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SHORT COMMUNICATION

THE APORPHINE ALKALOIDS OF *LITSEA GLUTENOSA**

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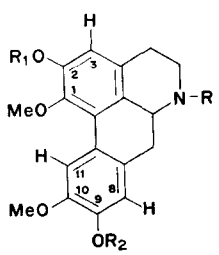
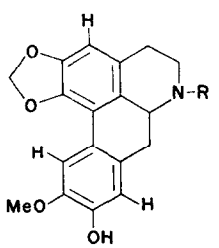
Abstract—The aporphine alkaloids, norboldine, boldine, laurotetanine, *N*-methyllaurotetanine, actinodaphnine and *N*-methylactinodaphnine have been isolated from *Litsea glutenosa* var. *glabraria* Hook.

INTRODUCTION

ETHANOLIC extractives of *Litsea glutenosa* var. *glabraria* Hook. (Lauraceae) on being put through a wide biological screen showed spasmolytic activity.[1] Chemical investigation of the plant resulted in the isolation of boldine (II), a base with physiological activity[2] and five other aporphine alkaloids norboldine (I), laurotetanine (III), *N*-methyllaurotetanine (IV) actinodaphnine (VI) and *N*-methylactinodaphnine (VII). These bases were isolated from the crude alkaloidal fraction of the ethanolic extract of the plant by chromatography on neutral Al_2O_3, SiO_2 and preparative TLC.





(I) R = R_1 = R_2 = H (IV) R = R_1 = Me, R_2 = H (VI) R = H
(II) R = Me, R_1 = R_2 = H (V) R = R_1, R_2 = Me (VII) R = Me
(III) R = R_2 = H, R_1 = Me

RESULTS AND DISCUSSION

The molecular formulae of the isolated alkaloids were confirmed by their mass spectra. UV maxima at 221, 282 and 303–310 nm, present in the spectra of the bases, indicated that

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TABLE 1. MASS SPECTRA DATA ON APORPHINES FROM *Litsea glutenosa*

Alkaloids	M^+	M^{2+}	M^+-1	M^+-15	M^+-17	M^+-29	M^+-31	M^+-43	M^+-58	M^+-74
I ($C_{18}H_{19}O_4N$)	313	156·5	312	298	296	384	282	—	255	239
II ($C_{19}H_{21}O_4N$)	327	163·5	326	312	310	—	296	284	269	253
III ($C_{19}H_{21}O_4N$)	327	163·5	326	312	310	298	296	—	269	253
IV ($C_{20}H_{23}O_4N$)	341	170·5	340	326	324	—	310	298	283	267
V ($C_{21}H_{25}O_4N$)	355	177·5	354	340	338	—	324	312	297	281
VI ($C_{18}H_{17}O_4N$)	311	155·5	310	296	294	—	M^+-30 281	—	253	237
VII ($C_{19}H_{19}O_4N$)	325	162·5	324	310	308	—	M^+-30 295	282	267	251

these bases were aporphines substituted at positions 1, 2, 9 and 10.[3,4] The mass fragmentation pattern (Table 1) of these bases are typically those of aporphine alkaloids.[5]

The relative intensities of the peaks, especially those of M^+ and the base peak (M^+-1), were in conformity with the substitution pattern suggested earlier by the UV spectra of these bases. The NMR spectra (Table 2) of these compounds were also informative. A low field one proton signal characteristic of a deshielded proton at position-11 of the aporphine system,[6] was present at τ 1·87–2·20 in the spectra of all the bases. A three protons signal for a shielded methoxyl group at position-1, appeared at τ 6·29–6·40 in the spectra of boldine, norboldine, laurotetanine and *N*-methyllaurotetanine. The characteristic AB quartet[6] of a methylenedioxy group located at position 1, 2 was discernible at τ 3·92–3·97, $\Delta\nu$ 8·5 Hz; $J = 2$ Hz in the NMR spectra of actinodaphnine (VI) and *N*-methylactinodaphnine (VII).

The relative positions of the hydroxyl and methoxyl groups in these bases was readily established by base-catalysed deuterium exchange experiments.[7] The phenolic bases boldine

TABLE 2. NMR (τ) DATA ON APORPHINES FROM *Litsea glutenosa*

No.	Alkaloids	6	1	2	9	10	H_3	H_8	H_{11}
1	I	—	6·20	—	—	6·02	3·38	3·01	1·80
2	I*	—	6·63	—	—	6·39	3·48	3·39	2·37
3	II	7·42	6·39	—	—	6·08	3·40	3·10	2·01
4	III	—	6·30	6·03	—	6·02	3·38	3·00	2·20
5	IV	7·48	6·39	6·12	—	6·11	3·42	3·19	2·00
6	V	7·41	6·29	6·02	6·03	6·00	3·30	3·10	1·97
7	VI	—	3·82	3·92	—	6·02	3·38	3·00	2·24
8	VII	7·43	3·82	4·00	—	6·04	3·40	3·10	2·25

* Spectrum in TFA. Aliphatic protons attached to rings B and C gave complex pattern at τ 6·3–7·7.

