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TWO NEW ALKALOIDS FROM BERBERIS LAURINA BILLB.(1)

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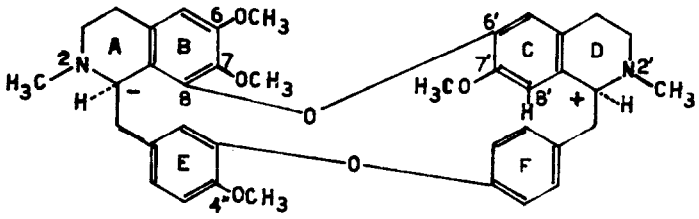
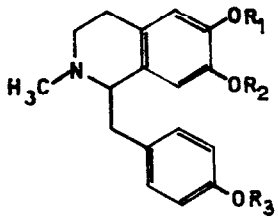
Berberis laurina Billb. is a common shrub in the Rio de la Plata region and in south Brazil. From the leaves we have been able to isolate berberine, (-)-tetrahydropalmatine and protopine. In the trunk bark and root, there are at least six alkaloids of which we have isolated four: berberine, previously reported (2,3), and three bisbenzylisoquinoline bases: obaberine (O-methyloxyacanthine) (4) (see Table I) and two new alkaloids. One of these from the evidence which follows is a diastereomer (absolute configuration -+) (5) of O-methylthalicberine (++) (5), and we have named it O-methylisothalicberine (I); the other we have called lauberine (IIIa).

O-Methylisothalicberine, m.p. 208-209° and $[\alpha]_D$-195° (c, 0.5 in $CHCl_3$) has m.w. 622 (m.s.). Its formula $C_{38}H_{42}O_6N_2$ and its u.v. spectrum and o.r.d. curve are consistent with a bisbenzylisoquinoline structure, which from the i.r. spectrum (KBr) contains methylimino groups (band at 2875 cm^{-1}). Two such groups are evidently present from the n.m.r. spectrum (Table I), together with four methoxyls.

O-Methylisothalicberine was reduced with sodium in liquid ammonia (6), yielding (-)O-methylarmepavine (IIa), $[\alpha]_D$ -65° ($CHCl_3$) and (+)N-methylisococlaurine (IIb), $[\alpha]_D$ +84° (MeOH) which afforded N-methyl-O,O-diethylisococlaurine (IIc) after treatment with diazoethane. IIa and IIc had n.m.r. spectra identical with those reported by Tomita et al. (7) for these compounds.



I



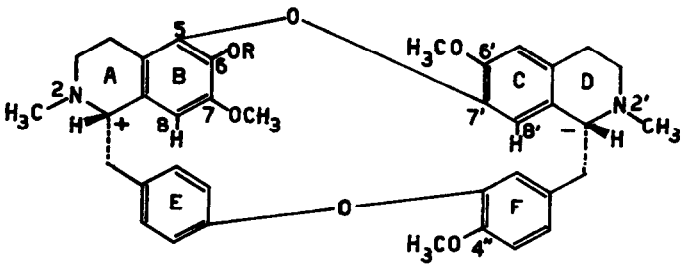
	R_1	R_2	R_3
IIa	Me	Me	Me
IIb	H	Me	H
IIc	Et	Me	Et
IId	Me	H	Me
IIe	Et	Me	H
IIf	Me	Me	H

The n.m.r. spectra of O-methylisothalicberine (I) and O-methylthalicberine are similar (Table I), the main differences being in the high-field methoxyl and N-methyl resonances. The N-methyl in position 2 of O-methylthalicberine is at very high field because it tends to pass over the shielding region of ring E in the particular structure and configuration (+ +) ascribed to this alkaloid by Fujita et al. (8). Molecular models of O-methylisothalicberine (I) show that the diastereomeric configuration (- +) should give an $N_{(2)}$-methyl which absorbs at lower field because it no longer tends to come over ring E to such an extent; on the other hand the methoxyl at 7' should be somewhat shielded by this ring.

The mass spectrum of O-methylisothalicberine (I) is in general similar to those reported for bisbenzylisoquinoline alkaloids (9,10) and in particular, to that of O-methylthalicberine (11).

The other new alkaloid, lauberine (IIIa), crystallised as its dihydrobromide $C_{37}H_{40}O_6N_2 \cdot 2HBr$ from ethanol, m.p. 250-255° (after drying at 100°/0.07 Torr); $[\alpha]_D$ -335° (c=0.6, MeOH). Its o.r.d. curve and other spectral data will be published more fully elsewhere.

