been reported from this plant family.[3,5-7] The early structural studies established the presence of a *cis*-cinnamic lactone grouping or its dihydro equivalent, three aromatic oxygen functions (methoxyl and/or hydroxyl), two aromatic nuclei, and a tertiary nitrogen.[8] Hydrogenation of the *cis*-cinnamic double bond and methylation of the phenolic hydroxyl groups interrelated a number of these alkaloids to four basic structures—methyldecinine, methyldecamine, dimethyldecodine, and dimethyldihydroverticillatine (series A, B, C, D, respectively, in Table I).

Chemical and X-ray crystallographic studies established structure I for lythrine.[9,10] The structures of decinine (II) and the other group A alkaloids follow directly from I. The lythrine skeleton could be assigned to the other alkaloids in Table I because of the similarities in the mass spectra of methyldecinine, methyldecamine, dimethyldecodine, and dimethyldihydroverticillatine.[9] What remained to be determined was the relative configurations and aromatic substitution patterns of the B, C, and D series of alkaloids. This is the subject of this paper.

Table I. Interrelationships of Lythraceae Alkaloids[a,b]

| Series | Cinnamic lactone | Dihydrocinnamic lactone | *O*-Methyldihydrocinnamic lactone |
|---|---|---|---|
| A | *Lythrine* (2) | *Decinine* (2) | Methyldecinine |
| | *Lyfoline* (1) | Dihydrolyfoline (1) | |
| B | *Vertine* (cryogenine) (2) | *Decamine* (2) | Methyldecamine |
| C | *Nesodine* (2) | Dihydronesodine (2) | Dimethyldecodine |
| | | *Decodine* (1) | |
| D | *Verticillatine* (1) | *Dihydroverticillatine* (1) | Dimethyldihydroverticillatine |

[a] Naturally occurring bases are italicized. [b] The number of methoxyl groups is given by the number in parentheses. The *O*-methyl derivatives all have three methoxyl groups.

The structure of the vertine (B) series of alkaloids will be considered first. Previous studies established that the A and B series of alkaloids had the same aromatic substitution pattern since identical ultraviolet (uv) spectra were observed for both groups of alkaloids.[8] This was verified by oxidation studies in which III (Chart I) was isolated from both lythrine and vertine.[11] Therefore the differences between the A and B series must be configurational variations within the quinolizidine ring system.

(1) Direct correspondence to J. P. F. at RPI. Supported by grants from Smith, Kline and French Laboratories and the U. S. Public Health Service (MY-4748).

(2) Previous paper in this series: J. P. Ferris, C. B. Boyce, and R. C. Briner, *Tetrahedron Lett.*, 5129 (1966).

(3) (a) USPHS Career Development Awardee (GM 6380) of the National Institute of General Medical Sciences; (b) abstracted fom the doctoral dissertations of C. B. Boyce [*Diss. Abstr. B*, 27 (12), 4301 (1967); *Chem. Abstr.*, 67, 117015 (1967)] and R. C. Briner, [*Diss. Abstr. B*, 27 (11), 3845 (1967); *Chem. Abstr.*, 67, 100290 (1967)] submitted to Florida State University, Dec 1966. R. C. B. was a NSF Summer Fellow 1962 and a USPHS Predoctoral Fellow 1962–1965.

(4) J. P. Ferris, *J. Org. Chem.*, 27, 2985 (1962).

(5) R. N. Blomster, A. E. Schwarting, and J. M. Bobbitt, *Lloydia*, 27, 15 (1964).

(6) B. Douglas, J. L. Kirkpatrick, R. F. Raffauf, O. Ribeiro, and J. A. Weisbach, *ibid.*, 27, 25 (1964).

(7) H. Appel, A. Rother, and A. E. Schwarting, *ibid.*, 28, 84 (1965).

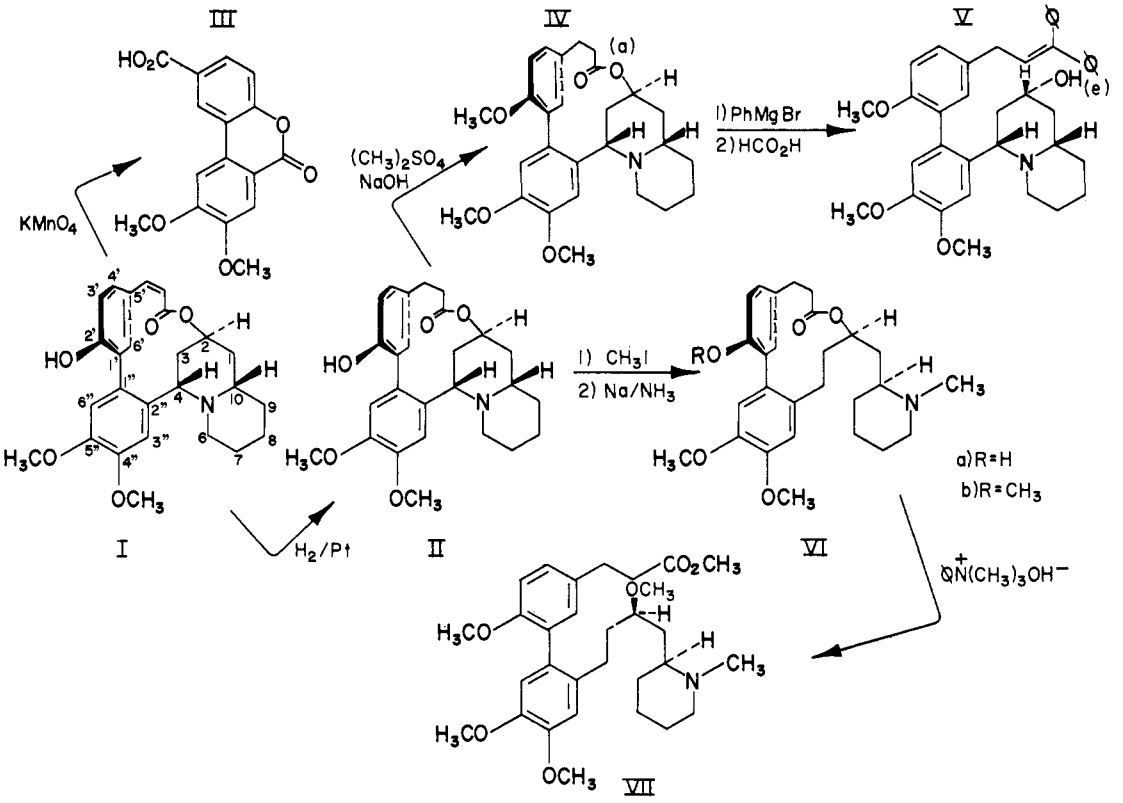
(8) J. P. Ferris, *J. Org. Chem.*, 28, 817 (1963).

(9) D. E. Zacharias, G. A. Jeffrey, B. Douglas, J. A. Weisbach, J. L. Kirkpatrick, J. P. Ferris, C. B. Boyce, and R. C. Briner, *Experientia*, 21, 247 (1965).

(10) The absolute configurations of these alkaloids are discussed in paper X of this series [*J. Amer. Chem. Soc.*, 93, 2963 (1971)]. However, the structures given in this paper depict the correct absolute configuration.

(11) A. Rother, H. Appel, J. M. Kiely, A. E. Schwarting, and J. M. Bobbitt, *Lloydia*, 28, 90 (1965).

Chart I




Lythrine has four centers of asymmetry so one would expect 16 isomeric forms of structure I. However, the quinolizidine ring can exist in either one trans or two cis conformations in each of these structures leading to 48 possible isomers. The quinolizidine ring may exist in both boat and chair conformations; however, after inspection of molecular models, we decided that boat forms were not likely possibilities. In this paper we will be concerned only with the relative configuration and will have to determine which of the 24 enantiomeric pairs, one of which has already been assigned to lythrine, is the structure of vertine.

The number of structures to be considered was halved by the observation that the A and B series had virtually identical optical rotatory dispersion (ORD) spectra. The principal (uv) chromophore in these alkaloids is the biphenyl grouping; hence the ORD curve reflects configuration at the biphenyl linkage. Since the ORD curves are the same, the configurations at the biphenyl linkage must be the same in the A and B series. Consequently, stereochemical difference(s) must be associated with the quinolizidine ring.

One of the differences between the A and B series is the presence of a trans-fused quinolizidine in the former and a cis in the latter. This conformational difference was demonstrated by a number of independent methods. First the nuclear magnetic resonance (nmr) chemical shift of H-4 is greater in the B series than in the A series (Table II). It appears as an AB quartet centered at $\tau$ 5.40 ($J$ = 10; 1–2 Hz) in methylvertine and $\tau$ ~6.25 in methyllythrine. Saturation of the double bond results in an upfield shift of the H-4 resonance to 5.93 in methyldecamine and 6.86 in methyldecinine. Bohlmann, *et al.*,[12] have shown that the H-4 resonance in *cis*-4-phenylquinolizidine is at lower field than in the corresponding trans isomer. It was possible to assign the cis geometry to the quinolizidine ring in the B series and the trans geometry to the A series by comparison with Bohlmann's results. Furthermore, the coupling constants require that H-4 be axially oriented in both series.

The upfield shift observed for H-4 on hydrogenation of the remote *cis*-cinnamic double bond is a novel observation. This decrease in shielding may be due to an increase in the torsional angle between the two phenyl rings in the hydrogenation product. As the torsional angle increases, the conjugation between the two rings and hence the shielding at H-4 should decrease. Alternatively the lactone carbonyl group may deshield H-4 by an inductive electron withdrawal through the biphenyl system in the olefin derivatives, an effect which would be removed when the double bond is hydrogenated.

The relative rates of quaternization also reflect the geometry of the quinolizidine ring. The A series reacts much slower than the B series with methyl iodide. Inspection of models shows that the *trans*-quinolizidine has four axial hydrogens blocking axial attack of the alkylating agent while the *cis*-quinolizidine shows only two 1,3 diaxial interactions.

The nmr spectra of the methiodides is consistent with the above assignments. The *N*-methyl resonance of methyldecamine methiodide is at lower field than that of methyldecinine methiodide, in agreement with the presence of a cis fusion in the former and a trans in the latter.[13] Finally, the absence of "Bohlmann bands" in the infrared spectra of the B series of alka-

(12) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Lett.*, 2705 (1965).

(13) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *ibid.*, 6797 (1965).

