# Belarine, a New Bisbenzylisoquinoline Alkaloid

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*Summary* Belarine gives *O*-methylisothalicberine on methylation, and the structures of both alkaloids have been determined unequivocally by deuteriation experiments, including a novel Birch reduction in $ND_3$.

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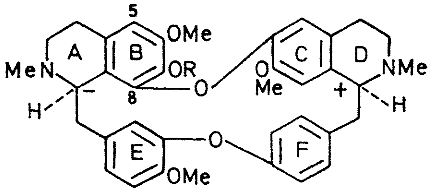
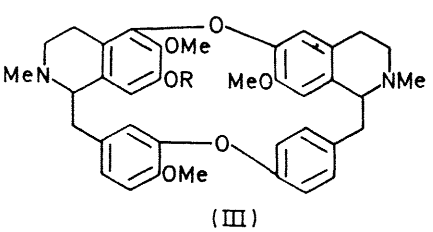
BELARINE, m.p. 158—160°, $[\alpha]_D$ − 222 (*c* 0·2, $CHCl_3$), has been isolated from the root bark of *Berberis laurina* Billb., in addition to several other alkaloids[1,2] including *O*-methylisothalicberine[1] (Ib). Analyses together with n.m.r. and mass spectrometry indicated that belarine had a similar structure to the latter base, with a hydroxy- replacing a methoxy-group: thus in their n.m.r. spectra the two alkaloids each showed two *N*-methyl and three $O\text{-}CH_3$ resonances at corresponding fields, but *O*-methylisothalicberine had an extra higher-field methoxy-group peak. Belarine in fact gave a product identical with the latter base on methylation with diazomethane.

The position of the hydroxy-group in belarine was found by ethylation with diazoethane, followed by reduction of the product with sodium in liquid ammonia to give (IIa) and the phenolic product *N*-methylcoclaurine (IIb), which was ethylated to (IIc). The n.m.r. spectra and other properties of (IIa) and (IIc) were in accord with those reported by Tomita *et al.*[3] for these compounds. Thus belarine has a 7-hydroxy-group, and its structure (and stereochemistry) is represented by (Ia), provided (Ib) is accepted as the structure of *O*-methylisothalicberine.



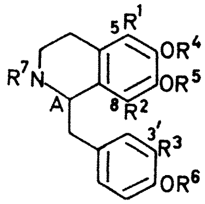
(I)

a; R = H
b; R = Me



(III)

a; R = Me
b; R = H



| (II) | A | R¹ | R² | R³ | R⁴ | R⁵ | R⁶ | R⁷ |
|---|---|---|---|---|---|---|---|---|
| a; | − | H | H | H | Me | Et | Me | Me |
| b; | + | H | H | H | H | Me | H | Me |
| c; | + | H | H | H | Et | Me | Et | Me |
| d; | − | H | H | H | Me | Me | Me | Me |
| e; | ± | H | H | H | H | Me | H | H |
| f; | − | D | H | H | Me | Et | Me | Me |
| g; | − | H | D | D | Me | Me | Me | Me |

Structure (Ib) was derived from a similar reduction experiment[1] on *O*-methylisothalicberine, which yielded (IId) and (IIb). The n.m.r. and mass spectra of (Ib) resembled those of the diastereomeric *O*-methylthalicberine[4] and precluded the possibility of head-to-tail ether links; however, the evidence did not rule out structure (IIIa) for *O*-methylisothalicberine which is biogenetically just as feasible as (Ib) and could be formed from two units of isococlaurine (IIe) by phenol oxidation.

The corresponding structure (IIIb) for belarine, however, seemed less likely than (Ia) since belarine did not exchange any aromatic protons for deuterium under basic conditions as would be expected if it had a free *ortho*-position to a phenolic group;[5] however, it exchanged one proton under acid conditions (m.s.). The product was ethylated and cleaved with sodium in liquid ammonia to give (IIb) and a deuteriated analogue of (IIa). That the latter had structure (IIf) with a deuterium at C-5 was shown by the n.m.r. spectrum in which the high-field aromatic singlet at $\tau$ 3·91 due to the C-8 proton[3] was still present but the one at $\tau$ 3·42 had disappeared. This evidence is in accord with structure (Ia) for belarine and (Ib) for *O*-methylisothalicberine.

These structures were confirmed by cleaving *O*-methylisothalicberine with sodium in trideuterioammonia† to form (IIb) and a dideuteriated derivative of (IId) (m.s.) in which the resonance at $\tau$ 3·42 was unchanged, but that at $\tau$ 3·91 had been reduced to less than 1/3 its former value; moreover, the 4-proton quartet between $\tau$ 2·84 and 3·24 in (IId) had altered to a multiplet in which the absorption was notably stronger below the mid-point than above. These observations are in accord with the structure (IIg) in which the C-8 and C-3′ hydrogens of (IId) have been largely replaced by deuterium. Since these deuteriums mark the terminals of the diphenylether links in rings B and E of *O*-methylisothalicberine, the latter must have structure (Ib), and belarine (Ia).

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† Prepared from $D_2O$ and $Mg_3N_2$ by a method based on that of Bouclier and Portier.[6]

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