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(II), *N*-methyllaurotetanine (V), and *N*-methylactinodaphnine (VII) were separately heated in sealed tubes in an atmosphere of nitrogen in the presence of potassium *t*-butoxide in D_2O at 100° for 120 hr. In the NMR spectra of the resulting deuterated aporphines, proton signals at τ 3·28 and 3·10 for the protons at position 3 and 8 respectively, in boldine and the one proton signal for the proton at position 8 in *N*-methyllaurotetanine and *N*-methylactinodaphnine had almost disappeared indicating the replacement of these protons with deuterium.

The fact that norboldine, laurotetanine and actinodaphnine are nor-bases was confirmed by converting these bases into the corresponding *N*-methyl derivatives by treatment with HCHO followed by $NaBH_4$[8] or alternatively, by heating with HCHO and HCOOH. Boldine was further converted into glaucine by treatment with diazomethane in methanol.

EXPERIMENTAL

IR, UV and 60 Mcs NMR spectra were recorded in KBr, EtOH and $CDCl_3$ with TMS as internal standard, respectively and $(\alpha)_D$ in EtOH. Silica gel-G plates were used for TLC, with $CHCl_3$–MeOH (19:1) and (9:1) and C_6H_6–Et_3N–EtOAc (7:1:2).

Isolation of bases. Air dried powdered leaves and stems (5 kg) of the plant collected in West Bengal in January were extracted with 95% EtOH (3 × 4 l.) and solvent removed below 60°. The resulting dark green viscous mass was extracted with 10% tartaric acid (5 × 200 ml), the acidic solution defatted with light petroleum (4 × 200 ml), basified with Na_2CO_3 and the liberated bases extracted with $CHCl_3$ (5 × 200 ml). The concentrated $CHCl_3$ extract (300 ml) was then extracted with citrate–phosphate buffer pH 4 (4 × 150 ml), washed with water, dried (Na_2SO_4) and solvent removed to give the alkaloidal mixture (A) (1·7 g). The combined buffer extract (600 ml) was basified with Na_2CO_3, extracted with $CHCl_3$ (4 × 150 ml), the $CHCl_3$ extract washed with water, dried (Na_2SO_4) and the solvent removed to yield alkaloidal mixture (B) (1·9 g).

Alkaloidal mixture (A) (1·7 g) was chromatographed on neutral Al_2O_3 (100 g). The column was successively eluted with C_6H_6, C_6H_6–$CHCl_3$ (1:1), $CHCl_3$ and $CHCl_3$–MeOH (49:1), (19:1), (9:1) and (17:3).

Boldine (II). The $CHCl_3$ and $CHCl_3$–MeOH (49:1) eluates yielded boldine (150 mg), m.p. 160–161°; $(\alpha)_D$ +105° (Lit.[9] 161–162°, ÷110°); λ_{max} 220, 283 and 304 nm (log ϵ 4·6, 4·21 and 4·23).

O-Methylation of boldine. The base (50 mg in MeOH (2 ml) was treated with an ethereal solution of CH_2N_2 to give glaucine m.p. 118° (Lit.[10] 120°), λ_{max} 218, 281 and 303 nm (log ϵ 4·58, 4·18 and 4·16).

Deuteration of boldine. A mixture of the base (80 mg), potassium *t*-butoxide (120 mg) and D_2O (1 ml) was heated at 100° in N_2 in a sealed tube for 120 hr. The resulting solution was cooled, NH_4Cl added and the liberated base was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and solvent removed. The NMR spectrum of the deuterated compound (45 mg) was identical with that of boldine except that the signals for aromatic protons at positions 3 and 8 that had almost disappeared. In an experiment when the exchange experiment was done for 40 hr, the NMR spectrum of the product indicated that deuterium exchange had occurred to the extent of 90% at position 3 and 33% at position 8. The identity of the deuterated base was established by comparison with boldine (TLC, m.p., IR and UV) and by its NMR and mass spectra.

N-*Methyllaurotetanine* (IV). The $CHCl_3$–MeOH (9:1) eluates of SiO_2 column afforded the base (65 mg). It was homogenous on TLC but could not be crystallized. λ_{max} 215, 283 and 305 nm (log ϵ 4·52, 4·17 and 4·08). Base HBr m.p. 220–222°; $(\alpha)_D$ +68° (Lit.[11] 223–224°; +72·8°).

The base (20 mg) in MeOH (1 ml) was treated with an ethereal solution of CH_2N_2 to give glaucine m.p. 118°; $(\alpha)_D$ +110° ($CHCl_3$) (Lit.[10] 120°, +115°).

Deuteration of N-*methyllaurotetanine.* A mixture of *N*-methyllaurotetanine (40 mg), potassium *t*-butoxide (100 mg) and D_2O (0·5 ml) under N_2 in a sealed tube was heated at 100° for 110 hr. The resulting mixture was worked up as in the case of deuterated boldine. The NMR spectrum of the deuterated compound was identical with that of *N*-methyllaurotetanine except the signal at τ 3·19 for an aromatic proton at position-8 had considerably reduced in intensity (80 per cent).