Table II. Proton Chemical Shifts for the Lythraceae Alkaloids ($\tau$)

| Alkaloids | Series | H-4[a] | *O*-Methyl | *N*-Methyl of methiodide | H-3′′ | H-3′′ in *N*-oxide | *N*-Oxide mp, °C | Methiodide mp, °C |
|---|---|---|---|---|---|---|---|---|
| Methyllythrine | A | 6.25 | 6.06, 6.12, 6.20 | | | | 171–172 | 258–260 |
| Methylvertine | B | 5.40 | 6.06, 6.10, 6.22 | | | | 185–188 | 247–248 |
| Methyldecinine | A | 6.86 | 6.08, 6.15, 6.26 | 6.51 | 2.98 | 1.90 | 177–179 | 235–237 |
| Methyldecamine | B | 5.93 | 6.10, 6.14, 6.26 | 6.10 | 3.00 | 1.62 | 193–194 | 227–230 |
| Acetyllythrine | A | 6.30 | 6.05, 6.14 | | 2.93 | 1.87 | *d* | *d* |
| Acetylvertine | B | 5.45 | 6.05, 6.14 | | 2.96 | 1.74 | *d* | *d* |
| Acetyldecinine | A | 6.86 | 6.05, 6.15 | | 2.91 | 1.64 | *d* | *d* |
| Acetyldecamine | B | 6.00 | 6.06, 6.16 | | 2.98 | 1.50 | *d* | *d* |
| Dimethyldecodine | C | 6.97 | 6.13, 6.31, 6.31 | 6.64 | 2.83[c] | 1.85[c] | 193–195 | *d* |
| Dimethyldihydro-verticillatine | D | 6.30 | 6.12, 6.30, 6.31 | 6.25 | 2.80[c] | 1.67[c] | 182–191 | *d* |
| Diacetyldecodine | C | 6.90 | 6.13 | 6.57 | 2.63[c] | 1.67[c] | *d* | *d* |
| Diacetyldihydroverti-cillatine | D | 6.14 | 6.15 | 6.14 | 2.63[c] | 1.33[c] | 155–160 | 234–235 |
| Dimethylverticillatine | D | 5.70 | 6.12, 6.28, 6.30 | | 2.74[c] | 1.75[c] | *d* | *d* |
| Diacetylverticillatine | D | 5.65 | 6.15 | 6.17 | 2.62[c] | 1.50[c] | *d* | 228–230 |
| Nesodine | C | | 6.02, 6.31[b] | | | | *d* | *d* |

[a] Quartet with $J$ = 10–12, 1–2 Hz. [b] Reference 4. [c] $J$ = 9 cps. [d] Could not be purified or was not prepared.

loids is consistent with a cis juncture.[14] "Bohlmann bands" are present in the A series of alkaloids as would be expected for a trans fused quinolizidine. Furthermore, these "Bohlmann bands" persist in the A series when the lactone ring is cleaved by lithium aluminum hydride (LAH) and continue to be absent in the B series upon cleavage of the lactone ring. These data eliminate the possibility that the quinolizidine ring changes to a more stable conformer when the restraining influence of the lactone ring is removed.

The number of *cis*-quinolizidines to be considered for vertine was reduced to three by the observation of a low field aromatic proton at $\tau$ 1.5–1.9 in the nmr spectra of the *N*-oxides of lythrine and vertine derivatives (Table II). Examination of a Dreiding model of these alkaloids (*cf.* lythrine *N*-oxide VIII) reveals that the oxygen of the *N*-oxygen grouping is in close proximity to the 3′′ aromatic proton. This signal is not coupled with either an ortho or meta proton. H-3′′ is the only proton that fulfills this latter requirement. Since an unsplit one-proton peak with the same chemical shift is apparent in the *N*-oxides of the vertine series the oxygen of the *N*-oxide function must be in close proximity to H-3′′ in this series as well. Examination of molecular models reveals that there are only three *cis*-quinolizidine structures, which have the same chirality as lythrine at the biphenyl link, where such an interaction is possible (IX–XI).

One difference in the three structures under consideration for vertine is in the configuration at C-2. Structure IX has H-2 axial while it is equatorial in X and XI. One would expect that if H-2 were axial the nmr signal at 4.6–5.0 would be broad due to coupling with two adjacent axial protons ($J_{aa}$ = 10 Hz) as well as two equatorial protons ($J_{ae}$ = 5 Hz). If H-2 were equatorial then the signal will be much narrower with $J_{ae}$ = 5 Hz and $J_{ee}$ = 0–2 Hz. The half-height width of the H-2 signal is 7.5–9 Hz in all the *Decodon* alkaloids, a result which suggests that H-2 is equatorial in every case.[15] This conclusion is consistent with structure I which was assigned to lythrine on the basis of X-ray data.[9] Consequently IX was eliminated as the structure of vertine.

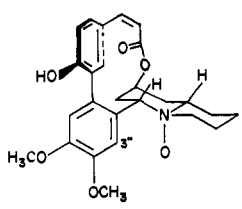
The axial nature of the C-2 hydroxyl group was demonstrated further by its epimerization to the equatorial orientation (Chart I). Treatment of methyldecinine IV and methyldecamine IV-B with phenylmagnesium bromide followed by dehydration with formic acid yielded V. The acetate derivative of V in both the A and B series exhibited a H-2 proton signal with a half-height width of 13–14 Hz as would be expected if H-2 were now axial. This isomerization is reminiscent of the solvolytic isomerization of axial 3-tropinols to the equatorial isomers *via* a carbonium ion which is stabilized by participation of the nitrogen atom.[16] A similar stabilized carbonium ion is possible in these alkaloids as well.

The conformational stabilities of alkyl-substituted quinolizidines has been studied in detail by Katritzky, *et al.* These workers observed that with the 1-, 2-, 3-, or 4-methylquinolizidines the trans fusion is favored.[13] However, Bohlmann, *et al.*,[12] observed that *trans*-4-phenylquinolizidine with an axial phenyl group is less stable than the cis conformer with an equatorial phenyl group. Once the lactone ring is cleaved in the alkaloids under investigation the only conformation that would need to be considered would be one with the 4-biphenyl system equatorial. Furthermore, the configuration of the 2-hydroxyl would have little or no influence on the geometry of the ring juncture since Katritzky, *et al.*, found that a 2-methyl group had no effect. With these conclusions in mind it is immediately apparent with the aid of molecular models that IX and X are not likely vertine structures. The bridged biphenyl lactone ring maintains the cis fusion in the quinolizidine rings of IX and X. Once this lactone ring is cleaved the *cis*-quinolizidine should readily isomerize to the trans-fused isomer and this isomerization should be detected by the appearance of "Bohlmann bands" in

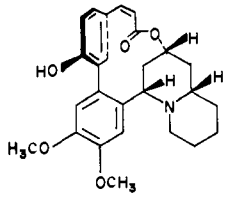
(14) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

(15) A. C. Huitric, J. B. Carr, W. F. Troger, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963); H. Feltkamp and N. H. Franklin, *ibid.*, **21**, 1541 (1965); H. S. Aaron, G. F. Wicks, and C. P. Rade, *J. Org. Chem.*, **29**, 2248, 2252 (1964). Our previous conclusion that these alkaloids differed in configuration at C-2 was in error.[8] This decision was based on the difference in chemical shift of H-2 in the acetate derivatives of the C-2 alcohol. However, inspection of the nmr spectra of a wide range of these alkaloids reveals very little difference in the chemical shift of H-2.

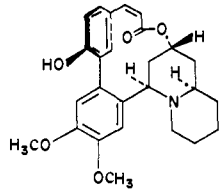
(16) H. O. House and W. M. Bryant, III, *J. Org. Chem.*, **30**, 3634 (1965).



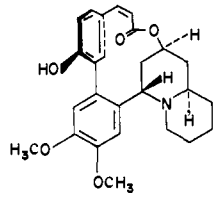
VIII



IX



X



XI

the ir spectra of these vertine derivatives.[16] However, the *cis*-quinolizidine would be favored when the lactone ring of XI is cleaved since nitrogen inversion would lead to an axial biphenyl grouping at the 4 position. As discussed previously the lactone cleavage products in the B series do not exhibit "Bohlmann bands" so that it was concluded that XI is the structure of vertine.

However, there have been instances where *trans*-quinolizidines did not exhibit "Bohlmann bands" [13] so it was felt necessary to confirm the structure assigned to vertine by degradation experiments. The approach was to effect a stepwise elimination of the asymmetric centers in the A and B series of alkaloids and to compare the properties of each series of degradation products. For example, if the asymmetry at C-2 were removed then the A and B series would converge if vertine were structure IX. Elimination of the asymmetry at the biphenyl link and at C-2 would yield mirror image degradation products if X is the correct structure for vertine and diasteriomers if XI is correct. Finally, if the asymmetry at C-2, C-4, and the biphenyl link is removed the degradation product of I and IX will be identical while enantiomeric pairs will be produced from the A and B series if vertine is structure X or XI.

Our initial degradation experiments were not successful because the reactions yielded noncrystalline products or the reactions were nonspecific. For example, reductive cleavage of the lactone ring with phenylmagnesium bromide or LAH proceeded cleanly and in good yield (*e.g.*, V, Chart I), but with few exceptions the products were resistant to crystallization. This lack of crystallinity when the lactone ring is opened probably reflects the many rotational degrees of freedom in the product. Furthermore, the primary hydroxyl group produced by the LAH reduction of the lactone usually interfered with the subsequent degradations of the quinolizidine ring. Cleavage of the cinnamic double bond with either ozone or oxmium tetroxide periodate also led to intractable products. It was possible to cleave the quinolizidine ring *via* the Emde degradation (Chart I, II → VI).[17] This reaction proceeded most efficiently when a phenolic hydroxyl group was present. Apparently the negative charge on the phenoxide anion protected the biphenyl system from reduction. Attempted Hofmann degradation of the methiodide of VI resulted in cleavage of the lactone with formation of a methyl ester. Methylation of the phenolic hydroxyl group with trimethylanilinium hydroxide[18] resulted in cleavage of the lactone ring to yield the novel ester–ether derivative VII. Presumably as the reaction mixture is distilled (150° *in vacuo*) the anions of both the lactone carboxylic acid and alcohol groupings are formed and then methylated by the trimethylaniline hydroxide. However, VII was not crystalline and degradation reactions of VII led to amorphous or oily products.

A number of degradation reactions afforded a hydroxyl group in the 2 position of the quinolizidine ring. However, despite numerous attempts with a battery of chemical agents we were unable to produce a clean keto derivative from this alcohol. The alcohol was either resistant to oxidation or else the oxidation product exhibited ir absorption at 1675 $cm^{-1}$ as well as the expected absorption at 1700 $cm^{-1}$, suggesting that elimination of the nitrogen was taking place or the amine was being oxidized to the enamine. Simple dehydration of the hydroxyl group either led to total destruction of the molecule or no reaction. From these data it was painfully apparent that a successful degradation scheme must (1) retain some geometrical restraint in the degradation products; (2) not generate a primary hydroxyl group from the lactone carbonyl; (3) cleave the quinolizidine ring in such a way as to modify the 2-hydroxyl without unfavorable interference from the nitrogen atom.

We were able to devise two degradation schemes which met these requirements. In the first method (Chart II)[19] we were able to convert the cinnamic lactone to the *n*-propyl derivative XIII. This had been accomplished previously by catalytic hydrogenolysis of the cinnamyl alcohol XII resulting from LAH reduction.[8] Higher yields were obtained using the LAH–$AlCl_3$ system directly on the alkaloid[20] by or hydrogenolysis of the cinnamyl alcohol with sodium–ammonia–ethanol[21] followed by catalytic hydrogenation of any remaining unsaturation. The latter process gave higher yields as it did not involve separation of the reaction products from aluminum salts.

The next objective was the introduction of conformational rigidity into the molecule by restricting the rotation at the biphenyl link. We were able to accomplish this and also remove the biphenyl asymmetry by an internal SN2 displacement of the quaternary nitrogen by the 2′-phenoxide anion. This reaction proceeded in excellent yield to give the crystalline dibenzopyran XIV. The structure of this degradation product was established by its nmr spectrum (to be discussed later) and by oxidation to the lactone of 5′-*n*-propyl-2′-hydroxy-4,5-dimethoxy-2-biphenylcarboxylic acid (XV).

