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CO-OCCURRENCE OF APORPHINE AND BIPHENYL CONSTITUENTS IN *LITSEA TURFOSA*

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Key Word Index—*Litsea turfosa*; Lauraceae; boldine; laurolitsine; dehydrodiengenol.

Litsea turfosa (Lauraceae) occurs widely in the peat swamps of Sarawak. A chloroform extraction of the ground bark shows anti-fungal activity and the metabolites may also possess anti-tumor activity. For this reason a detailed chemical examination of the constituents of the bark was undertaken. Extraction of the crude $CHCl_3$ extract with dil. H_2SO_4 separated the basic and non-basic fractions.

Basic fraction. Both column and TLC on neutral alumina were necessary to separate the bases and two aporphine alkaloids, boldine (I) and laurolitsine (II) (also known as norboldine), were isolated as the major components. Both alkaloids were identified by their UV spectra [I, λ_{max} (log ϵ) 219 (4·5), 282 (4·1), 303 nm (4·1); (II), λ_{max} (log ϵ) 222 (4·33), 283 (4·09), 304 nm (4·07)] which were typical spectra for 1,2,9,10-tetrasubstituted aporphines[1] as were the chemical shifts of the aromatic protons in the NMR spectra.[2] These were at 3·50 (H-3), 3·30 (H-8) and 2·22 τ (H-11) for I and at 3·57 (H-3), 3·40 (H-8) and 2·14 τ (H-11) for II.

Boldine also showed a 3 proton singlet at 7·55 τ (N–Me) which was absent in the NMR spectrum of laurolitsine. The MS of both metabolites are in agreement with the data previously reported.[2] The structure of boldine was confirmed by direct comparison (IR, m.m.p.) with an authentic sample.[3] Both alkaloids have been reported in several *Litsea* species, sometimes occurring together.[4]

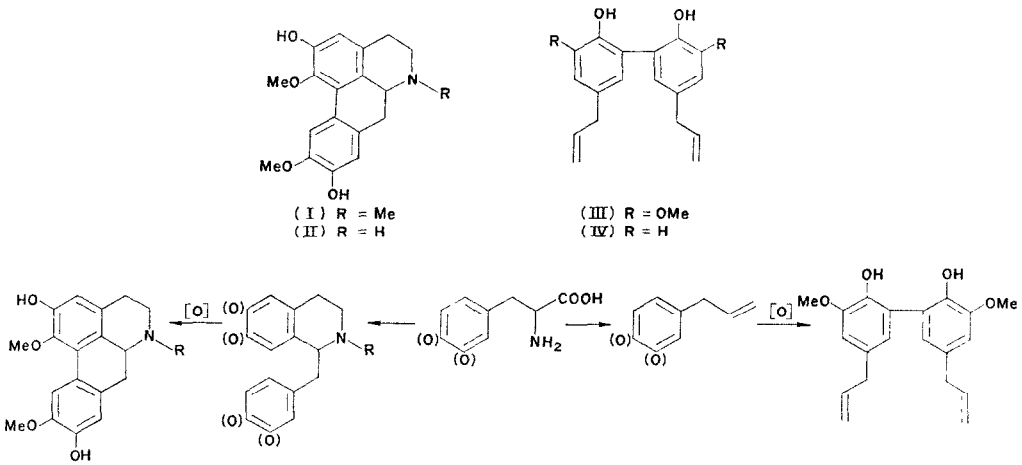
Pharmacological tests on boldine have indicated that it has an LD_{50} in mice of about 150 mg/kg (i.p. propylene glycol) and causes clonic convulsions at this concentration; it has also shown some activity against *Phytophora palmivora*. However, it is inactive against sarcoma 180 and L1210 tumors at sublethal doses.

