# THE CONSTITUENTS OF *DYSOXYLUM LENTICELLARE*. I. PHENYLETHYLISOQUINOLINE, HOMOERYTHRINA, AND DIBENZAZECINE ALKALOIDS

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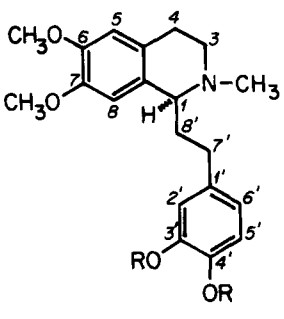
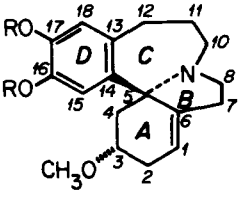
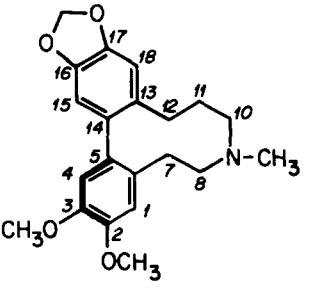
ABSTRACT.—Two new alkaloids possessing the 1-phenylethyltetrahydroisoquinoline skeleton, dysoxyline (**1**) and *S*-(+)-homolaudanosine (**2**), have been isolated from *Dysoxylum lenticellare* Gillespie (family Meliaceae) along with known homoerythrina alkaloids 3-epischelhammericine (**3**) and 2,7-dihydrohomoerysotrine (**4**). Also isolated was a new alkaloid with a novel dibenz[d,f]azecine skeleton, dysazecine (**5**). The macrocycle **5** represents the trapping of a biosynthetic intermediate in the postulated conversion of the phenylethylisoquinoline skeleton to the homoerythrina skeleton. None of these alkaloid skeleta have been found previously in plants of the Meliaceae.

The genus *Dysoxylum* of the family Meliaceae is comprised of about 60 species of trees in Polynesia and Indomalaysia. Phytochemical screening of many species of *Dysoxylum* has indicated that some contain alkaloids (1–3); however, no chemical structures have been determined. We report here the first structure determinations of alkaloids from the genus which were isolated from *D. lenticellare* Gillespie grown in the Fiji Islands.

Leaves of *D. lenticellare* were extracted with methanol, and the extract was defatted with pentane. Further partitioning gave a chloroform extract containing the alkaloids **1**–**5**, which were separated by chromatographic techniques and were purified, in most cases, as their picrate salts.







**1** R,R = $-CH_2-$ **3** R,R = $-CH_2-$ **5**

**2** R = $-CH_3$ **4** R = $-CH_3$

Major alkaloids **1** (0.01%) and **2** (0.03%) were identified as simple 1-phenylethyltetrahydroisoquinolines initially by means of their mass spectra. While the parent ions of **1**, *m/e* 355.1802 (agrees with $C_{21}H_{25}NO_4$) and **2**, *m/e* 371.2210 (agrees with $C_{22}H_{29}NO_4$), differ by 16 amu, both compounds show a base peak at *m/e* 206 resulting from the loss of a phenylethyl radical from the parent ion. A similar loss of the C–1 benzyl radical produces the base peak in the ms of benzylisoquinolines (4). The difference of 16 amu between **1** and **2** is explained by the presence of a methylenedioxy group on the side chain aromatic ring in **1** and two methyoxyl groups in **2**. The difference is confirmed by the presence of the tropylium ions derived by cleavage of the C–7' to C–8' bonds in the ms of **1** at *m/e* 135 and **2** at *m/e* 151.

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Proton nmr spectra are in full agreement with structures **1** and **2**. Additional evidence for these structures is obtained from the $^{13}C$ nmr spectra shown in table 1 with literature values for the benzylisoquinoline alkaloid, laudanosine (5). The circular dichroism (cd) spectra obtained for **1** and **2** each contain positive Cotton effects near 280 and 240 nm. Since the cd spectrum of *S*-(+)-laudanosine contains bands of a similar sign at these wavelengths (6), the absolute configuration for alkaloids **1** and **2** must be *S*.

Despite their simplicity, phenylethylisoquinolines **1** and **2** are new natural products. Prior to this report, only one simple phenylethylisoquinoline alkaloid had been isolated from a natural source (7). Racemic **2** has been synthesized and has been called homolaudanosine (8–10). Compound **2** is thus *S*-(+)-homolaudanosine. A corresponding name for **1** is not available, however, since the homologous benzylisoquinoline has not been described in the literature. We propose the name dysoxyline for **1**.

