Conversion of Tetrahydroberberine into Pavinane-type Alkaloids

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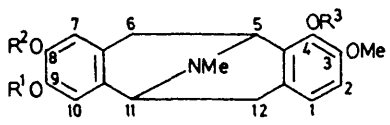
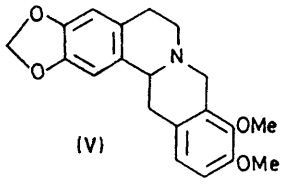
Summary *OO*-Dimethylmunitagine (III) has been synthesised from tetrahydroberberine (V) through a series of reactions which culminate in the Stevens rearrangement.

MUNITAGINE (I), 4,9-dihydroxy-3,8-dimethoxy-*N*-methylpavinane,† was first isolated from *Argemone munita* (Papaveraceae)[1]. These alkaloids are normally synthesized by acid-catalysed rearrangement of *N*-methyl-1,2-dihydro-1-benzyltetrahydroisoquinolines oxygenated at suitable positions.[2] This type of synthesis is usually applicable to symmetrically substituted *N*-methylpavinanes (*e.g.*, the C-2, -3, -8, and -9 oxygenated forms such as argemonine)

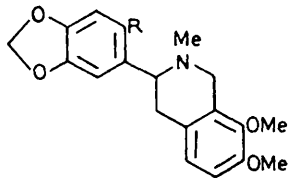
† We use the nomenclature suggested by C.-H. Chen and T. O. Soine in *J. Pharm. Sci.*, 1972, **61**, 55. The numbering system is different from that in ref. 1.



(I) $R^1 = R^3 = H$, $R^2 = Me$
(II) $R^1 = R^2 = Me$, $R^3 = H$
(III) $R^1 = R^2 = R^3 = Me$
(IV) $R^1, R^2 = -CH_2-$, $R^3 = Me$

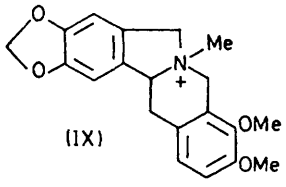


(V)

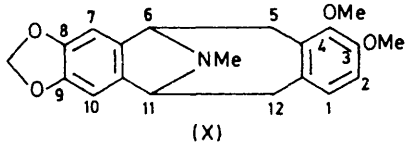


(VI) Methiodide of (V)

(VII) R = CH=CH$_2$
(VIII) R = CH$_2$OH



(IX)



(X)

and was recently used by Stermitz and his co-workers[3] to synthesise platycerine (II) from the corresponding *N*-methyl-7,8-oxygenated benzylisoquinoline.

We report an alternative synthesis of *OO*-dimethylmunitagine (III) from tetrahydroberberine (V) through a series of reactions which culminate in the Stevens rearrangement[4] to give the tetracyclic *N*-methylpavinane with the correct oxygenation pattern.

Hofmann degradation of (±)-tetrahydroberberine methiodide (VI), m.p. 245—248°, according to the method of Simanek and his co-workers,[5] gave the styrene derivative (VII), m.p. 111—112°. Oxidation of (VII) with OsO_4–$NaIO_4$ followed by reduction with $NaBH_4$ afforded the benzyl alcohol derivative (VIII), m.p. 151—152°, $C_{20}H_{23}O_5N$. Treatment of (VIII) with $MeSO_2Cl$ in pyridine gave a cyclic quaternary methomesylate which was characterized as its methiodide (IX), m.p. 224—226°, $C_{20}H_{22}O_4NI$. This methiodide (IX) was stirred with an excess of phenyllithium in ether at room temperature overnight to yield two types of rearrangement products,

The first had m.p. 174—175°, *m/e* 339 (M^+) and was assigned structure (IV). This assignment was fully substantiated by its u.v. and n.m.r. spectra which are similar to those of the known alkaloid, *OO*-dimethylmunitagine (III). Final proof, however, rested upon cleavage of the methylenedioxy-group of (IV) with BCl_3 followed by methylation with diazomethane to give a non-phenolic base which had i.r., u.v., and n.m.r. spectra which were identical with those of authentic *OO*-dimethylmunitagine (III).

The second compound, an oil, *m/e* 339 (M^+) was tentatively assigned structure (X) on the basis of its n.m.r. data: δ 2·92 (2H, q, *J* 6 and 16 Hz, 5- and 12-H), 3·36 (2H, q, *J* 7 and 16 Hz, 5- and 12-H), and 3·80—4·00 (2H, m, 6- and 11-H).

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