Non-basic fraction. A biphenyl has been isolated from the non-basic fraction by preparative TLC on silica gel. This compound has been identified as dehydrodieugenol (III). MS gave a molecular ion at *m/e* 326 ($C_{20}H_{22}O_4$) and the UV spectrum was indicative of a biphenyl with restricted rotation between the aromatic rings α_{max} (log ϵ) 221 (4·66), 289 nm (3·78). The IR spectrum shows the presence of hydroxy-groups (ν-3200–3400 cm^{-1}) and an olefinic stretching frequency (ν-1645 cm^{-1}). The NMR spectra showed methoxyl absorption at 6·2 τ(6-H, *s*) and distinctive absorptions for the allyl side chains at 6·72 τ (*d*, *J* 7 Hz), 5·0 τ (complex) and 3·9–4·3 τ (complex) which were assigned to the benzylic methylene,

[1] PELLETIER, S. W. (1970) *Chemistry of the Alkaloids*, Van Nostrand-Reinhold, London.
[2] UPRETY, H., BHAKUNI, D. S. and DHAR, M. M. (1972) *Phytochemistry* **11**, 3057.
[3] *Koch–Light Laboratories* ex *Peumus boldus*.
[4] TEWARI, S., BHAKUNI, D. S. and DHAR, M. M. (1972) *Phytochemistry* **11**, 1149; NAKASATO, T. and NOMURA, S. (1959) *Yakugaku Zasshi* **79**, 1267; JOHNS, S. R., LAMBERTON, J. A. and SIOUMIS, A. A. (1969) *Australian J. Chem.* **22**, 1311.

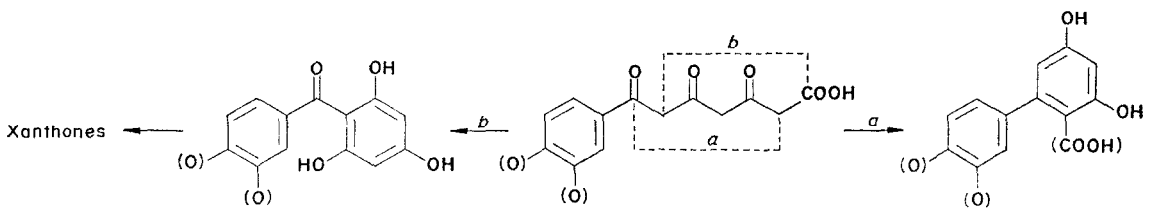
terminal methylene and methine protons respectively. The four aromatic protons gave a broad singlet at 3·37τ which indicated a symmetrical structure, but accidental equivalence could also occur in structure III. Confirmation was obtained by direct comparison (IR, m.m.p.) with a synthetic sample of dehydrodieugenol prepared by oxidative coupling of eugenol following the method of Fujita and Shigenoi.[5] Although this biphenyl has been known for some time this is the first report of its natural occurrence.

Biphenyls are rare natural products, and inspection of dehydrodieugenol would suggest that it could be biosynthesized by oxidative coupling of a phenolic arylpropanoid. In a recent review,[6] Gottlieb cites only one other biphenyl, magnalol (IV) that has been isolated from amongst the families of the Magnoliales. III and IV are both considered to be neolignan since allylbenzenes are involved in the coupling process whereas for lignan formation β,β-coupling occurs in propenylbenzene side chains.[6]



SCHEME 1. POSSIBLE BIOGENESIS OF APORPHINE AND BIPHENYL CONSTITUENTS INVOLVING MODIFICATION OF A PHENYLALANINE AND OXIDATIVE COUPLING IN *Litsea turfosa*.

The co-occurrence of boldine, laurolitsine and dehydrodieugenol supports Gottlieb's suggestions[6] that there are evolutionary similarities in the biogenesis of aporphines and neolignans. Thus both the aporphines and the phenylpropanoids are probably derived by well defined steps from phenylalanine or its hydroxy derivatives. Formation of aporphines and dehydrodieugenol both require oxidative coupling in their biogenesis (Scheme 1), and it has been suggested[6] that the same enzyme may be involved in both oxidations.