Two alkaloids having the homoerythrina skeleton were isolated, and these have been identified as 3-epischelhammericine, (**3**, 0.007%), and 2,7-dihydrohomoerysotrine, (**4**, 0.004%) by spectroscopic measurements and by comparison with authentic samples (11). Alkaloid **3** was initially isolated as a minor component of a binary mixture separable only by reverse-phase hplc. The structure of the alkaloid which cochromatographs with **3** is still under investigation.

The minor alkaloid **5** (0.002%) is isomeric with dysoxyline (**1**); however, the mass spectral fragmentation pattern of **5** bears no resemblance to that of **1**. In **5** the molecular ion, *m/e* 355, is also the base peak. Loss of small, neutral, nitrogenous fragments give the principal high-mass ions; and a major ion is observed at *m/e* 70 corresponding to $C_4H_8N$. The facile loss of various nitrogenous fragments suggested the presence of the nitrogen atom in a large heterocyclic ring.

The proton nmr spectrum of **5** reveals four non-coupled aromatic protons, a methylenedioxy group, two methoxyl groups, and an *N*-methyl group in a uniquely shielded position at 2.10. The $^{13}C$ nmr spectrum shows the presence of four oxygenated quaternary aromatic carbons ($\delta$ 144.7–148.3), four quaternary aromatic carbons ($\delta$ 133.0–135.4), four protonated aromatic carbons ortho to oxygens ($\delta$ 107.5–112.8), and five aliphatic methylene groups (two deshielded by attachment to nitrogen at 49.6 and 59.0 and three others resonating between 27.8 and 30.5). The narrow ranges of the chemical shifts within some groups precludes individual assignments in the absence of model compounds.

Alkaloid **5** is a new natural product for which we propose the name dysazecine to reflect both its source and its chemical structure. By analogy to dysoxyline (**1**) and 3-epischelhammericine (**3**), we depict dysazecine with the 3-carbon bridge between nitrogen and the methylenedioxyphenyl ring. Spectral data does not allow us to distinguish between this possibility and that in which the third methylene group is on the dimethoxyphenyl side of the nitrogen. Further work is required to settle this point unambiguously.

The circular dichroism (cd) spectrum of **5** is dominated by strong ($\theta > 10^4$) Cotton effects (CE's) at 295 (positive) and 232 nm (negative). Since **5** contains no chiral carbons, its optical activity arises solely from the inherently dissymmetric biphenyl ring system held in one chiral conformation by the 6-atom o,o'-bridge.

The literature contains a report of the transformation of the homoerythrina alkaloid schelhammeridine to optically active, bridged biphenyls which differ from **5** by the absence of both methoxyl groups at C–2 and C–3 and by the presence of *N*-acetyl and chiral C–7 hydroxyl functions (12). Three diastereomers were isolated, and the chirality of the biphenyl system in each was assigned on the basis of stereochemical arguments. The *R*-chirality (13) for the biphenyl system was associated with a positive CE at 290 nm in the optical rotatory dispersion spectrum of these compounds (12). This assignment seems to be in agreement with the signs of the CE's generally observed in the cd spectra of optically active biphenyls

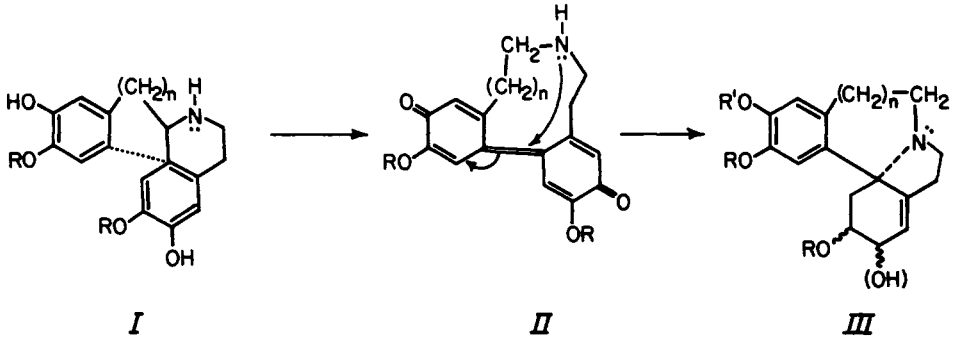
(14). Moreover, a recent compilation of cd data for aporphine alkaloids also associated positive long-wavelength CE's (~270 and 295 nm) and a negative short-wavelength CE (235–245) with the *R*-biphenyl configuration (15).