The free base oxidises rapidly in air and could not be crystallised. It has m.w. 608 (m.s.) and $[\alpha]_D$ -481° (C, 0.2 in $CHCl_3$); its n.m.r. spectrum shows three methoxyl and two N-methyl groups (Table I). It contains a cryptophenolic hydroxyl group, and although the base



IIIa R = H
IIIb R = Me
IIIc R = Et

is insoluble in alkali, it is acetylated with acetic anhydride in pyridine at room temperature, affording the acetyl derivative (i.r. in KBr, 1770 cm^{-1} for $-COCH_3$). With diazomethane, lauberine yields O-methyllauberine (IIIb), $[\alpha]_D$ -369° (C, 0.2 in $CHCl_3$) (n.m.r.: four methoxyls; m.s.: M^+=622) (Table I) and with diazoethane it yields O-ethyllauberine (IIIc) (n.m.r.: three methoxyls and one ethoxyl; m.s.: M^+=636) (Table I).

O-Ethyllauberine (IIIc) was reduced with sodium in liquid ammonia, giving (-)O,N-dimethylcoclaurine (IId), $[\alpha]_D$ -48° ($CHCl_3$) and (+)N-methyl-6-O-ethylisococlaurine (IIe), crystallised as the oxalate, m.p. 214-216°, $[\alpha]_D$ +107° (MeOH), whose i.r. spectrum (KBr) is practically identical with that of armepavine oxalate (IIf). IId and IIe had n.m.r. spectra identical with those reported by Tomita et al (7) for the same compounds. O-Methyllauberine (IIIb) on sodium-ammonia reduction yielded IId and (+) armepavine, identical with an authentic sample. Bearing these facts in mind, the lauberine hydroxyl must be at position 6 (IIIa), and one of the points of attachment of the ether bridge which joins nuclei B and C must be at the 7' carbon; the other point is at carbon 5, which follows from the n.m.r. and m.s. data.

The n.m.r. spectrum of lauberine, as well as those of its O-alkyl derivatives are quite different from those of alkaloids of the thalicberine, oxyacanthine, berbamine and repandine types (Table I).

In lauberine (IIIa), the chemical shifts of the methoxyl groups suggest a comparatively loose and flexible molecule, with a larger macro ring than those of the above-mentioned alkaloid types, which have 18 or 19-membered macro rings. In O-methyllauberine (IIIb), the methoxyl at the 6 position appears to be subjected to the influence of rings C and/or F, but the remaining methoxyls are not subject to any particular shielding effect from other rings.

In the bisbenzylisoquinoline alkaloids, the 8' proton is generally placed in the shielding region of ring F and absorbs at relatively higher fields than the rest of the aromatic protons (13); for example, the 8' proton of O-methylisothalicberine (I) resonates at 4.25 τ [the 8' proton of O-methylisothalicberine appears as a doublet (J=2 cps), coupled with a proton at

TABLE I

τ Values of N.M.R. Resonances of O-Methyl and N-Methyl Groups.

	O-Me					N-Me		Absol.	
	4''	6	6'	7	7'	2'	2	Conf.	Ref.
O-Me-thalicberine	6.12	6.15	--	6.25	6.36	7.45	7.90	+ +	(7)
O-Me-isothalicberine	6.09	6.16	--	6.21	6.49	7.40	7.62	- +	(§)
Oxyacanthine	--	6.27	6.44	6.85	--	7.52	7.52	+ -	(12)
O-Me-oxyacanthine	6.10	6.21	6.40	6.80	--	7.35	7.45	+ -	(12)
idem (from B.laurina)	6.12	6.23	6.38	6.81	--	7.35	7.44	+ -	(§)
Repandine	--	6.27	6.62	6.98	--	7.50	7.50	+ +	(12)
O-Me-repandine	6.05	6.25	6.60	6.95	--	7.45	7.45	+ +	(12)
Berbamine	--	6.18	6.35	6.85	--	7.35	7.75	- +	(12)
Isotetrandrine (O-Me-berbamine)	6.05	6.22	6.37	6.82	--	7.40	7.72	- +	(12)
Lauberine	6.05	--	6.08	6.08	--	7.35	7.70	+ -	(§)
O-Me-lauberine	6.07	6.36	6.07	6.07	--	7.33	7.75	+ -	(§)
O-Et-lauberine	6.07	(‡)	6.10 (6.07)	6.07 (6.10)	--	7.35	7.77	+ -	(§)

(‡): $-O-\underline{CH_2}CH_3$, quartet 5.98τ (J=7 cps); $-O-CH_2\underline{CH_3}$, triplet 8.94τ (J=7 cps)

(§): This work.