Attempted removal of the asymmetry at the carbon atom adjacent to the nitrogen by oxidation to the enamine or Hofmann degradation was not successful. However, it was possible to remove the asymmetry at C-2 by elimination of the mesylate. This reaction proceeded cleanly and in high yield. The structure

(17) D. B. Clayson, *J. Chem. Soc.*, 2016 (1949). For recent references, see K. W. Bentley and A. W. Murray, *ibid.*, 2501 (1963).

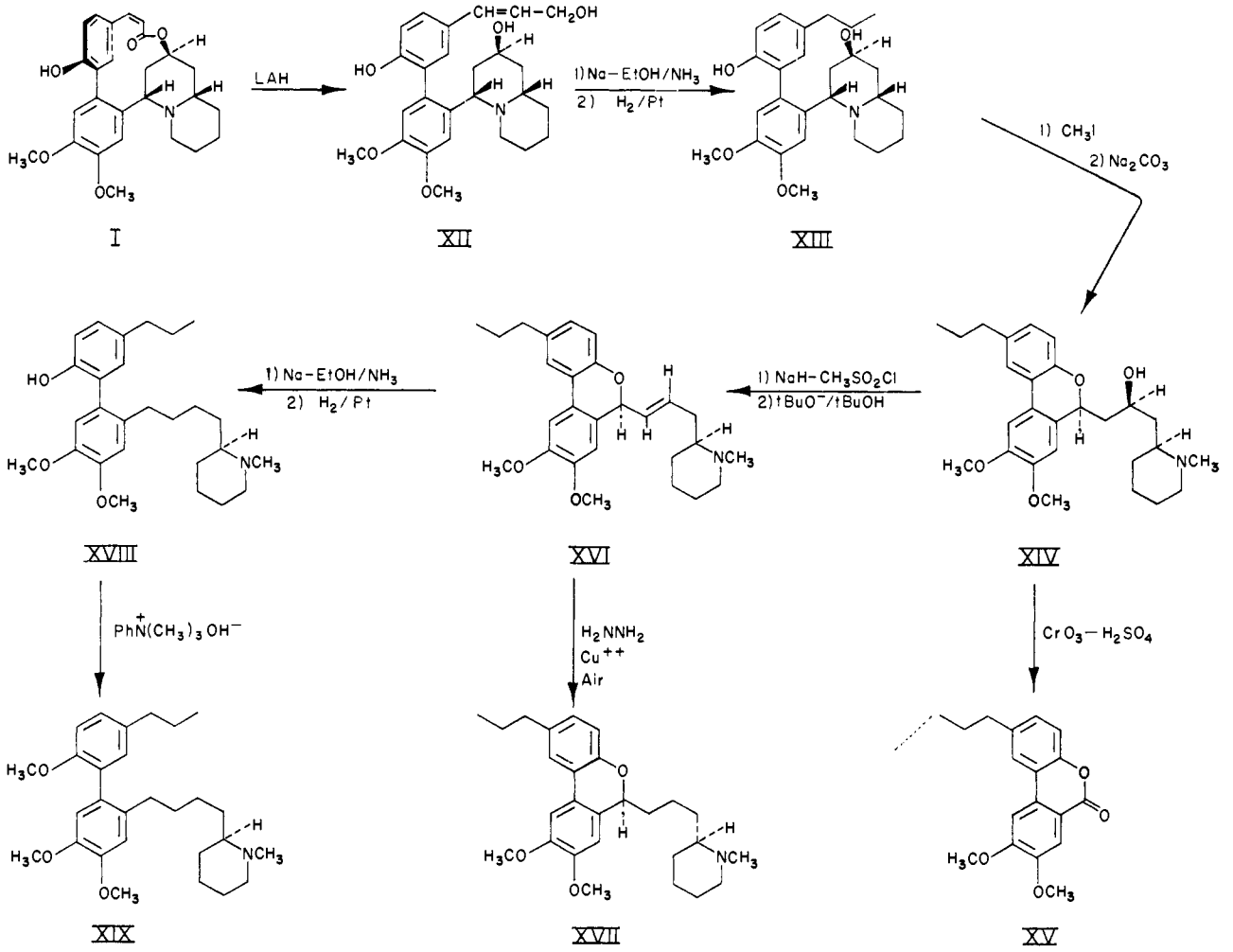
(18) F. Rodinov, *Bull. Soc. Chim. Fr.*, **39**, 305 (1926); **45**, 109 (1929).

(19) The degradations were carried out on both the A and B series; however, only the A series is depicted in Chart II.

(20) A. J. Birch and M. Slaytor, *Chem. Ind. (London)*, 1542 (1956).

(21) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

Chart II




of XVI was assigned by comparison of the nmr spectra of the alcohol and the olefin. The C-4 proton is a well-defined doublet of a doublet ($J$ = 10, 2 Hz) at $\tau$ 4.53 in XIV which is shifted downfield in XVI. If the double bond were at the 1,2 position one would expect that the proton at H-10 would shift to lower field in going from the alcohol (XIV) to the olefin (XVI). However, this proton is at 7.1 in the alcohol and 7.2 in the olefin. Finally the presence of a trans-disubstituted olefin was apparent by the observation of ir absorbtion at 973 $cm^{-1}$ which was absent in the alcohol and the corresponding dihydro derivative XVII.

It was at first surprising that the elimination of the mesylate proceeded cleanly in high yield to give only one trans-olefinic product. Presumably this is the result of intramolecular catalysis of the reaction by the nitrogen atom *via* a six-membered transition state.[22] The observation that the reaction proceeds in dimethylformamide in the absence of added base supports this hypothesis.

The physical properties of XVI were then compared with the corresponding degradation product in the B series. There were small but significant differences in the nmr and ir spectra of these two degradation products. The melting point of XVI (84–85°) was depressed (77–92°) on admixture with the corresponding derivative in the vertine series (107–108°). These data demonstrate that the two degradation products are diastereomers as predicted by structure XI and not identical or mirror images as would be expected if IX or X, respectively, were the structure for vertine.

It was possible to demonstrate further that lythrine and vertine were enantiomeric at C-10 by removal of the asymmetry at C-4. Hydrogenolysis of the allylic benzylic ether XVI followed by reduction of the double bond gave XVIII in both series with one center of asymmetry at C-10. The phenolic hydroxyl group of XVIII was converted to the methyl ether XIX with phenyltrimethylanilinium hydroxide ($PhN^+(CH_3)_3OH^-$). These derivatives could not be obtained in crystalline form; however, they were purified by column chromatography (tlc). The optical rotation of XVIII was −31° in the lythrine series and +31° in the vertine series. This result conclusively demonstrates that the A and B series are enantiomeric at C-10.

A second degradation scheme also revealed that lythrine and vertine are enantiomeric at C-10. In these experiments (Chart III) the conformational rigidity of the alkaloid was maintained by keeping the lactone ring intact. This was accomplished by conversion of the lactone to a cyclic ether XX by the procedure of Pettit.[23] Emde reduction[17] cleaved the quinolizidine ring in XX to XXI. O-Methylation of XXI followed by cyanogen bromide N-demethylation and LAH reduction resulted in the secondary amine XXIV. Nu-

(22) A. M. Braun, C. E. Ebner, G. A. Grob, and F. A. Jenny, *Tetrahedron Lett.*, 4733 (1965).

(23) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, 27, 2127 (1962).

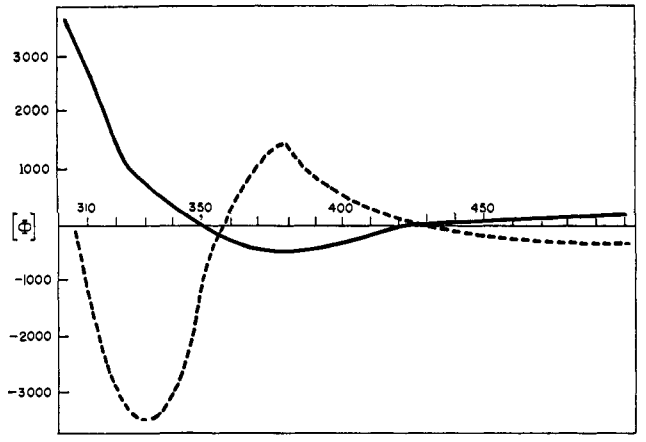



Figure 1. ORD spectra of *N*-nitroso degradation products: ———, XXV-A (lythrine series); – – – –, XXV-B (vertine series).

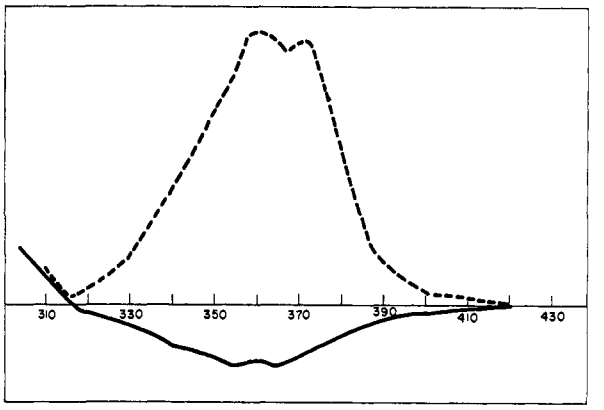
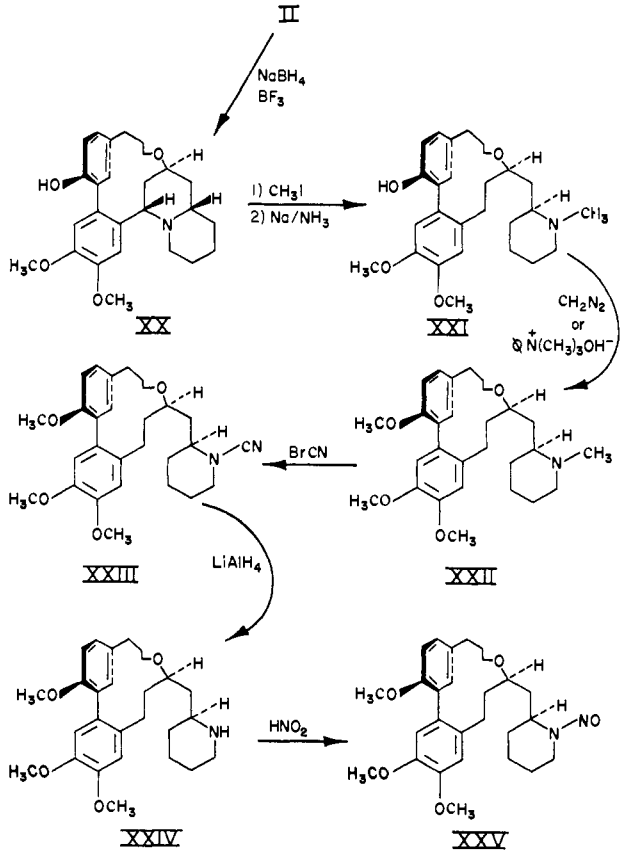



Figure 2. CD spectra of *N*-nitroso degradation products: ———, XXV-A (lythrine series); – – – –, XXV-B (vertine series).