SCHEME 2. POSSIBLE BIOGENESIS OF BENZOPHENONES AND BIPHENYL CONSTITUENTS INVOLVING AN ALDOL OR CLAISEN TYPE CYCLIZATION OF AN ARYLPOLYKETIDE IN GUTTIFERAE

[5] FUJITA, Y. and SHIGENOI, J. (1966) *Nippon Kagaku Zasshi* **87**, 1002. This paper was kindly translated by Professor N. Kawano, Nagasaki University.

[6] GOTTLIEB, O. R. (1972) *Phytochemistry* **11**, 1537.

An alternative biogenetic proposal for the formation of a biphenyl involves aldol type cyclization (a) of an arylpolyketide;[7] such biphenyls probably occur in Guttiferae[8] where the alternative Claisen type cyclization (b) leads to benzophenones which are the precursors of xanthones (Scheme 2).[7]

EXPERIMENTAL

All UV spectra were determined in MeOH, IR spectra as Nujol mulls. NMR spectra were measured in $CDCl_3$ or $(CD_3)_2CO$ on a Varian HA 100 instrument and MS with A.E.I. MS12 and MS9 spectrometers. Column and preparative chromatography were carried out with silica gel (Merck Kieselgel G) or neutral alumina (Woelm).

Extraction of Litsea turfosa. The powdered bark was extracted continuously for 24 hr with hot $CHCl_3$. Evaporation of the solvent left a dark red tar which was poured into dil. H_2SO_4 and stirred vigorously. The aqueous solution was then extracted with $CHCl_3$ which yielded a brown oil *A*. The aqueous solution was basified with dil. NH_4OH and extracted several times with $CHCl_3$. Evaporation of the $CHCl_3$ left a brown solid *B*.

Examination of oil A. TLC of oil *A* showed a white fluorescent spot (R_f 0·38) in C_6H_6–EtOAc (17·3). Preparative TLC followed by recrystallization from EtOH afforded a crystalline solid m.p. 106–7°. λ_{max} (log ϵ): 221 (4·66), 289 nm (3·78). This compound was identified as dehydrodieugenol by direct comparison with a synthetic sample.

Examination of solid B. Solid *B* was chromatographed on a column of neutral alumina eluting with C_6H_6, $CHCl_3$ and MeOH and mixtures of these solvents. Elution was followed by TLC. *Boldine.* TLC of the fractions obtained from $CHCl_3$ and $CHCl_3$–MeOH (1%) elutions afforded boldine m.p. 163–4° (Lit[9] 161–3°) λ_{max} (log ϵ) 219 (4·5), 282 (4·1) and 303 nm (4 1). Its MS gave a molecular ion at *m/e* 327. The base was found to be identical with an authentic sample of boldine (IR, m.m.p.). *Laurolitsine.* TLC of the fractions obtained from $CHCl_3$–MeOH (5%) elutions afforded laurolitsine m.p. 133–5° (Lit.[9] 136°) λ_{max} (log ϵ): 222 (4·38) 283 (4·11), 304 nm (4·09). Its MS gave a molecular ion at 313·1298 (Calc. for $C_{18}H_{19}O_4N$: M 313·1314) and its NMR was assigned as follows: Three one-proton singlets at 3·54 τ (C-3), 3·36 τ (C-8) and 2·44 τ (C-11) and methoxyl absorptions at 6·24 τ (C-10 MeO) and 6·46 τ (C-1 MeO).

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[7] DOUGLAS, J. L. and MONEY, T. (1967) *Can. J. Chem.* **45**, 1990.
[8] HOLLOWAY, D. M., OWEN, P. J. and SCHEINMANN, F. (1972) *Autumn Meeting of the Chemical Society*, University of Nottingham, and forthcoming publication.
[9] KAMETANI, T. (1969) *The Chemistry of the Isoquinoline Alkaloids*, pp. 81–108, Elsevier, London.

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PALLIDINE AND CORYDINE FROM *THALICTRUM DIOICUM*

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Plant. Thalictrum dioicum L., collected in central Pennsylvania. *Previous work.* None. *Isolation and identification.* The powdered whole plant was extracted with EtOH, and the