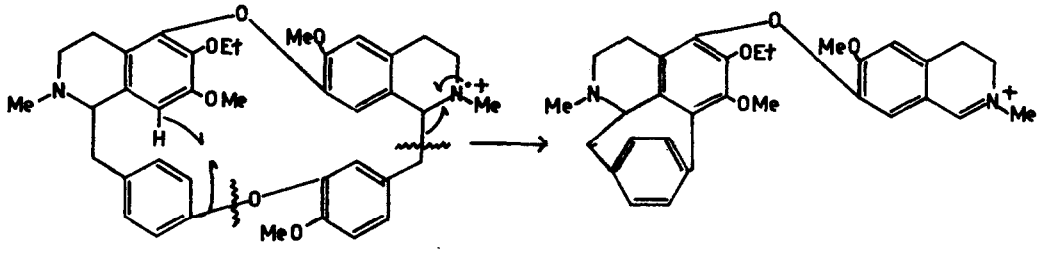
2.83τ (J=2 cps), as proved by double resonance experiments] and in O-methyloxyacanthine at 4.53τ. In lauberine (IIIa), two protons appear as broad singlets at 3.88 and 3.94τ (in O-methyllauberine (IIIb) they appear at 3.80 and 3.97τ, and in O-ethyllauberine (IIIc) at 3.89 and 4.04τ), suggesting the presence of protons at positions 8 and 8'. Molecular models of structure III show that in some particular conformations, the proton at position 8 comes over the top of ring E and the proton at position 8' appears in the shielding region of ring F.

The mass spectra of lauberine and its O-alkyl derivatives are in agreement with structure III. The O-ethyllauberine (IIIc) m.s. is particularly illuminating, showing the following peaks:

m/e	Intensity o/o base peak	m/e	Intensity o/o base peak
636 (M^+)	54	205.5 (‡)	20
529 (M-107)	2	205	70
499 (M-137)	1	192	11
410	30	191.5 (‡)	9
409 (base peak)	100	191	32
395	25	175.5 (‡)	3
393	10	175	13
381	71	174	9
379	23		

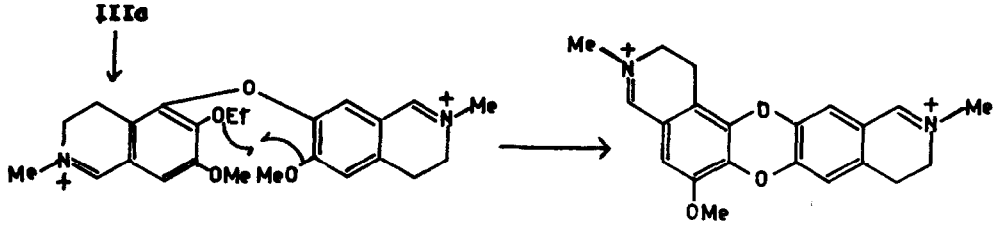
(‡): Isotopic peak

It has been established (9) that the appearance of an ion M-107 can be rationalized if it is assumed that a neutral fragment, formed from ring E and its benzylic carbon, with hydrogen transfer from position 8', is eliminated; in the same way, the elimination of ring F with its benzylic carbon and hydrogen transfer from position 8 gives the ion M-137:



M-137

The doubly-charged ion m/e 205 formed by elimination of nuclei E and F, loses the elements of ethylmethylether, giving the dibenzo-1,4-dioxine ion, m/e 175 (9,10,11):

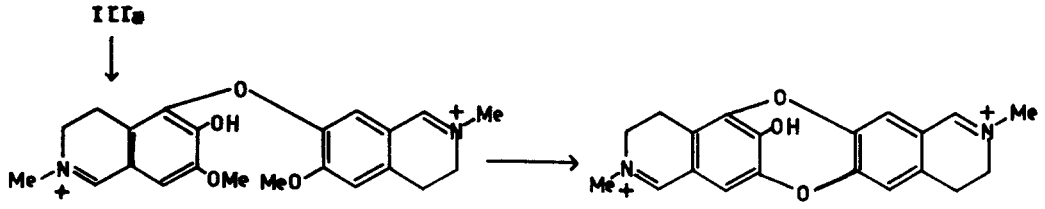


m/e 205 m/e 175

As the ethoxyl group in O-ethyllauberine (IIIc) is at the 6 position, the appearance of a m/e 175 ion indicates that the oxygen bridge is at position 5; if it were at the 8 position, a homologous dibenzo-1,4-dioxine ion would be expected at m/e 182. The remaining peaks of O-ethyllauberine follow the established fragmentation pattern (9,10,11).

The m.s. of O-methyllauberine (IIIb) also shows an ion at m/e 175 (36 o/o) with an isotopic peak at m/e 175.5 (9 o/o).

The lauberine (IIIa) m.s. shows inter al. an ion at m/e 191 (36 o/o) (isotopic peak m/e 191.5 (12 o/o)), which by analogy with nortenuipine (9) may lose the elements of dimethyl ether, giving a low-intensity ion at m/e 168 (4 o/o):



m/e 191 m/e 168

The structure of lauberine accords with Barton's concept of biosynthesis of bisbenzylisoquinoline alkaloids through phenol oxidative coupling. (14).

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15. All compounds whose molecular formulae are shown gave satisfactory elemental analyses. The n.m.r. spectra were run in $CDCl_3$ with TMS as internal standard.

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