On this precedent we assign the *R*-chirality to **5**. It should also be noted that the *R*-relationship between the aromatic-rings in **5** is opposite to the stereochemical relationship of the aromatic D-ring and the cyclohexene A-ring in homoerythrina alkaloids **3** and **4** (21).

A recent review emphasizes the parallels between the well-studied family of erythrina alkaloids and the more recently discovered family of homoerythrina alkaloids (16). As shown in scheme 1, erythrina alkaloids (III, n=1) have been demonstrated to arise *in vivo* from 1-benzyltetrahydroisoquinoline (I) precursors (17). By direct feeding experiments with doubly-labelled precursors, the presence of a symmetrical azonine intermediate (II, n=1) has been rigorously established in the biosynthesis of erythrina alkaloids (17,18). In one *Erythrina* species such an intermediate is presumably converted to the *N*-methylazonine alkaloid, erybidine, which has been isolated as a racemic natural product (19).

By analogy to the erythrina, the homoerythrina alkaloids (III, n=2) have been postulated to arise from 1-phenylethyltetraydroisoquinolines (I) by way of an azecine intermediate (II, n=2) (20). Thus our finding of alkaloids with all three carbon skeleta (I–III, n=2) in *D. lenticellare* represents the best circumstantial evidence to date supporting the postulated biogenetic pathway for the homoerythrina alkaloids.

*Scheme 1. Biogenesis of Erythrina and Homoerythrina Alkaloids*




*I* *II* *III*

## EXPERIMENTAL[2]

PLANT MATERIAL.—*Dysoxylum lenticellare* Gillespie (Meliaceae) was collected on 28 August, 1963, near the Boy Scout camp, Coli-Suva, Viti Levu in the Fiji Islands by George Uhe. Voucher

[2]Melting points were determined in a Mel-Temp apparatus and are uncorrected. Specific rotations were determined in a 1 dm, jacketed tube in a Perkin-Elmer model 241 MC polarimeter. Infrared (ir) spectra were recorded on a Perkin-Elmer model 457A grating spectrophotometer. Ultraviolet (uv) spectra were obtained on a Bausch and Lomb Spectronic 2000 spectrophotometer. Circular dichroism (cd) spectra were obtained on a Cary 61 cd spectropolarimeter in a 1 cm cell. All nmr spectra are reported in ppm with tetramethylsilane as an internal standard. $^1$H nmr spectra were recorded on a Varian T-60 spectrometer and at high resolution on a Brucker HX-270 spectrometer in the Fourier transform mode. $^{13}$C nmr spectra were recorded in concentrated $CDCl_3$ solutions in sealed 1.7 mm capillary tubes on a Varian Ft-80A instrument. Mass spectra (ms) were obtained at low resolution on a Finnigan-MAT 212 spectrometer with an SS200 data system and at high resolution on a CEC 21-110B mass spectrometer with electron impact ionization at 70 ev. All reported relative intensities were obtained from the low resolution ms. Thin layer chromatography (tlc) was carried out on alumina-coated plastic sheets (Bakerflex IB-F). Preparative tlc (ptlc) was performed on glass plates precoated with a 1.5 mm layer of alumina $GF_{254}$ (E Merck). Visualization of chromatograms was by uv light; alkaloids were also visualized by Dragendorff's spray reagent. Column chromatography was carried out on neutral aluminum oxide (Brockmann activity grade I). High pressure liquid chromatography (hplc) was performed with a Waters Liquid Chromatograph. Elemental analyses were performed by Strauss Analytical Laboratory, Oxford, England.

TABLE 1. $^{13}C$-nmr Data for Benzyl and Phenylethyl Tetrahydroisoquinolines in $CDCl_3$.

