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LYTHRACEAE ALKALOIDS
STRUCTURE AND STEREOCHEMISTRY OF THE MAJOR ALKALOIDS OF DECODON AND HEIMIA (1)

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The first chemical reports on the Lythraceae plant family described the isolation of the alkaloids of Decodon verticillatus and presented part structures for several of these compounds. (2) Subsequently, the isolation of the alkaloids of Heimia salicifolia and myrtifolia was reported and several of these bases were interrelated with those isolated from Decodon. (3,4) Four groups of structurally related alkaloids emerged from these studies (designated as series A, B, C and D in Table I) which have the same basic skeleton but which differ in the oxidation pattern of the aromatic nuclei and/or in configuration at one or more asymmetric centers. A combination of x-ray crystallographic and chemical studies established V ($R=CH_3$) for lythrine and with appropriate modification to the alkaloids of the A series. (5)

The complete structures of the alkaloids of the B, C and D series were still to be determined and are the subjects of this communication.

First, the optical rotatory dispersion curves of the alkaloids are similar showing that all have the same configuration at the biphenyl linkage. Therefore, configurational variation must be at the quinolizidine ring.

It was possible to deduce these stereochemical differences in decinine and decamine by several independent methods. Comparison of the

n.m.r. spectra of the N-oxides of methyldecinine (A series) and methyldecamine (B series) with those of the parent alkaloids reveals a 1-1.5 τ shift in one of the aromatic protons to lower field. (Table I) Examination of a Dreiding model of methyldecinine N-oxide (A series) shows that the N-oxide oxygen is adjacent to H-3'' so the shift must be due to the deshielding effect of the polar oxygen atom on this proton. Since the same effect is observed in methyldecamine any structure that is considered for the B series of alkaloids must allow for the oxygen of the N-oxide next to H-3''. Using this criterion, one needs to consider only structures II-IV (Chart I) for the B series. (7)

Evidence for the cis fusion in vertine and its derivatives may be found in the low field shift of the H-4 in the vertine series (B) as compared to the lythrine series (A). (8) Also the N-CH_3 resonances (Table I) of the methiodides of the B series also are at lower field than the A series. (9) Finally, compounds of the A series exhibit "Bohlmann bands" in the 2800-2730 cm^{-1} in the infrared characteristic of the trans-quinolizidine and these are absent in the B series in agreement with the cis-quinolizidine assignment. (10) Further, these "Bohlmann bands" persist in the A series and again are absent in the B series when the lactone ring is cleaved. Using these criteria one needs to consider only the cis-fused quinolizidines III and IV for the B series.

It was possible to assign IV to vertine and with appropriate modification to the B group of alkaloids in general on the basis of a parallel series of degradations on lythrine and vertine (Chart II). Reductive cleavage of the lactone function of lythrine (V, R=CH_3) with lithium aluminum hydride followed by hydrogenolysis with sodium-ethanol-ammonia yielded VI (n.m.r., C-CH_3 9.03 τ, triplet J, 6.5 c.p.s.). Compound VI was not isolated but was converted directly to the methiodide in 51% yield from V (m.p. 125-126.5°; C, 57.33%, H, 6.92%). Base treatment converted VI methiodide into chromone VII in 78% yield (m.p. 90-91°; analytical results were anomalous due to chloroform solvation; n.m.r., H-4, 4.53 τ, doubled doublet, J, 10.0, 3 c.p.s., H-10, 7.0 τ, doublet, J, 10 c.p.s., N-CH_3, 7.58 τ). The mesylate of VII eliminated with potassium t-butoxide to give a 55% yield of the

TABLE I

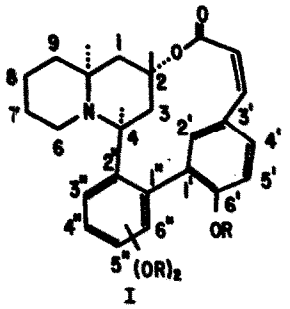
Proton Chemical Shifts for the Lythraceae Alkaloids (τ)