merous attempts to remove the asymmetry in XXIV by dehydrogenation to the pyridine or oxidation to the enamine yielded mixtures and noncrystalline products. However, treatment with nitrous acid yielded

Chart III




crystalline *N*-nitrosamine derivatives (XXV) in both series. The absorption of the *N*-nitroso chromophore (350 nm, $\epsilon$ 200) is sufficiently removed from the methoxylated biphenyl absorption maxima (290 nm, $\epsilon$ 7000) so that it was possible to observe its ORD and circular dichroism (CD) effects independent of those of the biphenyl grouping. The Cotton effect at 350 nm reflects the configuration at C-10 next to the nitrogen atom. The ORD and CD curves have the opposite sign in this region (Figures 1 and 2), thus confirming that the A and B series have the different configurations at C-10.[24,25] The curves are not symmetrical but this is probably a result of the intense positive extremum at 305 nm due to the biphenyl system. Unfortunately the absolute configuration cannot be ascertained with certainty from these curves.[26]

With the structures of the A and B series of alkaloids in hand we then focused on the nesodine (C) and verticillatine (D) series of bases. We had already concluded that all the alkaloids listed in Table I have the same carbon skelton based on the similarity of their mass spectral cracking patterns and the fact that the ir spectra and nmr spectra are quite similar. However, differences are apparent in the uv spectra. Methyldecinine IV and methyldecamine IV-B have $\lambda_{max}$ 293 nm ($\epsilon$ 7180) and dimethyldecodine and dimethyldihydroverticillatine have $\lambda_{max}$ 285 nm ($\epsilon$ 4980). These data show that the alkaloids differ in the aromatic oxygenation pattern and this was confirmed by permanganate oxidation studies. Methyldecinine and dimethyldecodine yielded metahemipinic acid and hemipinic acid, respectively, on vigorous oxidation along with 4-methoxyisophthalic and succinic acids.[8]

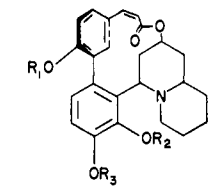
Either of two gross structures (XXVI or XXVII) may be assigned to the alkaloids of the C and D series on the basis of the permanganate oxidation studies. Schwarting, *et al.*,[7] concluded XXVI ($R_1 = R_3 = CH_3$; $R_2 = H$) was the structure of nesodine because the phenolic hydroxyl absorption was broad and shifted to 2700–2500 $cm^{-1}$ (KBr) in the infrared. This broad absorption together with the lack of reactivity was attributed to hydrogen bonding to the nitrogen atom. However, XXVII ($R_2 = R_3 = CH_3$; $R_1 = H$) is also in agreement with these data. In this structure the phenolic hydroxyl would be unreactive because it is blocked by the adjacent phenyl ring and the ir absorption represents partial proton transfer from oxygen to nitrogen in the solid state to give an ionic species. Nesodine and verticillatine are yellow while the methyl ethers are colorless, suggesting the presence of some of the phenoxide form ($\lambda_{max}$ 300–323 nm) in crystalline natural bases.[27]

(24) C. Djerassi, E. Lund, E. Bunnenberg, and B. Sjoberg, *J. Amer. Chem. Soc.*, **83**, 2307 (1961).

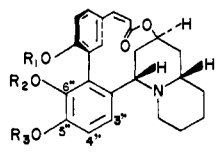
(25) We thank Drs. U. Weiss and N. Sharpless for these determinations.

(26) H. Ripperger and K. Schreiber, *Tetrahedron*, **21**, 1485 (1965).

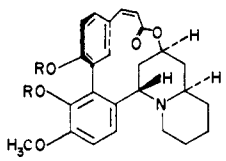
(27) The two "isomeric" forms of verticillatine may be understood on the basis of the amount of phenoxide form present.[4] Crystallization of verticillatine from chloroform yields white crystals while crystal-



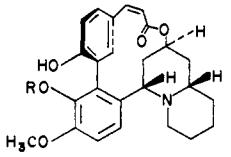
XXVI



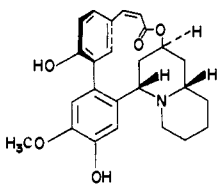
XXVII



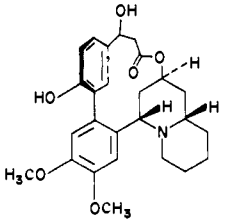
XXVIII



XXIII



XXIV



XXV

One other line of evidence may be cited in support of the biphenyl oxygenation pattern in XXVII for nesodine. The methoxyl resonances in the nmr are widely separated (6.02 and 6.31). The former may be assigned to 5''-$OCH_3$ and the latter to the 6''-$OCH_3$ which is deshielded by the adjacent phenyl ring.[28] These data do not eliminate XXVII ($R_1$ = $R_3$ = $CH_3$; $R_2$ = H) for nesodine. However, the fact that no presently known naturally occurring Lythraceae alkaloid has a 6''-$OCH_3$ suggests this methoxylation pattern is improbable.

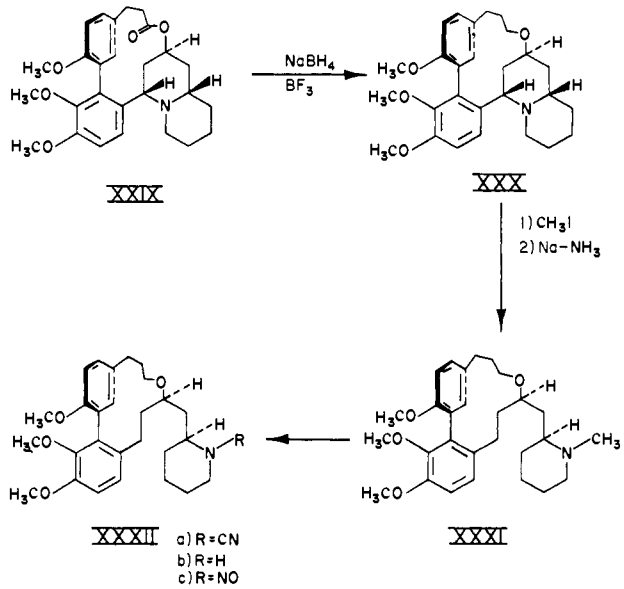
The oxygenation pattern in XXVII was confirmed by the nmr spectra of the *N*-oxides of the alkaloids of the C and D series. As in the A and B series these compounds show a low field aromatic proton due to the interaction of the *N*-oxide with H-3''; however, in the C and D series H-3'' is half of an AB quartet ($J$ = 8 Hz) as would be expected if it were coupled to an adjacent proton.

With the assignment of gross structure XXVII to the cinnamic alkaloids of the C and D series the stereochemistry of these bases remained to be determined. From an inspection of the chemical and physical properties of these alkaloids it became apparent that the C series of alkaloids contains a *trans*-quinolizidine with the same stereochemistry as in the A series and that the D series alkaloids contains a *cis*-quinolizidine with the same stereochemistry as the B series. Consequently, structure XXVIII (R = $CH_3$) is assigned to dimethylverticillatine and structure XXVII (R = $CH_3$) and double bond saturated) to dimethyldecodine. The evidence in support of these assignments is the same as that discussed earlier for the A and B series of bases so it need only be tabulated here for the C and D alkaloids: (1) the difference in chemical shift of H-4 in the bases and N-$CH_3$ in the methiodides of the C and D series (Table II); (2) the low-field shift of H-3'' in alkaloid *N*-oxides (Table II); (3) the difference in rates of quaternization with the D series reacting more rapidly than the corresponding C series derivatives (Table II); (4) the presence of "Bohlmann bands" in the C series and not the D series; (5) the half-height width of ~9 Hz for H-2 in the nmr spectra demonstrating that H-2 is equatorial in both series; (6) the ORD spectra of the dimethyldecodine and dimethyldihydroverticillatine are virtually identical.

It was hoped to bring about a stepwise elimination of the asymmetric centers in these alkaloids as was done for the A and B series (Chart II). However, this was not possible because we did not have a supply of a cinnamic alkaloid (*e.g.*, nesodine) in the C series. Use of the dihydrocinnamic alkaloid decodine required that the primary hydroxyl group be carried through the degradation reactions; consequently it was impossible to obtain a clean olefin by elimination of the mesylate groups.

It was possible to demonstrate that the C and D series are enantiomeric at C-10 by a parallel series of degradations to *N*-nitroso derivatives. These are illustrated in Chart IV for the C series. The reactions

Chart IV




XXIX XXX XXXI XXXII

are the same as described previously for the A and B bases. The ORD curves of the *N*-nitroso derivatives XXXIIc and XXXIIc-D reflected the difference in configuration at C-10 with a positive extremum at 350 nm in the C series and a negative extremum at 350 in the D series and provided further support for structures XXVII and XXVIII.

The methoxylation pattern of the C and D alkaloids was established by a combination of spectral and chemical studies. Methoxyl groups at the 2' or 6'' positions are shielded by the adjacent phenyl ring and resonate at $\tau$ 6.2–6.3,[29] upfield from methoxyl groups at one of the other positions (6.05–6.15). Furthermore if it is possible to form an internal ether (*cf.* XIII → XIV), then a 2'-OH is present. The internal ether is readily characterized by nmr peaks for H-4 at 4.7 (AB quartet, $J$

lization from methanol yields yellow crystals containing an ionic form of verticillatine. Methylation of either species yields identical forms of dimethylverticillatine.

(28) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and N. J. Vernengo, *J. Chem. Soc.*, 1896 (1961); W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *ibid.*, 4778 (1964).

(29) *Cf.* H-11 of the aporphine alkaloids: M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, 64, 59 (1964).

= 10, 2 Hz) and H-6′ [29] at 1.8 ($J$ = 2 Hz; meta coupling).

Decodine exhibits a methoxyl resonance at 6.13 in the nmr which reflects a 5′′-$OCH_3$ group since dimethyldecodine has methoxyl peaks at 6.13, 6.31, and 6.31. The presence of the 2′-OH was established by the formation of an internal ether. Consequently decodine must be XXXIII (R = H and double bond saturated). The same observations were made for verticillatine derivatives, thus establishing XXVIII (R = H) for verticillatine. It is now possible to assign the completed structure XXVII ($R_1$ = H; $R_2$ = $R_3$ = $CH_3$) to nesodine and XXXIII (R = $CH_3$ and double bond saturated) to dihydronesodine (methyldecodine);[8] however, it would be helpful to confirm these assignments by internal ether formation.

There are insufficient spectral and chemical data to assign the methoxylation pattern of the A series alkaloid lyfoline. However, one may provisionally assign structure XXXIV on the basis of current knowledge of biphenyl coupling in alkaloid biosynthesis.[2,30]

Finally the structure of lythridine (sinine) has been established. This alkaloid has the same structure as lythrine but with the double bond hydrated (XXXV).[31]

## Experimental Section

Only the basic experimental details and spectra are reported herein. Each preparation is described in detail in the doctoral disserrations of C. B. B. and R. C. B.[3b]

**General Procedures.** Since the chemistry of the A and B series and C and D series is similar only the A alkaloid structures are given in Charts I, II, and III and only the C alkaloid structures are given in Chart IV. Consequently, derivatives of the B series are given the compound number for the corresponding A derivative but with a "B" designation; *e.g.*, decinine is I and decamine is I-B The same numbering system was adopted for the D series.

