Bridged Protoberberine Alkaloids

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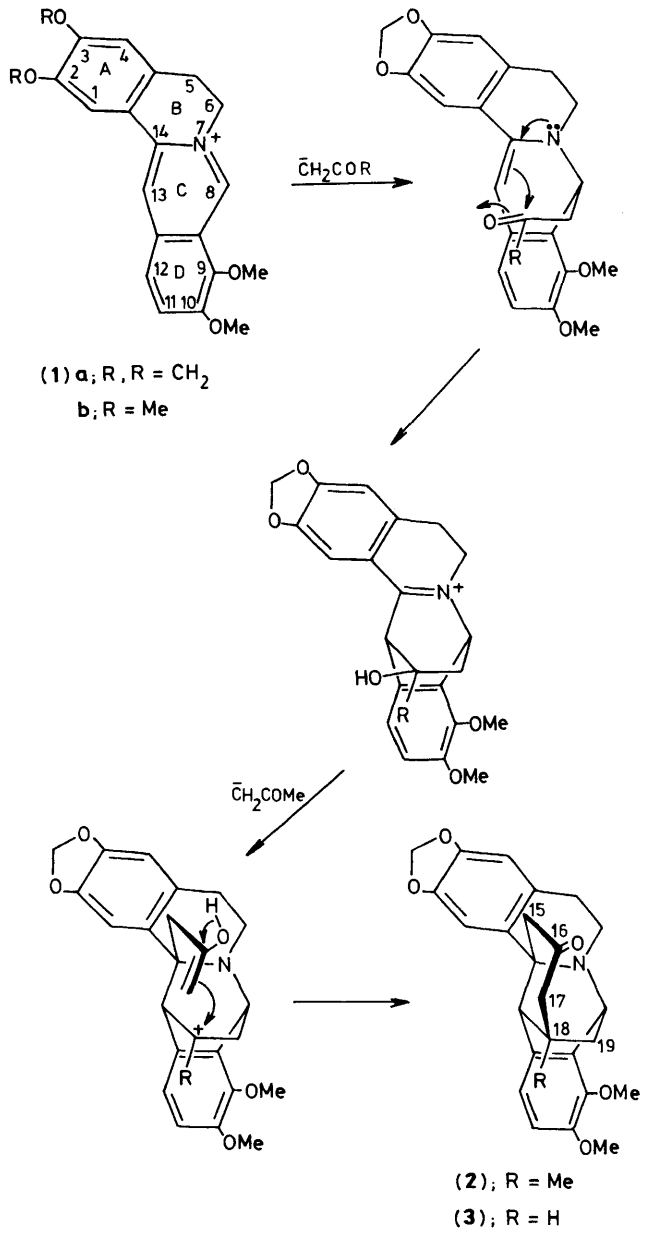
Berberis valdiviana Phil. (Berberidaceae) has yielded the alkaloid (±)-valachine (**3**) which is a nor analogue of the known bridged protoberberine (±)-karachine (**2**).

The alkaloid (±)-karachine (**2**) is an unusual bridged protoberberine originally isolated from Pakistani *Berberis aristata* DC (Berberidaceae).[1,2] In order to establish the general availability of karachine (**2**), it was decided to search for this alkaloid in a Chilean barberry, *Berberis valdiviana* Phil. (20 kg dry).† It was reasoned that if karachine is indeed a true alkaloid, some of its analogues could also be isolated. A particularly good candidate in this respect seemed to be the analogue derived from palmatine (**1b**) which would bear four methoxy substituents.

We deliberately set out, therefore, to compare carefully by t.l.c. every column chromatographic fraction obtained from the *B. valdiviana* extracts with an authentic sample of karachine (**2**) in our possession, in the hope of detecting analogous or near analogous spots. Eventually, it was found that a fraction obtained from elution of the silica gel column using methanol–chloroform (5:95) gave two almost overlapping spots of interest. These could be cleanly separated by t.l.c. using the system ethyl acetate–hexane (30:70). The faster but minor spot (1 mg) corresponded in all respects to (±)-karachine (**2**). The major and slightly more polar compound, named (±)-valachine (20 mg), readily crystallized from ethyl acetate–methanol–diethyl ether as colourless crystals, m.p. 237—238 °C.

Interestingly, the ketonic (±)-valachine (**3**), $C_{25}H_{25}NO_5$, $\nu_{max.}$ ($CHCl_3$) 1715 cm^{-1}, differed from (±)-karachine (**2**) not in the nature of the oxygenated aromatic substituents, but in the complexity of the alkyl bridge. The most salient feature of the ^1H n.m.r. (360 MHz, $CDCl_3$) spectrum of valachine, summarized in Figure 1, was the absence of the bridgehead

† The powdered plant was extracted with cold ethanol. The extracts were fractionated using dilute HCl and then dilute ammonium hydroxide. T.l.c. was on Merck Silica Gel G glass plates.



Scheme 1

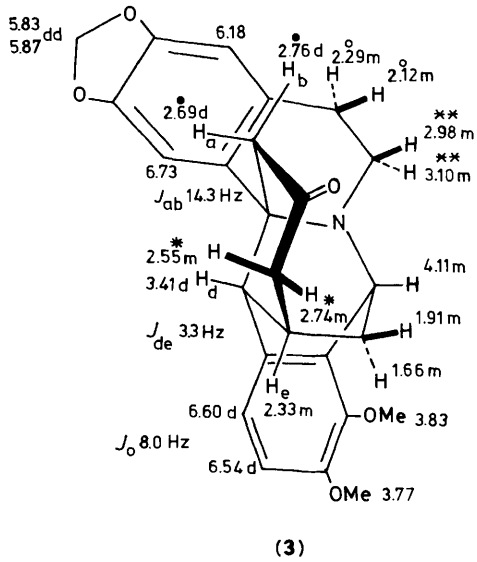


Figure 1. Details of the ^1H n.m.r. spectrum of (±)-valachine (**3**). Signals marked •, ○, *, **: assignments may be interchanged.