Alkaloids	Series	H-4[a]	O-Methyl	N-Methyl of Methiodide	H-3''	H-3'' in N-oxide
Methyllythrine	A	6.25	6.06, 6.12, 6.20			
Methylvertine	B	5.40	6.06, 6.10, 6.22			
Methyldecinine	A	6.86	6.08, 6.15, 6.26	6.51	2.98	1.90
Methyldecamine	B	5.93	6.10, 6.14, 6.26	6.10	3.00	1.62
Acetyllythrine	A	6.30	6.05, 6.14		2.93	1.87
Acetylvertine	B	5.45	6.05, 6.14		2.96	1.74
Acetyldecinine	A	6.86	6.05, 6.15		2.91	1.64
Acetyldecamine	B	6.00	6.06, 6.16		2.98	1.50
Dimethyldecodine	C	6.97	6.13, 6.31, 6.31	6.64	2.83[c]	1.85[c]
Dimethyldihydroverticillatine (Methylindicamine)[d]	D	6.30	6.12, 6.30, 6.31	6.25	2.80[c]	1.67[c]
Diacetyldecodine	C	6.90	6.13	6.57	2.63[c]	1.67[c]
Diacetyldihydroverticillatine	D	6.14	6.15	6.14	2.63[c]	1.33[c]
Dimethylverticillatine	D	5.70	6.12, 6.28, 6.30		2.74[c]	1.75[c]
Diacetylverticillatine	D	5.65	6.15	6.17	2.62[c]	1.50[c]
Acetylindicamine	D		6.10, 6.50			
Nesodine	C		6.02, 6.31[b]			

a. Quartet with J=10-12, 1-2 cps. b. Ref. 4 c. J=9 cps.

d. The isolation of indicamine will be described in a subsequent publication.

CHART I



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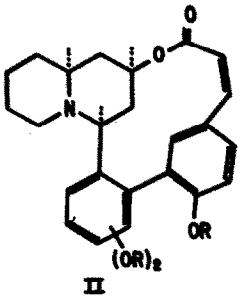

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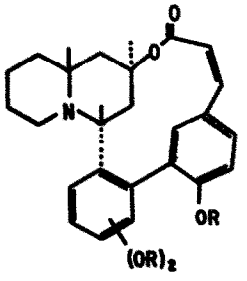
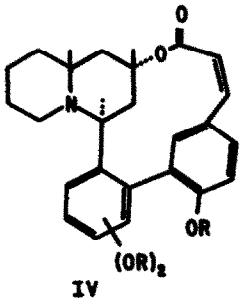
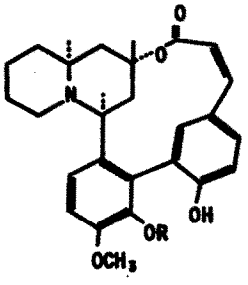


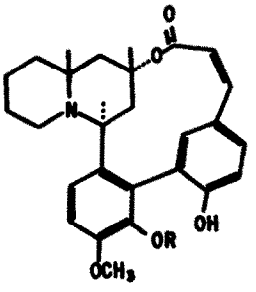
III



IV



XX



XXI

trans olefin VIII(m. p. 84-85°; C, 77.1%; H, 8.44%; n. m. r., H-2, H-3, H-4 complex pattern 4.1-4.7 τ, H-10, 7.2 τ, J, 10 c. p. s.; i. r. 973 cm^{-1}.) Hydrogenolysis and reduction of the double bond yielded IX as a non-crystalline gum.

