A Total Synthesis of the Alkaloid (±)-Kikemanine

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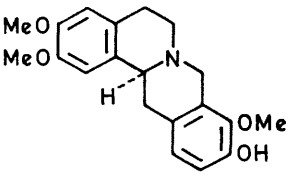
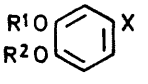
Summary (±)-Kikemanine was synthesised by Mannich reaction of 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline.

RECENTLY we isolated (−)-kikemanine (I) as one of many alkaloids from *Corydalis pallida* var. *tenuis* Yatabe and its structure was assigned as (I) on the basis of physical data.[1] Protoberberine alkaloids having a hydroxy-group at C-10 and a methoxy-group at C-9 have not yet been synthesised by Mannich reaction. The purpose of this investigation was to study the Mannich reaction under physiological conditions[2] of 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (VI) in order to obtain the corresponding protoberberine (VII) as a possible intermediate for the synthesis of (±)-kikemanine (X), leading eventually to an alternative total synthesis of (±)-kikemanine.

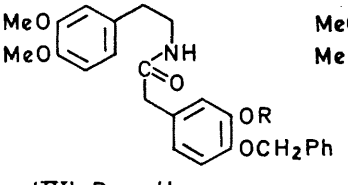
Fusion of 3,4-dimethoxyphenethylamine (II) with 4-benzyloxy-3-hydroxyphenylacetic acid (III),† m.p. 99—100°, which was obtained from 4-benzyloxy-3-tosyloxybenzyl cyanide,[3] gave the amide (IV), m.p. 124—126°, which was converted into the non-phenolic amide (V), m.p. 135—137°. Bischler–Napieralski treatment of the amide (V) with phosphoryl chloride in benzene, followed by reduction with sodium borohydride, gave the 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (VI), m.p. 146—147°. A mixture of (VI) and 37% formalin was allowed to stand at pH 6·4 at room



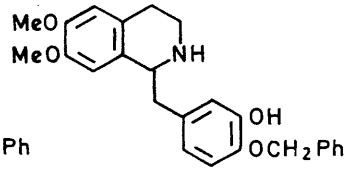
(I)



(II) $R^1 = R^2 = Me$, $X = CH_2CH_2NH_2$
(III) $R^1 = H$, $R^2 = CH_2Ph$, $X = CH_2CO_2H$



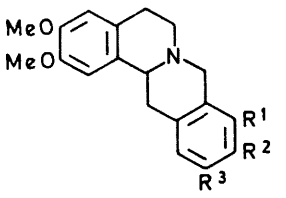
(IV) R = H
(V) R = CO_2Et



(VI)

† All new compounds gave satisfactory microanalytical data.

temperature for 16 h to give a mixture of (VII) and (VIII). Evaporation of the first eluate, followed by recrystallisation from methanol, gave a protoberberine (VII) as colourless needles (m.p. 112—113°, 52% yield) which were methylated with diazomethane to give the *O*-methyl derivative (IX),



(VII) $R^1 = OH$, $R^2 = OCH_2Ph$, $R^3 = H$
(VIII) $R^1 = H$, $R^2 = OCH_2Ph$, $R^3 = OH$
(IX) $R^1 = OMe$, $R^2 = OCH_2Ph$, $R^3 = H$
(X) $R^1 = OMe$, $R^2 = OH$, $R^3 = H$
(XI) $R^1 = H$, $R^2 = OCH_2Ph$, $R^3 = OMe$
(XII) $R^1 = H$, $R^2 = OH$, $R^3 = OMe$
(XIII) $R^1 = H$, $R^2 = R^3 = OMe$

m.p. 158—159°. Debenzylation of (IX) with ethanolic hydrochloric acid gave a phenolic base (X) (m.p. 185—187°, from MeOH, lit.,[4] m.p. 187·5—188·5°) whose i.r. [ν_{max} 2800—2720 cm^{-1} (Bohlmann band)], n.m.r. [δ (in $CDCl_3$) 3·73 (3H, s, OMe), 3·82 (6H, s, 2 × OMe), 6·60 (1H, Ar*H*), 6·73 p.p.m. (3H, s, Ar*H*)], and mass [*m/e* 341 (M^+), 340, 326, 192 (base peak), 190, 150, 135] spectra were superimposable on those of natural (—)-kikemanine (I).

On the other hand, removal of the second eluate afforded a protoberberine (VIII) as colourless needles m.p. 149—151,° from MeOH, 31% yield) whose methylation gave the *O*-methyl derivative (XI) as colourless needles (m.p. 166—167°, from MeOH). Debenzylation of (XI) gave a phenolic base (XII) as a colourless powder, m.p. 193—195°, whose methylation gave (±)-norcoralydine (XIII). The i.r. and n.m.r. spectra of (XIII) were identical with those of the authentic sample[5] and no depression was observed in a mixed m.p. determination.

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