

A Total Synthesis of the Alkaloid ($\pm$)-Kikemanine

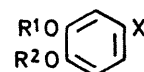
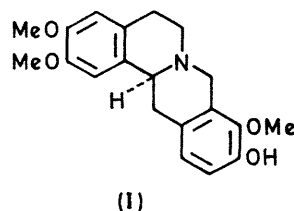
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Summary ($\pm$)-Kikemanine was synthesised by Mannich reaction of 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline.

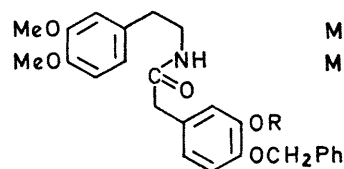
RECENTLY we isolated (–)-kikemanine (I) as one of many alkaloids from *Corydalis pallida* var. *tenuis* Yatabe and its structure was assigned as (I) on the basis of physical data.¹ Protoberberine alkaloids having a hydroxy-group at C-10 and a methoxy-group at C-9 have not yet been synthesised by Mannich reaction. The purpose of this investigation was to study the Mannich reaction under physiological conditions² 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 ($\pm$)-kikemanine (X), leading eventually to an alternative total synthesis of ($\pm$)-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



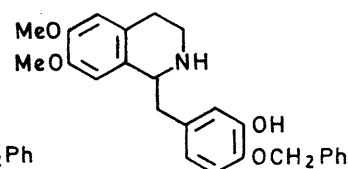
(II) $R^1 = R^2 = \text{Me}$,
 $X = \text{CH}_2\text{CH}_2\text{NH}_2$

(III) $R^1 = \text{H}$, $R^2 = \text{CH}_2\text{Ph}$,
 $X = \text{CH}_2\text{CO}_2\text{H}$



(IV) $R = \text{H}$

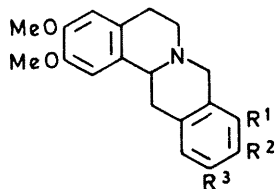
(V) $R = \text{CO}_2\text{Et}$



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

[†] 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) $R^1 = \text{OH}$, $R^2 = \text{OCH}_2\text{Ph}$, $R^3 = \text{H}$
 (VIII) $R^1 = \text{H}$, $R^2 = \text{OCH}_2\text{Ph}$, $R^3 = \text{OH}$
 (IX) $R^1 = \text{OMe}$, $R^2 = \text{OCH}_2\text{Ph}$, $R^3 = \text{H}$
 (X) $R^1 = \text{OMe}$, $R^2 = \text{OH}$, $R^3 = \text{H}$
 (XI) $R^1 = \text{H}$, $R^2 = \text{OCH}_2\text{Ph}$, $R^3 = \text{OMe}$
 (XII) $R^1 = \text{H}$, $R^2 = \text{OH}$, $R^3 = \text{OMe}$
 (XIII) $R^1 = \text{H}$, $R^2 = R^3 = \text{OMe}$

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, $2 \times \text{OMe}$), 6·60 (1H, ArH), 6·73 p.p.m. (3H, s, ArH)], 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 ($\pm$)-norcoralydine (XIII). The i.r. and n.m.r. spectra of (XIII) were identical with those of the authentic sample⁵ and no depression was observed in a mixed m.p. determination.

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⁴ S. A. Telang and C. K. Bradsher, *J. Org. Chem.*, 1965, **30**, 752.

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