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STRUCTURE OF CASEADINE†

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A reinvestigation of the spectral data of the synthetic 1-hydroxy-2,10,11-trimethoxyberbine and natural caseadine shows that their *nmr* spectra are almost identical with very minor differences; so are their ir spectra in solution except for an additional band at 720 cm^{-1} in the natural product. These minor differences could not be due to structural or stereochemical differences but perhaps due to some impurity in the natural sample.

Caseadine, caseamine and caseanadine are naturally occurring tetrahydroprotoberberines, isolated from Corydalis caseana A. Gray and assigned structures (1), (2) and (3) respectively[1]. Cava et al.[2] synthesised caseadine-O-methyl ether (4) and found it to be identical with the methyl ether of natural caseadine (1). Thus the oxygenation pattern in caseadine (1) was settled. By an independent route Ishiwata and Itakura[3] synthesised (4) and found it to be identical with the O-methyl ether of caseadine. Iida et al.[4] synthesised dl-caseadine (m.p.115-118°) and found the O-methyl ether to be identical

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† Studies in Protoberberine Alkaloids. Part XIII

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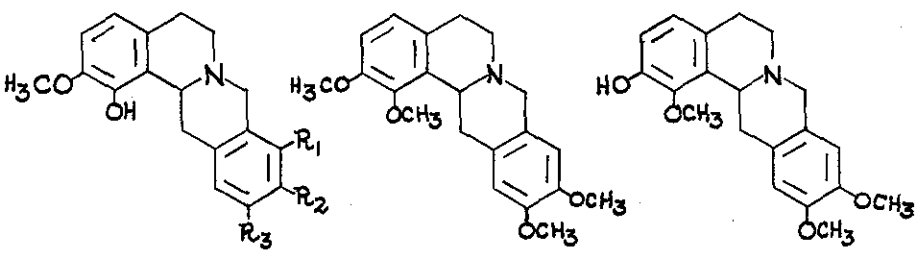
with Cava's[2] synthetic sample. dl-Caseadine (m.p. 90-93°) was also synthesised by Kametani et al.[5] who found that the O-methyl ether was identical with the methyl ether of natural caseadine;

Scheme 1



(1) R_1=H; R_2=R_3=OCH_3

(2) R_1=H; R_2=OH; R_3=OCH_3

(3) R_1=R_2=OCH_3; R_3=H

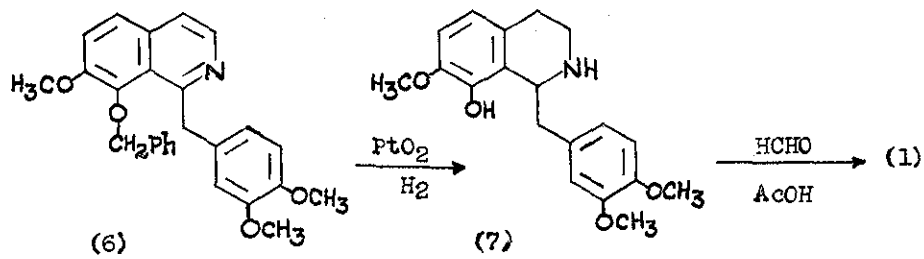
(4) (5)

but the ir spectrum of synthetic caseadine differed from natural caseadine. They also reported that natural caseadine showed a negative result in Gibbs test, but the synthetic sample gave a positive response. Thus they concluded that caseadine should be represented by structure (5). But exceptions to Gibbs test[6] are known; for eg., tetrahydroprotoberberine alkaloids having a C_3-hydroxy group are known to give a positive reaction[7], although Gibbs test is usually negative for compounds having substituents at p-position to the phenolic group.

We synthesised dl-caseadine (1) according to scheme 2. 1-(3,4-Dimethoxybenzyl)-8-benzyloxy-7-methoxyisoquinoline (6)[8] was catalytically reduced with Adams catalyst to the tetrahydroisoquinoline (7). Mannich cyclisation of this, according to

the procedure of Kametani et al.[5], yielded dl-caseadine (1), m.p. 90-92°.