Infrared spectra were recorded in $CHCl_3$ solution (gums and amorphous solids) or KBr (crystalline solids) on an Infracord spectrophotometer. "Bohlmann bands" were observed in deuteriochloroform on a Perkin-Elmer 521 spectrophotometer. Ultraviolet spectra were measured in methanol on a Cary 14 and nmr spectra were measured in $CDCl_3$ with tetramethylsilane as internal standard on a Varian A-60. Mass spectra were determined at 70 eV by Drs. P. T. Funke and A. K. Bose, using a CEC 21-103C spectrometer equipped with an all-glass inlet system, by Dr. R. Ryhage on a CEC 21-103C spectrometer equipped with an all-glass inlet system, and by Mr. T. Wachs and Mr. L. Dusold (Purdue) using a CEC 21-103C spectrometer equipped with a direct inlet system. Optical rotatory dispersion spectra were determined in methanol by Drs. N. Sharpless and U. Weiss (NIH), Mr. R. Williams (Berkeley), and Dr. N. Mitchell (Applied Physics Corp.) on Cary spectropolarimeters. Melting points were not corrected.

In general noncrystalline reaction products were purified by column chromatography using Woelm neutral alumina. Thin layer chromatography (tlc) on alumina using 1:19 methanol–benzene or ethyl acetate as developers was used to monitor the reactions and to ascertain to purity of the reaction products.

**Methiodides** were prepared by adding methyl iodide to a solution of the compound in ethyl acetate or methanol. This mixture was heated at reflux for 18 hr for the A and C series of alkaloids, or allowed to stand at room temperature for 2 or 3 hr for the B and D alkaloids. At the end of this time the solvents were evaporated and solid product was used directly in the next step. The methiodides could usually be crystallized from methanol or water with the exception of those which contained acetylated hydroxyl groups. These usually deacylated under these reaction conditions. The melting points for the crystalline methiodides are given in Table II.

**Acetylations** were carried out by dissolving the alkaloid in a 1:1 mixture of acetic anhydride and triethylamine. The solution was heated for 30 min on a steam bath or allowed to stand overnight at room temperature, then evaporated under vacuum. The residue was dissolved in ether and extracted with dilute HCl. The aqueous acid solution was made basic with sodium carbonate and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to about 1 ml. The alkaloid derivative was then allowed to crystallize from the ether solution in the cold.

***N*-Oxides** were prepared by dissolving 100 mg of the alkaloid derivative in methylene chloride and adding 50 mg of *m*-chloroperbenzoic acid. After 5 or 10 min the solution was washed with dilute sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated. The concentrated solution was diluted with ether and placed in a refrigerator. The crystals were collected and washed with ether. Owing to their instability, the *N*-oxides of acetylated alkaloids were difficult or impossible to purify by chromatography or recrystallization. The melting points for the crystalline *N*-oxides are listed in Table II.

**Phenolic methyl ethers** were prepared using $CH_2N_2$ in ether or ether–alcohol solution. Alternatively $(CH_3)_2SO_4$ was added to a solution of the alkaloid in aqueous base.[8]

**Methyldecamine (IVB).** To a rapidly stirred solution of 1.50 g of decamine (IIB), 5 g of sodium hydroxide, 25 ml of acetone, and 50 ml of water was added 0.75 ml of dimethyl sulfate. The solution was stirred 2 hr and the precipitate was filtered. This procedure was repeated three times or until no further precipitate was formed. The precipitates were combined, washed with water, and recrystallized from an acetone–water mixture, yielding 1.24 g: mp 227–228.5°. Recrystallization from methanol gave an analytical sample: uv max ($CH_3OH$) 293 nm ($\epsilon$ 8200), inflection 248 nm ($\epsilon$ 7400).

*Anal.* Calcd for $C_{27}H_{33}NO_5$: C, 71.81; H, 7.37; $OCH_3$, 20.62. Found: C, 71.24; H, 7.23; $OCH_3$, 20.51.

**Tetrahydrodecinine Methiodide.** To a solution of 1.00 g of decinine (11) in 50 ml of dry tetrahydrofuran was added 0.5 g of LAH. After refluxing 4 hr the excess hydride was decomposed by the addition of water. The solid residues were filtered and washed thoroughly with tetrahydrofuran and the filtrates treated with charcoal. Evaporation of the solvent yielded tetrahydrodecinine as a noncrystalline gum: ir (KBr) 3400 $cm^{-1}$ (OH), no absorption at 1720 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\tau$ 6.45 (t, 2, $J$ = 7 Hz, $CH_2CH_2OH$).

The gum was dissolved in tetrahydrofuran and treated with 5 ml of methyl iodide. After standing at room temperature for 2 days 0.70 g of methiodide was obtained: mp 196° dec; nmr ($CDCl_3$) $\tau$ 6.6 (s, 3, $N^+CH_3$).

***N*-Methylhexahydrodecinine.** To a solution of 400 mg of tetrahydrodecinine methiodide in 50 ml of liquid ammonia was added 0.4 g of sodium. The blue solution was stirred 30 min and the excess sodium was destroyed with ammonium chloride. The ammonia was distilled and the residue was dissolved in dilute NaOH and extracted with ether. The pH of the aqueous solution was adjusted to 9 and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated to yield 274 mg of an amorphous solid: nmr ($CDCl_3$) $\tau$ 7.78 (s, 3, $NCH_3$), 6.50 (t, 2, $CH_2OH$). Neither methylation with diazomethane nor preparation of the methiodide salt yielded a crystalline product.

***N*-Methyldihydrodecinine (VIa).** To a solution of 2.05 g (3.55 mmol) of decinine methiodide (11 methiodide) in 175 ml of liquid ammonia was added 0.29 g (12 mg-atoms) of Na. When the blue color had disappeared, the ammonia was allowed to evaporate. The residue was dissolved in water, the pH adjusted to 10, and the mixture extracted with $CHCl_3$. The $CHCl_3$ extract was dried and diluted with 95% ethanol, and the volume reduced until crystallization ensued. A yield of 1.19 g (74%) was obtained: mp 230–231°; uv max ($CH_3OH$) 292 nm ($\epsilon$ 8000), inflection 249 nm ($\epsilon$ 6800).

The **methiodide** was crystallized from methanol, mp 261–263° dec.

The **methyl ether** was prepared using diazomethane and the product was crystallized from ether, mp 174.5–175.5°.

*Anal.* Calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98. Found: C, 72.32; H, 7.97.

The **methiodide of the methyl ether** was crystallized from methanol, mp 254–257° dec.

***N*-Methyldihydrodecamine (VIb-B).** Using the same procedure as in the synthesis of VIa, 1.32 g of decamine methiodide (11-B-methiodide) and 0.25 g of Na yielded 0.76 g (74%) of product: mp

(30) In the preliminary paper our postulate for lyfoline was formulated incorrectly: J. P. Ferris, C. B. Boyce, and R. C. Briner, *Tetrahedron Lett.*, 3641 (1966).

(31) S. C. Chu, G. A. Jeffrey, B. Douglas, J. L. Kirkpatrick, and J. A. Weisbach, *Chem. Ind. (London)*, 1795 (1966).

222–226°; uv max ($CH_3OH$) 292 nm (ε 8100), inflection 247 nm (ε 7300).

*N*-**Methyldihydromethyldecamine (VIb-B).** To 80 ml of methylene chloride was added 3.60 g (7.95 mmol) of *N*-methyldihydrodecamine (VIa-B) and to this suspension was added 1.8 g of 80% *m*-chloroperbenzoic acid (8.4 mmol) in small portions. The solution was allowed to stand 1 hr, taken nearly to dryness, and dissolved in 0.3 *N* aqueous NaOH. The residual $CH_2Cl_2$ was removed and to the aqueous solution was added 10 ml of 12 *N* NaOH followed by 10 ml of $(CH_3)_2SO_4$ in 2-ml portions every 10 min. The solution was stirred 2.5 hr and extracted first with ether, then with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried, filtered, and reduced to dryness, yielding 3.46 g of a solid material which was hydrogenated at 40 psi over 0.3 g of platinum oxide for 12 hr in 95% ethanol. After filtration and evaporation of solvent, the residue was taken up in dilute HCl and extracted with ether. The aqueous acid solution was made basic with NaOH and extracted with ether. This ether extract was dried, filtered, and reduced to about 5 ml. The solution was cooled and the crystals were collected yielding 1.98 g (53%) of *N*-methyldihydromethyldecamine (VIb-B), mp 123–125°. An analytical sample was prepared by recrystallization from ether, mp 124.5–126°.

*Anal.* Calcd for $C_{28}H_{37}NO_5$: C, 71.92; H, 7.98. Found: C, 72.00; H, 7.91.

**The Reaction of *N*-Methyldihydrodecinine (VIa) with Trimethylanilinium Hydroxide. Synthesis of VII.** *N*-Methyldihydrodecinine (VIa) (500 mg) was added to a solution of trimethylanilinium hydroxide, prepared from 2 g of trimethylanilinium iodide and 1 g of $Ag_2O$, in 15 ml of methanol. The methanol and water were removed under vacuum, and the residue heated to 150° under vacuum. When dimethylaniline ceased distilling, the procedure was repeated with more trimethylanilinium hydroxide. The residue was taken up in ether and the ether solution was extracted with water followed by extraction with dilute HCl. The acid extract was made strongly basic with NaOH and extracted with ether. The ether extracts were dried and concentrated to 426 mg of a clear colorless oil. Tlc showed this material to be homogeneous, ir ($CHCl_3$) 1722 $cm^{-1}$ ($CO_2CH_3$).

**Methyldecinine (IV) and Phenylmagnesium Bromide. Synthesis of V.** To a solution of phenylmagnesium bromide prepared from 2 g of magnesium and 13 g of bromobenzene in tetrahydrofuran was added 1.75 g of methyldecinine. The solution was refluxed for 6 hr. The excess Grignard reagent was destroyed by the addition of ammonium sulfate solution and enough dilute sulfuric acid to adjust the pH to 8. The mixture was extracted with ether, the ether extracts were added to 50 ml of formic acid, and the ether was removed. The formic acid solution was heated on a steam bath, cooled, and extracted with $CCl_4$. The formic acid solution was evaporated nearly to dryness, made basic with dilute NaOH, and extracted with ether. The ether extracts were dried and concentrated to dryness. The residue was chromatographed on activity II neutral Woelm alumina. The product was eluted with benzene and 1:4 ether–benzene. That these two eluates contained a single compound was shown by tlc. Drying under 0.5 mm vacuum for 3 hr at room temperature yielded 1.88 g (82%) of V as a froth: mp 88–94°; ir ($CDCl_3$) 3610, 2796, 2764, 2730 $cm^{-1}$ (Bohlmann bands).

The acetate of V was prepared by dissolving 0.200 g of IV-A in 2 ml of pyridine and 1 ml of acetic anhydride. The solution was heated for 1 hr on a steam bath, then evaporated to dryness under vacuum. The resulting oil was chromatographed on activity II Woelm neutral alumina and the acetate was eluted with benzene and 1:19 ethyl acetate–benzene. Tlc indicated the colorless oil obtained on evaporation of the eluent to be a homogenous compound. The yield obtained was 0.108 g (50%): ir ($CDCl_3$) 2796, 2765, 2730 ("Bohlmann bands"), and 1726 $cm^{-1}$ (C=O); nmr ($CDCl_3$) τ 8.13 (s, 3, $CH_3CO_2$), 6.54 (d, 2, $J$ = 8 Hz, $PhCH_2CH$=), 5.04 (m, half-height width 13 Hz, base width 24 Hz, $AcOCH$–), 3.68 (t, 1, $J$ = 8 Hz, $CH_2CH$=$CPh_2$).