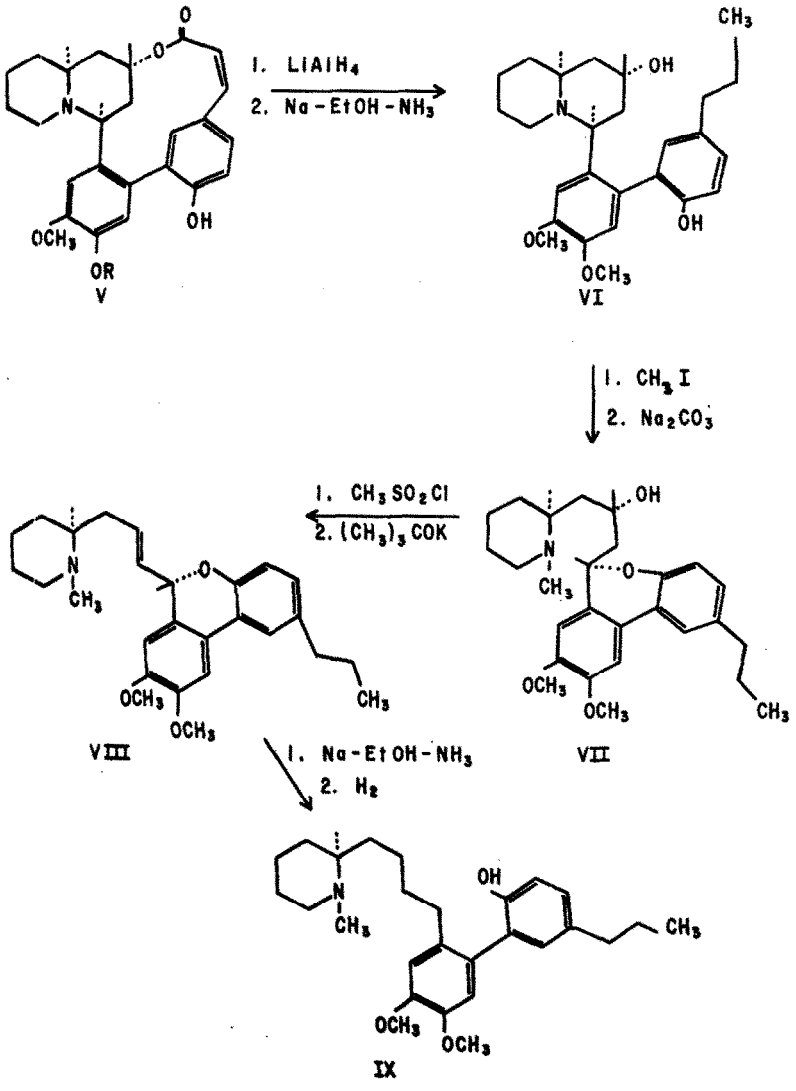
The series of degradations in Chart II were also performed on vertine. There were definite differences in the properties of the lythrine derivatives and the corresponding vertine derivatives. In particular the i. r. and n. m. r. spectra of VIII in both series show small but significant differences and the mixed melting point of the olefins is depressed (77-92°). These data require that the lythrine (A) and vertine (B) series differ in configuration at either C-10 or C-4. Since compound VIII as derived from vertine is neither identical with nor the mirror image of VIII derived from lythrine only structure IV remains for the vertine (B) series. The rotation of IX derived from lythrine was -31° and that of the IX derived from vertine was +31° consistent with C-10 as the point of asymmetry.

The asymmetry at C-10 was also demonstrated by degradations of the A series of alkaloids as outlined on Chart III. The conversion of decinine (X) to the cyclic ether (XI) (m. p. 219.5-220°) was effected in 82% yield with $NaBH_4$-BF_3. Emde reduction of the methiodide of XI resulted in cleavage of the quinolizidine ring to give XII (m. p. 202-203.5°). O-methylation followed by demethylation of the pipiridine ring in XII and treatment with nitrous acid yielded XIII (m. p. 125-126°, C, 69.71%; H, 7.76%; N, 6.22%).

The degradations shown in Chart III were also performed on decamine (Series B). The asymmetry at C-10 in XIII is clearly reflected in the Cotton effect for the nitroso group (11,12) with a positive extremum at 380mμ in the A series and the negative extremum at 380 mμ in the B series. Circular dichroism (CD) measurements show a positive maximum at 350mμ in the A series and a negative maximum at 350 mμ in the B series.

Oxidation and UV spectral studies require that the biphenyl nuclei of the alkaloids in the C and D series have oxygen substituents at the 3'', 4'' and 6' or 5'', 6'' and 6' positions. Schwarting and coworkers

CHART II


1. LiAlH4
2. Na-EtOH-NH3
OCH3
OR
OH
V
CH3
OH
OCH3
OCH3
OH
VI
1. CH3I
2. Na2CO3
1. CH3SO2Cl
2. (CH3)3COK
OH
N
CH3
O
OCH3
OCH3
CH3
VII
VIII
1. Na-EtOH-NH3
2. H2
OH
CH3
OCH3
OCH3
IX

have assigned the oxygen substituents to this 3'', 4'', 6' positions. (4)

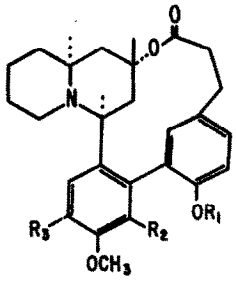
The n. m. r. spectra of the N-oxides of dimethyldecodine and dimethyldihydroverticillatine not only show the low field shift for H-3'' observed in the A and B alkaloid series but also show it clearly as half of an AB quartet at 1.8 τ (Table I). It is possible to discern the other half of this quartet among the other aromatic protons at 2.8 τ. An AB splitting pattern requires a proton at the 4'' position. These data clearly show that the C and D series have oxygen substituents at the 4'', 5'' and 6' positions.