| Carbon | dysoxyline 1 | homolaudanosine 2 | laudanosine[a] |
|---|---|---|---|
| 1 | 62.3 | 62.4 | 64.5 |
| 2 | — | — | — |
| 3 | 47.6 | 47.6 | 46.8 |
| 4 | 24.9 | 24.9 | 25.3 |
| 4a | 126.0 | 126.2 | 125.8 |
| 5 | 111.2 | 111.8 | 112.8 |
| 6 | 147.2 | 147.2 | 146.9 |
| 7 | 147.2 | 147.2 | 146.9 |
| 8 | 109.9 | 110.6 | 110.7 |
| 8a | 136.1[b] | 135.2[b] | 132.2 |
| 1' | 128.7[b] | 129.3[b] | 129.0 |
| 2' | 108.6 | 111.2 | 110.7 |
| 3' | 147.2 | 148.7 | 148.3 |
| 4' | 145.1 | 146.9 | 146.0 |
| 5' | 107.8 | 111.2 | 110.7 |
| 6' | 120.8 | 120.0 | 121.5 |
| 7' | 36.7 | 36.8 | 40.4 |
| 8' | 31.0 | 31.1 | — |
| $-OCH_2O-$ | 100.4 | — | — |
| $-OCH_3$ | 55.8 | 55.8 (2C) | 55.5 (2C) |
| $-OCH_3$ | 55.6 | 55.7 (2C) | 55.3 (2C) |
| $-NCH_3$ | 42.0 | 42.3 | 42.4 |

[a]Taken from ref. 5.
[b]Assignments may warrant changing.

specimens AK 157465 and AK 157466 are preserved in the Herbarium of the Auckland Institute and Museum, Auckland 1, New Zealand. After receiving negative results in the NCI antitumor plant screening program (sample B645818), Professor R. F. Raffauf of Northeastern University, Boston, kindly donated the plant material to us.

EXTRACTION.—Powdered leaf material (2.8 kg) was percolated with methanol until extracts tested negative to Dragendorff's reagent. The extract was concentrated to 1.8 liters and was partitioned against pentane in a continuous liquid-liquid extractor for several days. The pentane extract (96 g) contained no alkaloids (Dragendorff). The hydroalcoholic layer was filtered (27 g of flavonoid-positive material removed), and the filtrate was concentrated to a syrup. Approximately one-half of this syrup was diluted with an equal volume of water and was exhaustively extracted with chloroform. The chloroform solubles (48 g) redissolved in ethyl acetate were slurried with 75 g of alumina. The alumina was filtered and was washed with ethyl acetate to give, on removal of the solvent, 36 g of a crude alkaloid fraction.

Column chromatography on alumina with increasing amounts of ethyl acetate in cyclohexane eluted mixtures of alkaloids **3** and **4** prior to **5**, **1** and **2**. Preparative tlc on alumina with 5% ethanol in cyclohexane allowed the isolation of alkaloids **1**–**5**; tlc Rf values in the alcohol—cyclohexane system were **1** (0.55); **2** (0.43); **3** (0.65); **4** (0.57); and **5** (0.68).

DYSOXYLINE (**1**).—Ptlc fractions (121 mg) in absolute ethanol, on treatment with a saturated solution of picric acid in the same solvent, gave 160 mg of yellow crystals, mp 154–6°. Two recrystallizations from methanol containing 5% excess picric acid gave **1**-picrate, mp 159–61°.

*Anal.* Calcd. for $C_{27}H_{25}N_4O_{11}$: C, 55.47; H, 4.82; N, 9.58. Found: C, 55.32; H, 4.80; N, 9.53.

The free base, regenerated by passage of a methylene chloride solution of the picrate through a micro-column of basic alumina, showed the following properties: $[\alpha]^{25}D+22°$ (c=.34, EtOH); uv, max. (ε, EtOH), 286 (7800), 230 nm sh (13000); cd (EtOH) $[\theta]_{285}+9200$; $[\theta]_{235}+23000$; $^1H$ nmr (270 MHz, $CDCl_3$) δ 6.72 (d, *J* 8, 1H), 6.68 (d, *J* 2, 1H), 6.63 (dd, *J* 8, 2, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.91 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.41 (t, *J* 5, 1H, H-1), 3.18 (m, 1H), 2.66 (m, 4H), 2.47 (s, 3H, *N*-$CH_3$, overlaying m, 1H), 2.03 (q, *J* 5, 2H, H-8'); ms: 355.1802 ($M^+$, 1%, $C_{21}H_{25}NO_4$), 207 (16%) 206 (100%, $C_{12}H_{16}NO_2$), 191 (11%), 190 (21%, $C_{11}H_{12}NO_2$) 162 (8%, $C_{10}H_{12}NO$), 135 (20%, $C_8H_7O_2$).

*S*-(+)-HOMOLAUDANOSINE (**2**).—Ptlc fractions formed a picrate from abs. ethanol only with difficulty. Multiple recrystallizations from the same solvent (with added picric acid) gave **2**-picrate, mp 78–79°.