**The Reaction of Methyldecamine with Phenylmagnesium Bromide. Synthesis of V-B.** The same procedure was used in the synthesis of V. A 64% yield of product was crystallized from 95% ethanol, mp 173–174°.

The acetate of V-B was prepared by dissolving 200 mg of V-B in 2 ml of pyridine and 1 ml of acetic anhydride. The solution was heated on a steam bath for 10 min, then reduced to an oil by heating at 100° under vacuum. The residual oil was chromatographed on activity II Woelm neutral alumina. The acetate was eluted from the column with benzene and 1:20 ethyl acetate–benzene. Evaporation of the eluent and crystallization of the residue from ether yielded 136 mg (63%) of V-B acetate: mp 119–122°; ir ($CDCl_3$) 1726 $cm^{-1}$ (C=O) no maxima, 2800–2700 $cm^{-1}$; nmr ($CDCl_3$) τ 8.02 (s, 3, $CH_3CO_2$), 6.54 (d, 2, $J$ = 8 Hz, $PhCH_2CH$=), 4.77 (m, half-height width 14 Hz, base width 25 Hz, $AcOCH$–), 3.71 (t, 1, $J$ = 8 Hz, $CH_2CH$=$CPh_2$).

*Anal.* Calcd for $C_{41}H_{45}NO_5$: C, 77.94; H, 7.18. Found: C, 77.84; H, 7.21.

**Desoxytetrahydrodecinine (XIII).** A solution of 2.00 g of lythrine (I) in 250 ml of tetrahydrofuran was cooled to 5° on an ice bath. To this cold solution was slowly added a solution of 1.5 g of LAH in 100 ml of ether. The bright yellow solution was allowed to warm to room temperature. Within 1 hr the yellow color had been discharged and a white precipitate had appeared. The mixture was refluxed for 1.5 hr; then the excess hydride was destroyed with a solution of 50 g of sodium potassium tartrate in 150 ml of water. The tetrahydrofuran was evaporated and the remaining yellow aqueous solution was filtered to remove the residual aluminum salts. The aqueous solution was adjusted to pH 9 and extracted with methylene chloride. The organic extracts were dried over $Na_2SO_4$ and concentrated to dryness. The residue was dissolved in 250 ml of liquid ammonia and treated with 1 g of Na. To the blue solution was added absolute ethanol dropwise until the color was discharged. The ammonia was distilled and the residue was dissolved in water, the pH adjusted to 9, and the aqueous mixture extracted with methylene chloride. The organic extracts were dried over $Na_2SO_4$ and concentrated to dryness. This residue was dissolved in 50 ml of methanol and hydrogenated over 200 mg of platinum oxide for 12 hr. The platinum was filtered and the solvent evaporated yielding 1.72 g of crude XIII. Tlc showed this material to be contaminated with small amounts of primary alcohol: nmr ($CDCl_3$) τ 9.08 (t, 3, $J$ = 6 Hz, $CH_2CH_3$), 7.47 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 6.18 (s, 3, $PhOCH_3$), 6.12 (s, 3, $PhOCH_3$).

The **methiodide** was crystallized from ethanol–water: mp 225–226.5°; nmr ($CDCl_3$) τ 9.10 (t, 3, $J$ = 7 Hz, $-CH_2CH_3$), 7.44 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 4.50 (s, 3, $N^+CH_3$), 6.04 (s, 3, $PhOCH_3$), 6.16 (s, 3, $PhOCH_3$).

*Anal.* Calcd for $C_{27}H_{38}INO_4$: C, 57.14; H, 6.75. Found: C, 57.33; H, 6.92.

**Desoxytetrahydrodecamine (XIII-B).** Essentially the same procedure was used for the synthesis of XIII starting with 2.0 g of vertine (I-B). The final product was purified by chromatography on 25 g of Woelm activity III alumina. Concentration of the ether eluate yielded 1.3 g of crude XIII-B as a low-melting solid which could not be obtained crystalline although it appeared to be homogeneous by tlc: nmr ($CDCl_3$) τ 9.06 (t, 3, $J$ = 6 Hz, $CH_2CH_3$), 7.45 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 6.19 (s, 3, $PhOCH_3$), 6.13 (s, 3, $PhOCH_3$).

The **methiodide** was crystallized from ethanol–water: mp 236–238°; nmr ($CDCl_3$) τ 9.08 (t, 3, $J$ = 7 Hz, $CH_2CH_3$), 7.46 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 6.15 (s, 3, $N^+CH_3$), 6.06 (s, 3, $PhOCH_3$), 6.18 (s, 3, $PhOCH_3$).

*Anal.* Calcd for $C_{27}H_{38}INO_4$: C, 57.14; H, 6.75. Found: C, 56.86; H, 6.86.

**Preparation of 6*H*-Dibenzo[*b*,*d*]pyran (XIV).** A solution of 1.00 g of the methiodide of XIII, 1.0 g of sodium carbonate, and 5 ml of ethanol in 20 ml of water was heated 24 hr on a steam bath. The ether extracts were dried, filtered, and evaporated to dryness. The residue was chromatographed on activity III Woelm neutral alumina. The benzene, ether, and ethyl acetate eluates contained a single compound as determined by tlc. Evaporation of the solvents and crystallization of the residues from isopropyl ether–chloroform yielded 605 mg (78%) of XIV, mp 86–92°. An analytical sample was prepared by recrystallization from $CHCl_3$: uv max ($CH_3OH$) 324 nm (ε 11,800), 278 (10,600), 235 (19,700), 214 (38,200) inflection, 242 (16,200).

An analytical sample was prepared by recrystallization from chloroform. The crystals were air dried to constant weight.

*Anal.* Calcd for $C_{27}H_{37}NO_4 \cdot CHCl_3$: C, 60.18; H, 6.85. Found: C, 59.76; H, 6.71.

**Preparation of 6*H*-Dibenzo[*b*,*d*]pyran (XIV-B).** A 95% yield of XIV-B was obtained starting from the methiodide of XIII-B and using the previously described procedure for the synthesis of XIII. An analytical sample was prepared by molecular distillation: uv max ($CH_3OH$) 324 nm (ε 11,800), 278 (10,600), 235 (19,700), 214 (38,200) inflection, 242 nm (16,200).

*Anal.* Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H. 8.48. Found: C, 73.59; H, 8.34.

The *N*-**oxide** was crystallized from methylene chloride–ethyl acetate: mp 178–179°; nmr ($CDCl_3$) τ 9.03 (t, 3, $J$ = 7 Hz, $CH_2CH_3$), 7.40 (t, 2, $J$ = 6 Hz, $PhCH_2CH_2$), 6.80 (s, 3, $N(O)CH_3$), 6.12 (s, 3,

PhOC$H_3$), 6.04 (s, 3, PhOC$H_3$), 5.77 (m, 1, NC$H$), 4.51 (dd, 1, $J$ = 11, 3 Hz, [Ph][PhO]C$H$CH$_2$).

*Anal.* Calcd for $C_{27}H_{37}NO_5$: C, 71.18; H, 8.19. Found: C, 71.42; H, 8.14.

**The Lactone of 5′-*n*-Propyl-2′-hydroxy-4,5-dimethoxy-2-biphenylcarboxylic Acid (XV).** A solution of 450 mg (1.02 mmol) of XIV in 25 ml of acetone was cooled to 5° in an ice bath. To the cold solution was added 1.5 ml (4.0 mmol of $CrO_3$) of a solution of 2.67 g of chromic anhydride and 2.3 ml of concentrated sulfuric acid diluted to 10 ml in water. The mixture was stirred for 30 min on the ice bath, then diluted with 30 ml of water. Compound XV crystallized directly from the cold mixture. The crystals were filtered and washed with water yielding 239 mg of product which on recrystallization from chloroform yielded 210 mg (69%), mp 159–160°. An analytical sample was crystallized from ethanol: mp 159.5–160°; uv max ($CH_3OH$) 306 nm ($\epsilon$ 13,000), 288 (11,900), 256 (45,500), 222 (21,500), inflection 332 (7200), 320 (9200).

*Anal.* Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.45; H, 6.10.

**Elimination of the Hydroxyl Group from XIV.** A solution of 500 mg of XIV in 30 ml of anhydrous ether, 800 mg of 50% sodium hydride dispersion in oil, and 0.5 ml of methanesulfonyl chloride was stirred for 1 hr at room temperature. To the mixture was added 25 ml of *tert*-butyl alcohol. The solvents were distilled on a steam bath with the periodic addition of potassium *tert*-butoxide to keep the solution strongly basic. Water was added and the residual *tert*-butyl alcohol removed by distillation under vacuum. The oily aqueous mixture was extracted with ether. The ether extracts were dried and reduced to dryness. The residue was chromatographed on activity II Woelm neutral alumina. Tlc showed that the pentane, benzene, and ether eluates contained a single compound. The eluates were combined and evaporated to dryness, and the residue was crystallized from pentane. Recrystallization from isopropyl ether yielded 256 mg (53%) of XVI: mp 84–85°; uv max ($CH_3OH$) 324 nm ($\epsilon$ 11,800), 279 (10,600), 235 (23,100), 216 (41,000); ir ($CHCl_3$) 973 cm$^{-1}$ (*trans*-CH=CH).

*Anal.* Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37. Found: C, 77.10; H, 8.44.

**Elimination of the Hydroxyl Group from XIV-B.** The same procedure was used as described previously for the synthesis of XVI. Compound XVI-B (66%) was recrystallized from isopropyl ether: mp 107–108°; uv max ($CH_3OH$) 324 nm ($\epsilon$ 11,800), 279 (10,600), 235 (23,100), 216 (41,000); ir ($CHCl_3$) 973 cm$^{-1}$ (*trans*-CH=CH).

*Anal.* Calcd for $C_{27}H_{35}NO_3$: C, 76.92; H, 8.37. Found: C, 76.87; H, 8.16.

**Reduction of XVI-B with Diimide.** To a solution of 450 mg of XVI-B in ethanol was added 1 ml of hydrazine and a few crystals of cupric acetate. The mixture was heated at reflux for 4 days and then the ethanol was removed by distillation. The residue was dissolved in ether and washed with a dilute solution of NaOH. The ether layer was dried and evaporated. The residue was chromatographed on activity II Woelm neutral alumina. Tlc indicated that the benzene and ether eluates contained a single compound. Evaporation of the eluates yielded 342 mg (76%) of XVI-B as a colorless oil. This material could not be obtained crystalline. The infrared spectrum showed no significant absorption near 974 cm$^{-1}$. The methiodide and *N*-oxide derivatives also could not be obtained crystalline.