Scheme 2



The 220 MHz nmr chemical shifts of natural and synthetic caseadine in $CDCl_3$ and C_6D_6 are given in Table 1.

Table 1

	220 MHz NMR Chemical Shifts (δ, ppm)			
	Natural caseadine (1)		Synthetic caseadine	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
OCH_3	3.84 (s)	3.21 (s)	3.85 (s)	3.22 (s)
	3.85 (s)	3.39 (s)	3.86 (s)	3.39 (s)
	3.87 (s)	3.49 (s)	3.89 (s)	3.49 (s)
C_{13a}-H	4.10 (q) (J = 12 and 4 Hz)	4.29 (q)	4.15 (q) (J = 12 and 4 Hz)	4.36 (q)
C_9 and C_{12}-H	6.58 (s)	6.42 (s)	6.59 (s)	6.39 (s)
	6.61 (s)	6.53 (s)	6.61 (s)	6.48 (s)
C_3-H	6.66 (d) (J = 8 Hz)	6.44 (d)	6.67 (d) (J = 8 Hz)	6.43 (d)
C_4-H	6.76 (d) (J = 8 Hz)	6.62 (d)	6.77 (d) (J = 8 Hz)	6.60 (d)

The angular proton at C_{13a} of *trans* fused benzo[a]- and indolo[a]-quinolizidines resonates at a field higher than δ 3.80, whereas the *cis* fused compounds are characterised by a downfield signal below δ 3.80 for this proton[9]. The nmr spectrum of both synthetic and natural compounds showed the angular proton at δ 4.15 and 4.10 ppm respectively, in $CDCl_3$ and at δ 4.36 and 4.29 ppm in C_6D_6, as a quartet (J=12 and 4 Hz). This indicates that both the synthetic and natural compounds may be *cis* fused. This proton was not identified in the natural alkaloid[1], but the presence of *trans*-quinolizidine nucleus was inferred only on the basis of the presenee of Bohlmann bands[10] in its ir spectrum. Kametani *et al.*[5] and Iida *et al.*[4] reported the nmr spectral data for their synthetic compounds, but no mention has been made regarding configuration. The signal at δ 4.05 (in $CDCl_3$) was however assigned to the angular proton[5]. The ir spectra of our synthetic sample and natural compound have been compared in solution ($CHCl_3$; Figure 1) and the

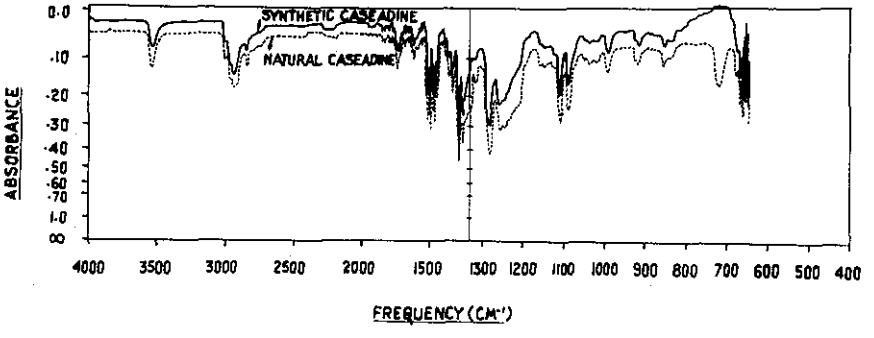


Figure 1

only difference is the presence of a band at 720 cm^{-1} in the ir spectrum of the natural compound. On the other hand, as is seen from Table 1, chemical shifts of various protons of natural caseadine and the synthetic compound are very close, especially those of the methoxy groups which are particularly identical. It appears somewhat doubtful whether structure (5) with a methoxyl at C_1 can account for this observation. In our opinion the synthetic and natural compounds are identical. The minor differences between the two may be due to the contamination of some other compound in the natural caseadine. Thus the assigned structure to caseadine seems to be valid; it is however worthwhile to establish the structure and stereochemistry by X-ray diffraction studies; it would be most interesting if 2-hydroxy-1,10,11-trimethoxyberbine could be synthesised. All our attempts to synthesise this compound proved infructuous.

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