*Anal.* Calcd for $C_{28}H_{32}N_4O_{11}$: C, 55.99; H, 5,33; N, 9.33. Found: C, 56.02; H, 5.26; N, 9.14.

The gum obtained after regeneration of the free base (as with **1**) gave the following properties: $[\alpha]^{25}D+11°$ (c=.21, EtOH); uv max. (ε, EtOH) 281 (5820), 226 nm sh (13600); cd (EtOH), $[\theta]_{280}+3900$, $[\theta]_{235}+22500$; $^1H$ nmr (270 MHz, $CDCl_3$) δ 6.80 (d, *J* 9, 1H), 6.75 (dd, *J* 9, 2, 1H), 6.73 (d, *J* 2, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 3.86 (s, 9H), 3.83 (s, 3H), 3.42 (t, *J* 5, 1H, H-1), 3.16 (m, 1H), 2.69 (m, 4H), 2.48 (s, 3H, *N*-$CH_3$), overlaying (m, 1H), 2.04 (q, *J* 5, 2H, H-8'); ms: 371.2110 ($M^+$, 2%, $C_{22}H_{29}NO_4$) 369 (1%), 355 (3%, M-$CH_4$), 354 (3%, M-$CH_5$), 340 (1%,

M–$C_3H_7$), 207 (23%), 206 (100%, $C_{12}H_{16}NO_2$), 192 (14%), 191 (12%), 190 (18%), 162 (7%, $C_{10}H_{12}NO$), 151 (20%, $C_8H_{11}O_2$).

3-EPISCHELHAMMERICINE (**3**).—Ptlc fractions of **3** showing one spot by tlc were found to be mixtures of two compounds with **3** as the minor (25%) component. Preparative hplc on a μ-Bondapak (Waters) $C_{18}$ reverse phase column using acetonitrile-methanol-water (36:4:60) gave purified **3** as the first eluting substance. The material was identified as **3** by co-tlc with an authentic specimen and by comparison with ir and ms data[3]. Crystalline **3**-picrate from ethanol, mp 169–71° [lit. (21,22) mp 169–172°], was also obtained.

2,7-DIHYDROHOMOERYSOTRINE (**4**).—Ptlc fractions of **4** were identified by co-tlc with **4** and by comparison of the ir and ms spectra with those of an authentic sample.[3]

DYSAZECINE (**5**).—Ptlc fractions (24 mg) gave 41 mg of crude picrate from ethanol. Two recrystallizations from absolute ethanol gave 20 mg of **5**-picrate, mp 217–19°.

*Anal.* Calcd for $C_{27}H_{28}N_4O_{11}$: C, 55.47; H, 4.82; N, 9.58. Found: C, 55.64; H, 4.88; N, 9.71.

The free base had the following properties: $[\alpha]^{25}D+83°$ (c=.22, EtOH); uv max. (ε, EtOH), 291 (7270), 230 sh (15000); cd max (EtOH, c=1.56 x $10^{-4}M$) $[\theta]_{295}+11900$, $[\theta]_{279}-2900$, $[\theta]_{250}+960$, $[\theta]_{232}-10600$; $^1H$ nmr (270 MHz, $CDCl_3$) δ 6.76 (s, 2H), 6.53 (s, 1H), 6.52 (s, 1H), 5.98 (d, *J* 1.5, 1H), 5.96 (d, *J* 1.5, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 2.66 (td, *J*=11, 3, 1H), 2.10 (s, 3H, N–$CH_3$). The remaining nine aliphatic hydrogens were found in three complex multiplets: 2.6–2.5, 2.4–2.15 and 1.8–1.4; $^{13}C$ nmr ($CDCl_3$) δ 148.3 (s), 146.8 (s), 146.2 (s), 144.7 (s), 135.4 (s), 134.7 (s), 133.7 (s), 133.0 (s), 112.8 (d), 110.8 (d), 109.7 (d), 107.5 (d), 100.7 (t), 59.0 (t), 55.8 (2C, q), 49.6 (t), 44.5 (q), 30.5 (t), 28.4 (t), 27.8 (t); ms: *m/e* 355.1767 ($M^+$, 100%, $C_{21}H_{25}NO_4$), 354 (4%), 340 (15%), 312.1353 (15, M–$C_2H_5N$), 297.1094 (11%, M–$C_3H_8N$), 284.1048 (15%, M–$C_4H_9N$), 283.0952 (35%, M–$C_4H_{10}N$), 70.0664 (72%, $C_4H_8N$), 58 (46%), 57 (67%).

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