**Hydrogenolysis and Hydrogenation of XVI.** To 35 ml of liquid ammonia was added 100 mg of XVI and 1 ml of absolute ethanol. Sodium was added in small pieces to this mixture until the solution remained blue for 10 min before decolorizing. The ammonia was evaporated and the residue was dissolved in water. The aqueous solution was adjusted to pH 10, then extracted with ether. The ether extracts were dried and evaporated. The residue was dissolved in 20 ml of ethyl acetate and hydrogenated over 0.1 g of platinum oxide for 8 hr. After filtration and evaporation the residue was chromatographed on activity III Woelm neutral alumina. The ether eluate was shown to consist of a single compound by tlc. The ether solution was concentrated to dryness and the residue was dried for 4 days at room temperature at 0.5 mm pressure. This yielded 56 mg (50%) of XVIII as a colorless oil, $[\alpha]^{24}D$ −31° (in ethanol).

**Hydrogenolysis and Hydrogenation of XVI-B.** The same procedure was used as in the synthesis of XVIII. The product XVIII-B (72%) was obtained as a colorless oil, $[\alpha]^{24}D$ +31° (in ethanol).

**O-Methylation of XVIII.** A solution of trimethylanilinium hydroxide was prepared from 2 g of trimethylanilinium iodide and 1 g of silver oxide in 10 ml of methanol. A 20-ml sample of the clear, filtered solution was added to 112 mg of XVIII. The resulting solution was heated under vacuum on a steam bath until the dimethylaniline ceased distilling. This procedure was repeated twice using 2-ml portions of the trimethylanilinium hydroxide solution. The residue was dissolved in benzene and chromatographed on activity II Woelm neutral alumina. Thin layer chromatography showed the ether eluate to contain a single compound. Evaporation of the ether eluate yielded 93.8 mg of XIX as a pale yellow oil: ir ($CHCl_3$) no OH absorption at 3400 cm$^{-1}$; uv max ($CH_3OH$) 285 nm ($\epsilon$ 8600), inflection 247 (7000); nmr ($CDCl_3$) $\tau$ 9.03 (t, 3, $J$ = 7 Hz), 7.80 (s, 3, NC$H_3$), 7.42 (m, 4, 2 [PhC$H_2$CH$_2$]), 7.2 (m, 1, NC$H$), 6.29 (s, 3, PhOC$H_3$), 6.20 (s, 3, PhOC$H_3$), 6.11 (s, 3, PhOC$H_3$).

**O-Methylation of XVIII-B.** The same procedure was used as for the preparation of XIX. Compound XIX-B (74%) was obtained as a colorless oil: ir ($CHCl_3$) no absorption at 3400 cm$^{-1}$; uv max ($CH_3OH$) 285 ($\epsilon$ 6600), inflection 247 (5500); nmr ($CDCl_3$) $\tau$ 9.03 (t, 3, $J$ = 7 Hz, CH$_2$C$H_3$), 7.80 (s, 3, NC$H_3$), 7.42 (m, 4, 2 [PhC$H_2$CH$_2$)], 7.2 (m, 1, NC$H$), 6.29 (s, 3, PhOC$H_3$), 6.20 (s, 3, PhOC$H_3$), 6.11 (s, 3, PhOC$H_3$).

**$NaBH_4$–$BF_3$ Reduction of II.** To a solution of 70 ml of freshly distilled $BF_3$ etherate and 70 ml of dry ether was added 1 g of LiCl and 2.39 g of II. After stirring 10 min, 1 g of $NaBH_4$ was added. After stirring 48 hr, the reaction mixture was poured into 400 ml of water and warmed to evaporate the ether. The solution was adjusted to pH 9 with ammonium hydroxide and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated, and the residue was crystallized from methanol to yield 2.14 g (82%) of XX, mp 205–208°. An analytical sample was prepared by treatment with LAH in tetrahydrofuran to remove unreacted II, chromatography, and recrystallization from methanol, mp 219.5–221°.

*Anal.* Calcd for $C_{26}H_{23}NO_4 \cdot CH_3OH$: C, 71.18; H, 8.19. Found: C, 70.81; H, 8.24.

**$NaBH_4$–$BF_3$ Reduction of II-B.** The same procedure was used as in the synthesis of XX. Compound XXI-B (94%) was crystallized from methanol, mp 225–226°.

*Anal.* Calcd for $C_{26}H_{33}NO_4 \cdot CH_3OH$: C, 71.18; H, 8.19. Found: C, 70.73; H, 8.21.

**The Emde Degradation of XX.** To a solution of 20 ml of acetic anhydride and 20 ml of triethylamine was added 2.14 g (5.06 mmol) of XX. The solution was heated on a steam bath for 30 min, then evaporated under vacuum. The residue was taken up in dilute HCl, made basic with $Na_2CO_3$, and extracted with ether. The ether solution was dried and evaporated, and the residue was dissolved in methanol and treated with 10 ml of methyl iodide for 3 days at room temperature, then refluxed for 3 hr and evaporated. The residue was suspended in 170 ml of liquid ammonia and 0.3 g (13 mmol) of sodium was added in three 0.1-g portions. When the blue color had been discharged, the ammonia was evaporated. The residue was taken up in dilute NaOH and extracted with chloroform. The organic extracts were dried, concentrated, diluted with 75 ml of methanol, and reduced to 20 ml. Upon cooling, 1.63 g (76%) of XXI was deposited, mp 202–203.5°. An analytical sample was prepared by recrystallization from 95% ethanol, mp 203–204°.

*Anal.* Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48. Found: C, 73.74; H, 8.44.

**The Emde Degradation of XX-B.** To a solution of 2.67 g of XX in 50 ml of tetrahydrofuran was added 10 ml of methyl iodide. After 2 hr, the methiodide salt was filtered, yielding 3.30 g. The salt (5.85 mmol) was suspended in 270 ml of liquid ammonia and treated with 0.4 g (17 mg-atoms) of sodium in 0.1-g portions. When the blue color had disappeared, the ammonia was evaporated. The residue was taken up in water and extracted with methylene chloride. The organic extracts were dried, concentrated, and diluted with 50 ml of 95% ethanol, and the volume was reduced to 20 ml. The solution was cooled and the crystals were collected yielding 2.24 g (82%) of XXI, mp 185–189°.

*Anal.* Calcd for $C_{27}H_{37}NO_4$: C, 73.77; H, 8.48. Found: C, 73.64; H, 8.41.

**O-Methylation of XXII.** A solution of trimethylanilinium hydroxide was prepared from 2 g of trimethylanilinium iodide and 1 g of $Ag_2O$ in 30 ml of methanol. To the solution was added 1.00 g of XXI. The mixture was heated to 140° under vacuum for 30 min. The procedure was repeated. The residue was crystallized from methanol yielding 0.76 g (74%) of XXII, mp 131–132.5°. An analytical sample was prepared by recrystallization from methanol: mp 131.5–133°; uv max ($CH_3OH$) 291 nm ($\epsilon$ 8100), inflection 249 (7900).

*Anal.* Calcd for $C_{28}H_{39}NO_4$: C, 74.14; H, 8.67. Found: C, 74.01; H, 8.75.

**O-Methylation of XXI-B.** The same procedure was used as in the preparation of XXII. Compound XXII-B (76%) was recrystallized from isopropyl ether: mp 99–100.5°; uv max ($CH_3OH$) 290 nm (ε 8200), inflection 249 (8300).

*Anal.* Calcd for $C_{28}H_{39}NO_4$: C, 74.14; H, 8.67. Found: C, 74.23; H, 8.70.

**The Reaction of CNBr with XXII.** To a solution of 1.49 g of XXII in 70 ml of absolute ether was added a solution of 1.5 g of cyanogen bromide in 10 ml of absolute ether. The solution was allowed to stand 4 hr and filtered, the filtrate was concentrated, and XXIII (1.28 g, 83%) crystallized, mp 130–148°. An analytical sample was prepared by chromatography on activity II Woelm acid alumina and two recrystallizations from wet ether, mp 146.5–148°.

*Anal.* Calcd for $C_{28}H_{36}N_2O_4 \cdot H_2O$: C, 69.68; H, 7.94. Found: C, 70.46; H, 7.92.

**The Reaction of CNBr with XXII-B.** The same procedure was used as described for XXII except that crude XXIII-B (87%) was crystallized from hexane, mp 138–141°. An analytical sample was prepared by chromatography on acid alumina and recrystallization from wet ether, mp 141–142.5°.

*Anal.* Calcd for $C_{28}H_{36}N_2O_4 \cdot H_2O$: C, 69.68; H, 7.94. Found: C, 70.60; H, 7.85.

**Reduction of Cyanamide XXIII.** To a solution of 1.13 g of XXIII in tetrahydrofuran was added 1 g of LAH. After 24 hr at reflux, the excess LAH was destroyed by the careful addition of water and the precipitate filtered; the filtrates were treated with charcoal and evaporated to dryness. The residue was crystallized from 8 ml of ether, yielding 0.89 g (83%) of crude XXIV, mp 107–113°. After chromatography on activity IV Woelm acid alumina and recrystallization from ether, the melting point was 116–117.5°.

**Reduction of Cyanamide XXIII-B.** The same procedure used as in the synthesis of XXIV gave XXIV-B (57%), mp 120–121°.

**Nitrosation of XXIV.** A mixture of 200 mg (0.44 mmol) of XXIV, 0.1 ml of 12 *N* HCl, and 5 ml of $H_2O$ was maintained at 5° during the addition of 50 mg (0.59 mmol) of $NaNO_2$ in 2 ml of $H_2O$. The solution was allowed to warm to room temperature overnight and the resulting precipitate was extracted with ether. The ether extract was washed with dilute hydrochloric acid, then with dilute sodium carbonate, dried, treated with charcoal, evaporated to about 1 ml, and set aside to crystallize. Collection of the crystals yielded 89 mg (42%) of XXV: mp 125–126°. Attempts to recrystallize XXV resulted in decomposition: uv max ($CH_3OH$) 350 nm (ε 200), 291 (7900), inflection 248 (12,200); ORD and CD spectra in Figures 1 and 2.

*Anal.* Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74. Found: C, 69.71; H, 7.76.

**The Nitrosation of XXIV-B.** The same procedure was used as for the reaction of XXIV except that the crude product was recrystallized first from isopropyl ether and then from ethyl acetate to give XXV-B (40%): mp 180–181.5°; uv max ($CH_3OH$) 348 nm (ε 200), 292 (8020), 217 (34,700), inflection 249 (11,900); ORD and CD spectra in Figures 1 and 2.

*Anal.* Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74. Found: C, 69.34; H, 7.74.

**$NaBH_4$–$BF_3$ Reduction of XXIX.** The same procedure was used as in the synthesis XX to give a 70% yield of XXX after crystallization from ether–methylene chloride, mp 160°. The necessity for treatment with LAH to remove unreacted starting material and $BF_3$ complexes was not appreciated when this derivative was prepared. As a consequence of the $BF_3$ complexes, a residue remained (boron carbides?) after combustion and poor analyses were obtained; ir ($CHCl_3$) no carbonyl absorption at 1720 $cm^{-1}$. The methiodide was not crystalline.

**$NaBH_4$–$BF_3$ Reduction of XXIX-D.** The same procedure was used as in the synthesis of XXX to give a 95% yield of crude product which was crystallized from ether–methylene chloride, mp 289°. The methiodide was not crystalline.