The identity of the base with *N*-methyllaurotetanine was confirmed by comparison (TLC and IR, UV, NMR and mass spectra) with a sample prepared by treatment of an authentic sample of laurotetanine with HCHO—HCOOH.

[7] L. J. HAYNES, K. L. STUART, D. H. R. BARTON and G. W. KIRBY, *J. Chem. Soc.* **C**, 1676 (1966).
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N-*Methylactinodephnine* (VII). The $CHCl_3$–MeOH (99:1) eluates of Al_2O_3 column afforded the base (65 mg), m.p. 204°; $(\alpha)_D$ +52° (Lit.[12] 206°; +52°). λ_{max} 221, 285, 309 nm.

Deuteration of N-*methylactinodaphnine*

A mixture of the base (45 mg), potassium *t*-butoxide (110 mg), D_2O (0·5 ml) in a sealed tube under N_2 was heated at 100° for 100 hr, and the product isolated as in the deuteration of boldine. The NMR spectrum of the deuterated compound was identical with that of *N*-methylactinodaphnine except for the signal at τ3·10 for an aromatic proton at position-8 which was greatly reduced in intensity (70%).

The identity of deuterated *N*-methylactinodaphnine was established by comparison with a sample of *N*-methylactinodaphnine (TLC, UV and IR) and by its NMR and mass spectra.

Alkaloidal mixture (B). The alkaloidal mixture (B) (1·9 g) was chromatographed on neutral Al_2O_3. The column was successively eluted with $CHCl_3$, $CHCl_3$–MeOH (99:1), (49:1), (19:1) and (9:1) and followed with the aid of TLC. Fractions containing mixtures were further resolved by preparative TLC.

Laurotetanine (III). The $CHCl_3$–MeOH (19:1) eluate gave the base (70 mg), as an amorphous powder which was homogenous on TLC; λ_{max} 220, 281 and 305 nm (log ϵ 4·42, 4·12, 4·17). The base (30 mg) when treated with Ac_2O/pyridine gave *N*-acetyllaurotetanine m.p. 142° (Lit.[13] 143°).

N-*Methylation of laurotetanine*. A mixture of the base (40 mg), HCHO (1 ml) and HCOOH (1 ml) was heated on a water bath for 0·5 hr. Excess of HCHO and HCOOH were removed and the residue taken up in dil. HCl. This solution was washed with ether, basified with Na_2CO_3, extracted with $CHCl_3$ and solvent was removed. The residue in $CHCl_3$ was passed through Al_2O_3 to give a *N*-methyl derivative identical with *N*-methyllaurotetanine (TLC, NMR and mass spectra).

Actinodaphnine (VI). The $CHCl_3$–MeOH (19:1) eluates when further subjected to preparative TLC afforded the base (35 mg) m.p. 204–206°; $(\alpha)_D$ +28° (Lit.[12] 203°; +30°); λ_{max} 221, 285 and 308 nm (log ϵ 4·47, 4·14 and 4·19). The base (25 mg) was treated with HCHO (1 ml) and HCOOH (1 ml) to give an *N*-methyl derivative identical with *N*-methylactinodaphnine (TLC, UV and mass spectrum).

Norboldine (I). The $CHCl_3$–MeOH (19:1) eluates showing single spot on TLC afforded the base (60 mg) as an amorphous powder. Base picrate m.p. 210° dec. (Lit.[12] 212°); base picronolate m.p. 236° (Lit.[12] 239°). λ_{max} 220, 283 and 307 nm (log ϵ, 4·43, 4·13 and 4·17). Treatment of the base (30 mg) with HCHO (1 ml) and HCOOH (1 ml) yielded its *N*-methyl derivative m.p. 160°; $(\alpha)_D$ +110°, identified as boldine (TLC, UV, IR, NMR and mass spectra).

N-*Methylation of crude bases*. The basic fraction (900 mg) of the total alkaloidal mixture which was sparingly soluble in $CHCl_3$ was dissolved in MeOH (30 ml), HCHO (4 ml) added and cooled to 0°. $NaBH_4$ (800 mg) was added with stirring over 45 min and more HCHO (1 ml) and $NaBH_4$ (250 mg) added. After 2 hr MeOH was removed from the resulting solution. The residue was taken in dil. HCl, extracted with ether, basified with Na_2CO_3 and the liberated bases extracted with $CHCl_3$. Chromatography of the methylated bases on neutral Al_2O_3 successive elution with C_6H_6, C_6H_6–$CHCl_3$, $CHCl_3$ and $CHCl_3$–MeOH (49:1) yielded boldine, *N*-methylactinodaphnine, and *N*-methyllaurotetanine.

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Key Word Index—Litsea glutenosa; Lauraceae; aporphine alkaloids; norboldine; boldine; actinodaphnine.