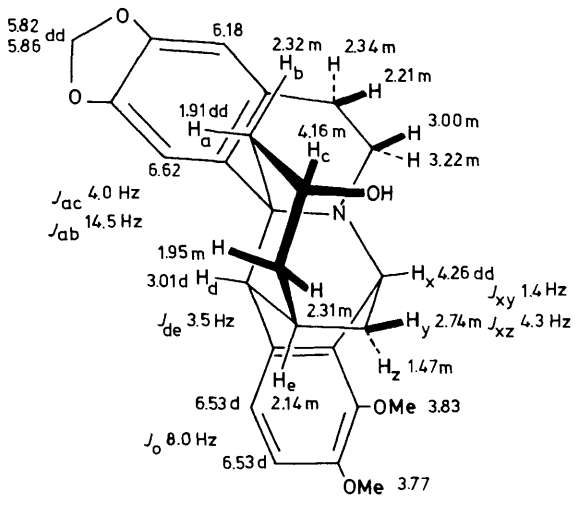


Figure 2. Details of the ^1H n.m.r. spectrum of (±)-dihydrovalachine (**4**).

C-methyl singlet absorption present in the spectrum of karachine (**2**) at δ 0.82.[1] There was visible instead a one-proton multiplet at δ 2.33. This was accompanied by a one-proton doublet at δ 3.41 representing a proton which resonated as a singlet at δ 3.07 in karachine. The rest of the spectrum was generally similar to that of karachine, with the assignments supported by appropriate spin decoupling experiments.

The mass spectrum of valachine (**3**),‡ showed a strong molecular ion peak *m/z* 419 (92%). Significantly, the base peak *m/z* 336 is the same as in karachine (**2**) and is representative of the berberine cation (**1a**).

The alkaloid was reduced with sodium borohydride in methanol to amorphous (±)-dihydrovalachine (**4**), $C_{25}H_{27}NO_5$, $\nu_{max.}$ ($CHCl_3$) 1475, 2365, 2920, 3000, 3670 cm^{-1}; details of the 360 MHz ^1H n.m.r. spectrum in $CDCl_3$ are given in Figure 2.‡

As further support for the structure of valachine (**3**) and in particular for the relative positions of the methylenedioxy and methoxy substituents, the alcohol (**4**) was subjected to a detailed n.m.r. nuclear Overhauser effect (n.O.e.) difference study,[3] the results of which are summarized in Figure 3. Irradiation of the methoxy singlet at δ 3.77 led to a 23.8% enhancement of the 11-H doublet at δ 6.53. It follows that the methoxy groups must be situated on ring D rather than ring A. Irradiation of the 1-H singlet at δ 6.62 caused a 7.5% nuclear Overhauser enhancement of the axial C-15 proton signal at δ 1.91, indicating that these two hydrogen atoms must be proximate. In turn, irradiation at δ 1.91 resulted in an 8.6% increase of the δ 4.16 signal representing the equatorial C-16

‡ Valachine (**3**), $\lambda_{max.}$ (MeOH) 282, 291sh nm (log ε 4.23, 4.23); *m/z* 420 $(M+1)^+$ (25%), 419 $(M)^+$ (92), 418 (34), 404 (10), 388 (9), 376 (19), 362 (4), 337 (24), 336 (100), 320 (13), 306 (10), 278 (13), 189 (12), 168 (12); R_f 0.49 acetone–$CHCl_3$ (5:95). Dihydrovalachine (**4**), $\lambda_{max.}$ (MeOH) 219sh, 292 nm (log ε 4.05, 3.50); *m/z* 421 $(M)^+$ (30%), 420 (6), 406 (6), 404 (5), 390 (3), 376 (14), 337 (24), 336 (100), 320 (10), 306 (9), 278 (11), 190 (25), 189 (16), 188 (17), 176 (20), 168 (14); R_f 0.49 MeOH–$CHCl_3$ (5:95).

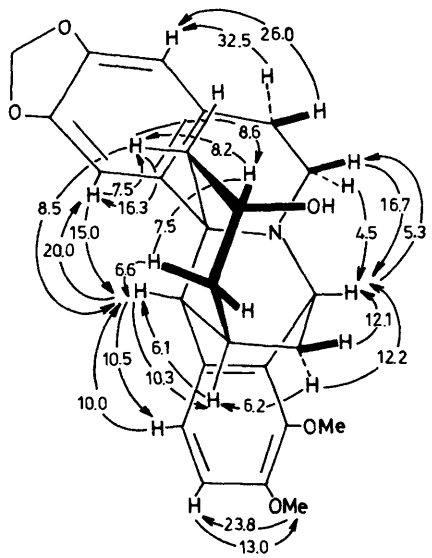


Figure 3. Results of a n.O.e. difference study on (±)-dihydrovalachine (**4**).

hydrogen. It thus became evident that the OH group at C-16 is axial, and that borohydride reduction of valachine (**3**) had occurred from the less hindered side of the molecule.

Karachine (**2**) is the product of the overall condensation of a mole of berberine (**1a**) with two acetone anions, but valachine (**3**) may be formed through initial condensation of berberine with the acetaldehyde anion, followed by a second condensation with an acetone anion as indicated in Scheme 1 where R = H.

We conclude that bridged protoberberines such as (±)-karachine (**2**) and (±)-valachine (**3**) are true natural products, and that there is a good probability that further analogues within this series will be obtained in the future.

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