The relative configurations of the quinolizidine rings in the C and D series remained to be established. If one compares the n. m. r. data in Table I it is immediately apparent that the configurations of the asymmetric centers at the A and C series are the same and that the configurations of the asymmetric centers of the B and D series are the same. "Bohlmann bands" (10) are present in the infrared spectra of the C series and absent in the D series confirming that a trans ring juncture is present in the former and absent in the latter. On this basis we assign I to the C series and IV to the D series.

Confirmation of these assignments was obtained by carrying out a series of degradations (Chart III) similar to those described for vertine and lythrine. The sequence is illustrated in Chart II with dimethyldecodine (XIV) as the starting point. The same degradations were also carried out on the D series. The Emde degradation products (XVI) were dissimilar in both series and the N-nitroso derivatives (XVII) reflected this difference in the ORD spectra at 350 mμ with a positive peak in the C series and a negative peak in the D series.

Finally, it is possible to assign the location of the methoxyl and hydroxyl groups in all the naturally occurring alkaloids in the A, B, C and D series on the basis of n. m. r. and chemical data. A 6' or 6'' methoxyl group is shielded by the adjacent phenyl ring and resonates at 6.2-6.3 τ while methoxyls at other positions (4'' or 5'' in particular) resonate at 6.05-6.15 τ. (13) One can discern the presence of a 6' OH if the methiodide derivative cyclizes to a chromone on treatment with base (e.g. VI $\rightarrow$ VII, Chart II). Derivatives of decinine, deca-

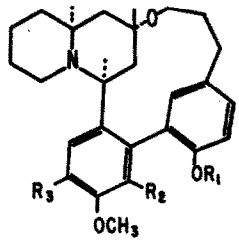
CHART III



X $R_1, R_2 = H, R_3 = OCH_3$

XIV $R_1 = CH_3, R_2 = OCH_3, R_3 = H$

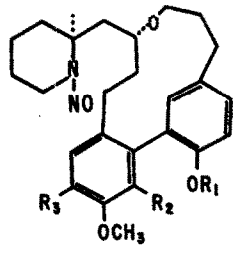
$NaBH_4$ / BF_3



XI $R_1, R_2 = H, R_3 = OCH_3$

XV $R_1 = CH_3, R_2 = OCH_3, R_3 = H$

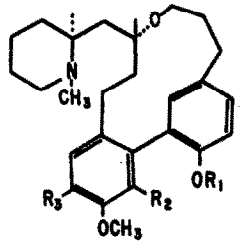
1. CH_3I
2. $Na-NH_3$



XIII $R_1 = CH_3, R_2 = H, R_3 = OCH_3$

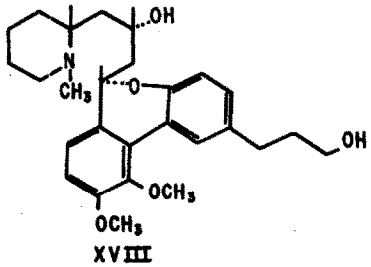
XVII $R_1 = CH_3, R_2 = OCH_3, R_3 = H$

1. CH_2N_2
2. CNBr
3. $LiAlH_4$
4. HNO_2

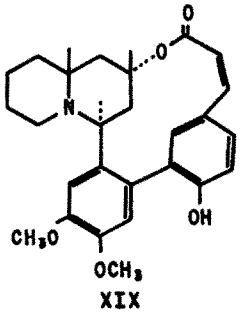


XII $R_1, R_2 = H, R_3 = OCH_3$

XVI $R_1 = CH_3, R_2 = OCH_3, R_3 = H$



XVIII



XIX

mine, decodine, dihydroverticillatine and indicamine form chromones (e. g. XVIII is the chromone in the indicamine series) clearly demonstrating the presence of the 6' OH in these alkaloids. From these data and the chemical shift of the methoxyl group (s) in Table I complete structures may be assigned to the following naturally occurring Lythraceae alkaloids: lythrine, V ($R=CH_3$) (5); decinine, dihydro V ($R=CH_3$) (5); vertine, XIX; decamine, dihydro XIX; decodine, dihydro XX (R=H); verticillatine, XXI (R=H); dihydroverticillatine, dihydro XXI (R=H); and indicamine, dihydro XX ($R=CH_3$). On the basis of the data available (4) and biogenetic considerations one can assign structures XX ($R=CH_3$) to nesodine and V (R=H) to lyfoline with reasonable certainty.

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(1) Address inquiries to J. P. F. at The Salk Institute.

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(11) We wish to thank Drs. U. Weiss and N. Sharpless (NIH) for their assistance with some of the ORD and CD measurements.

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