**The Emde Degradation of XXX Methiodide.** To a solution of 490 mg of XXX methiodide in 100 ml of liquid ammonia was added 100 mg of Na. After 10 min $NH_4Cl$ was added to destroy the blue color, the ammonia distilled, and the residue was dissolved in 100 ml of $H_2O$. Extraction with $CHCl_3$ yielded 400 mg of product which was chromatographed on Woelm activity III acid alumina. A yield of 273 mg (40%) of XXXI was obtained which could not be obtained crystalline; nmr ($CDCl_3$) τ 7.8 (s, 3, $NCH_3$).

**The Emde Degradation of XXX-D Methiodide.** The same procedure that was used for the synthesis of XXXI was applied to XXX-D methiodide. Each time the reaction was performed a 1:1 mixture of XXXI-D and XXX-D was obtained as shown by tlc and nmr. The mixture was not separated but was used directly in the CNBr degradation. It was possible to do this since XXX-D is inert to CNBr.

**The Reaction of CNBr with XXXI.** Essentially the same procedure was used as in the synthesis of XXIII. The cyanamide (XXXIIa) was obtained in 60% yield; ir ($CHCl_3$) 2200 $cm^{-1}$ (C≡N).

**The Reaction of CNBr with XXXI-D.** The same procedure was used as in the CNBr reaction with XXXI. From 500 mg of a 1:1 mixture of XXXI-D and XXX-D was obtained 150 mg of cyanamide (XXXIIa-D); ir ($CHCl_3$) 2200 $cm^{-1}$ (C≡N).

**Reduction of Cyanamide XXXIIa.** The same procedure as was used in the synthesis of XXIV was applied to XXXIIa. The basic product (XXXIIb) was purified by chromatography on Woelm activity II neutral alumina; however, it could not be induced to crystallize.

**Reduction of Cyanamide XXXIIa-D.** The same procedure as was used in the synthesis of XXXIIb was applied to XXXIIb-D. The basic product could not be obtained crystalline.

**Nitrosation of XXXIIb.** The same procedure as was used for the synthesis of XXV was applied to XXXIIb. A 65% yield of amorphous XXXIIc was obtained. The ORD spectrum showed a positive extremum at 350 nm (Φ = 600) ($CH_3OH$).

**Nitrosation of XXXIIb-D.** The same procedure as was used for the synthesis of XXV was applied to XXXIIb-D. A 65% yield of amorphous XXXIIc-D was obtained after chromatography on neutral Woelm alumina. This amorphous material was shown to be an *N*-nitroso derivative by elemental analysis. The ORD spectrum shows a negative extremum at 350 nm (Φ = 600) ($CH_3OH$).

*Anal.* Calcd for $C_{27}H_{36}N_2O_5$: C, 69.20; H, 7.74. Found: C, 69.14; H, 7.85.

**Preparation of Hexahydroverticillatine.** To a solution of 1 g of dihydroverticillatine in 300 ml of tetrahydrofuran was added 1 g of $LiBH_4$ and the mixture brought to reflux for 48 hr. Water was added and the solution was concentrated to 0.8 g of a white froth: ir ($CHCl_3$) 3500 $cm^{-1}$ (OH), no absorption at 1720 $cm^{-1}$. The methiodide was prepared in the usual manner but was not characterized.

**Preparation of Tetrahydrodecodine.** The same procedure was used as in the synthesis of hexahydroverticillatine. Tetrahydrodecodine was obtained in virtually quantitative yield. Attempted crystallization from methanol yielded an amorphous solid.

*Anal.* Calcd for $C_{25}H_{33}NO_5 \cdot CH_3OH$: C, 68.50; H, 8.27. Found: C, 68.89; H, 8.13. The methiodide was prepared in the usual manner and was an amorphous solid.

**Preparation of a 6*H*-Dibenzo[*b*,*d*]pyran from Hexahydroverticillatine Methiodide.** The same procedure was used as in the synthesis of XIV. The dibenzopyran derivative was obtained in about 50% yield as a noncrystalline solid: nmr ($CDCl_3$) τ 7.30 (s, 3, $NCH_3$), 7.25 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 6.15 (s, 3, $PhOCH_3$), 4.70 (dd, 1, $J$ = 11, 3, Hz, [Ph][PhO]$CH$$CH_2$), 1.60 (d, 1, $J$ = 2 Hz, Ph$H$). The **methyl ether** was prepared using $CH_2N_2$ and was an amorphous solid: uv max ($CH_3OH$) 307 nm (ε 1460), 272 nm (ε 6400); nmr ($CDCl_3$) τ 7.68 (s, 3, $NCH_3$), 7.25 (t, 2, $J$ = 7 Hz, $PhCH_2CH_2$), 6.22 (s, 3, $PhOCH_3$), 6.10 (d, 1, $J$ = 2 Hz, Ph$H$).

*Anal.* Calcd for $C_{27}H_{37}NO_5 \cdot CH_3OH$: C, 68.96; H, 8.48. Found: C, 69.52; H, 8.14.

The **methiodide** of the **methyl ether** was crystallized from ether, mp 193–195°.

*Anal.* Calcd for $C_{28}H_{40}NO_5I$: C, 56.28; H, 6.75. Found: C, 55.89; H, 7.00.

**Preparation of a 6*H*-Dibenzo[*b*,*d*]pyran from Tetrahydrodecodine Methiodide.** The same procedure was used as in the synthesis of XIV. The dibenzopyran was obtained in about 50% yield as an amorphous solid. The phenolic hydroxyl group in the dibenzopyran was methylated with diazomethane. This derivative was then converted to the diacetate and purified by chromatography on Woelm acid alumina grade III. This material was then converted to a crystalline methiodide, mp 120°.

*Anal.* Calcd for $C_{32}H_{44}NO_7I$: C, 56.39; H, 6.51. Found: C, 56.49; H, 6.48.

Reduction with LAH in tetrahydrofuran cleaved the *O*-acetate groups and converted $=N^+(CH_3)_2$ to $=NCH_3$: nmr ($CDCl_3$) τ 7.59 (s, 3, $NCH_3$), 6.23 (s, 3, $PhOCH_3$), 6.10 (s, 3, $PhOCH_3$), 4.57 (m, 1, $J$ = [Ph][PhO]$CH$$CH_2$), 1.45 (s (broad), 1, Ph$H$).

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# Lythraceae Alkaloids. VIII. The Structure and Stereochemistry of the Biphenyl Ether Alkaloids from *Decodon verticillatus*[1,2]

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**Abstract:** Two new alkaloids have been isolated from *Decodon verticillatus* by an improved procedure for fractionation of the crude alkaloids. The new alkaloids have been converted to the known alkaloids vertaline and decaline by methylation of a phenolic hydroxyl group in each. Vertaline had been assigned structure II previously on the basis of X-ray data and decaline is assigned structure V on the basis of a series of degradative and spectral studies of both alkaloids. A key degradation was the conversion of VI to X and XI by sodium–ammonia. The new des-*O*-methyl alkaloids were assigned structures V and V-B (4″-OH, 5″-$OCH_3$) on biogenetic grounds.

The Lythraceae plant family elaborates a number of crystalline alkaloids, some of which have been assigned the biphenylquinolizidine skeleton I (R = H and $CH_3$). The alkaloids differ in three ways: (1) the nature of the substituents and the pattern of substitution on the biphenyl ring system, (2) the presence of a cinnamic or dihydrocinnamic lactone, (3) the stereochemistry at C-10.[2]

Our initial investigations of the Lythraceae plant *Decodon verticillatus* indicated that two of the alkaloids,[4] decaline and vertaline, differed structurally from those to which the biphenyl structure (I) has recently been assigned.[2] The structures of these two minor alkaloids became of increased interest with the isolation of relatively large amounts of their des-O-methyl derivatives from *Decodon* by an improved procedure for the fractionation of the crude alkaloid (see Experimental Section). The presence of a lactone ring and two methoxyl groups was evident in decaline and vertaline from spectral studies and by the lithium aluminum hydride (LAH) reduction of the lactone grouping in vertaline to a diol (tetrahydrovertaline). However, analytical data suggested the presence of another oxygen function which did not manifest itself chemically or spectroscopically and therefore was assumed to be present as an ether.

Once the structure of the biphenyl alkaloid lythrine was determined,[5] the biphenyl ether structure was considered to be a likely possibility for decaline and vertaline. This was suggested by the presence of six aromatic protons in the nuclear magnetic resonance (nmr) spectra of these bases and by the absence of any nmr signals that might be attributed to the protons of an aliphatic ether (other than methoxyl groups). The mass spectra of these bases showed fragments that could be assigned to a biphenyl ether grouping. Finally, the presence of both biphenyl and biphenyl ether alkaloids in the same plant is consistent with current biogenetic theory.[6]

These postulates were confirmed with the assignment of II to vertaline by an X-ray crystallographic study.[7] The biphenyl ether grouping is present in II together with a cis-fused quinolizidine ring containing an axial lactone grouping.

With the structure of vertaline in hand we set out to establish the structure of decaline. It was immediately apparent that decaline has the same skeleton and methoxylation pattern as vertaline as shown by the identity of the ultraviolet (uv) and mass spectra and the close similarity of the nmr and infrared (ir) spectra. Consequently, the differences in the two bases must be stereochemical. Since we already observed that the biphenyl alkaloids occur in pairs which differ stereochemically at C-10, structure V, which only differs from II by the configuration at C-10, seemed the most likely structure for decaline. This assignment was verified by a detailed structure analysis.

Decaline was shown to have the same configuration as vertaline at the biphenyl ether link since the optical rotatory dispersion (ORD) and circular dichroism

(1) Direct correspondence to J. P. F. at RPI. Supported by grants from Smith, Kline and French Laboratories and the U. S. Public Health Service (MY-4748).

(2) The previous paper in this series: J. P. Ferris, C. B. Boyce, and R. C. Briner, *J. Amer. Chem. Soc.*, **93**, 2942 (1971). Some of this work was presented in preliminary form: J. P. Ferris, R. C. Briner, and C. B. Boyce, *Tetrahedron Lett.*, 5125 (1966).

(3) (a) USPHS Career Awardee (GM 6380) of the National Institute of General Medical Sciences. (b) Abstracted from the doctoral dissertations of C. B. Boyce [*Diss. Abstr. B*, 27 (12), 4301 (1967); *Chem. Abstr.*, 67, 117015 (1967)] and R. C. Briner [*Diss. Abstr. B*, 27 (11), 3845 (1967); *Chem. Abstr.*, 67, 100290 (1967)] submitted to Florida State University, Dec 1966. R. C. B. was an NSF Summer Fellow (1962) and a USPHS Predoctoral Fellow (1962–1965).

(4) J. P. Ferris, *J. Org. Chem.*, 27, 2985 (1962).

(5) D. E. Zacharias, G. B. Jeffery, B. Douglas, J. A. Weisbach, J. L. Kirkpatrick, J. P. Ferris, C. B. Boyce, and R. C. Briner, *Experientia*, 21, 247 (1965).

(6) J. P. Ferris, C. B. Boyce, and R. C. Briner, *Tetrahedron Lett.*, 5129 (1966). Tracer experiments consistent with this proposal have been reported by A. Rother and A. E. Schwarting, *Chem. Commun.*, 1411 (1969), and S. H. Koo, R. N. Gupta, I. D. Spenser, and J. T. Wrobel, *ibid.*, 396 (1970).

(7) J. A. Hamilton and L. K. Steinrauf, *Tetrahedron Lett.*, 5121 (1966); *J. Amer. Chem. Soc.*, **93**, 2939 (1971).