BIOMIMETIC TRANSFORMATION OF HODGKINSINE, A PYRROLIDINOINDOLINE ALKALOID

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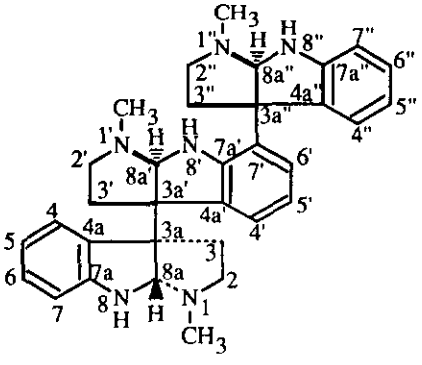
Abstract - The transformation of hodgkinsine **1** under mild acidic conditions provides a new compound whose structure has been shown to possess calycanthine and pyrrolidinoindoline subunits. This compound could be identified with calycosidine **2** previously isolated from *Calycodendron milnei*. General implications of this reaction are discussed.

In a preliminary paper[1] we reported the isolation of hodgkinsine **1** along with calycosidine **2**, a new minor indole alkaloid from the stem bark of *Calycodendron milnei* .

The biological activity of several compounds belonging to this family of indole alkaloids has been previously described and antibiotic activity [2], human platelet aggregation inhibition[3], cytotoxicity [4], as well as activity on the central nervous system [5] has been demonstrated. We therefore set out to study chemical transformations of hodgkinsine **1**, whose structure had been ascertained by X-ray analysis[6], showing it to possess three N-methylpyrrolidinoindoline units as depicted in formula **1**.



1 hodgkinsine

Previous studies had established that the acid catalyzed isomerisation of (-)-chimonanthine **3**, *meso*-chimonanthine **4** and racemic chimonanthine **5** led to respectively (+)-calycanthine **6** [7], *meso*-calycanthine **7** and racemic calycanthine **8**[7,8] , as the only observed reaction products. A mechanism has been proposed for this reaction (Figure 1) which allows for the retention of configuration of carbon atoms 3a and 3a' in these

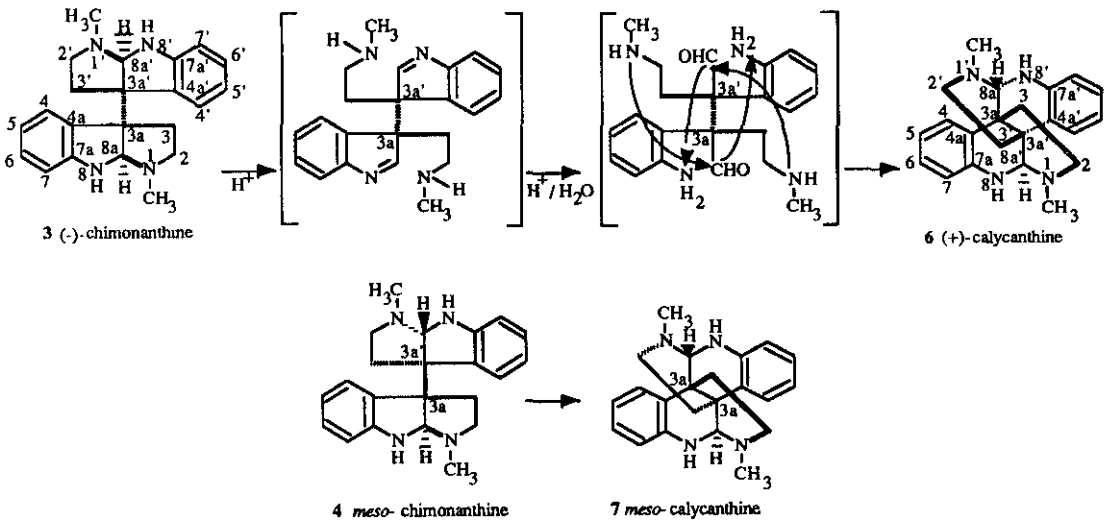


Figure 1

transformations. Under similar conditions hodgkinsine **1** was not converted into any calycanthine isomer [7] in spite of the existence of a *meso*-chimonanthine subunit [6]. In our hands, treatment of hodgkinsine with boiling 0.1N acetic acid during 8 h led to the isolation of a major product which could be identified with calycosidine (identical spectral data, especially identical optical rotation), which has formerly been extracted from *Calycodendron milnei* [1].

Therefore both natural calycosidine and the transformation product derived from hodgkinsine will be considered as the same compound in the following.

Its structure was determined through the analysis of its mass and ^{1}H-and ^{13}C-nmr spectral data.

The fragmentation pattern in the mass spectrum of calycosidine **2** is quite different from that of hodgkinsine **1**. For instance, while the base peak in the mass spectrum of hodgkinsine is found at m/z 344 (100 %) corresponding to a cleavage between C-3a and C-3a' of the chimonanthine subunit, the base peak in the mass spectrum of **2** corresponds to the molecular ion peak m/z 518 (100 %). Other fragments m/z 461 (M-57, 29 %) and m/z 403 (461-58, 19 %) are analogous to those observed for calycanthine **6** or **8** [9] due to the subsequent loss of C_3H_7N and C_3H_8N (Figure 2).

The presence of a calycanthine moiety in calycosidine **2** was confirmed by ^{1}H- and ^{13}C-nmr investigations particularly by comparison with the spectral data of racemic chimonanthine **5** and racemic calycanthine **8**. The chemical shift values of protons and carbon atoms of these molecules (Table 1) were confirmed by two 2D-nmr experiments : a proton-proton shift correlation (COSY-45) and a carbon-proton shift correlation*.

*The presence of several conformations in solution didn't allow us to fully interpret the 2D experiments of hodgkinsine.

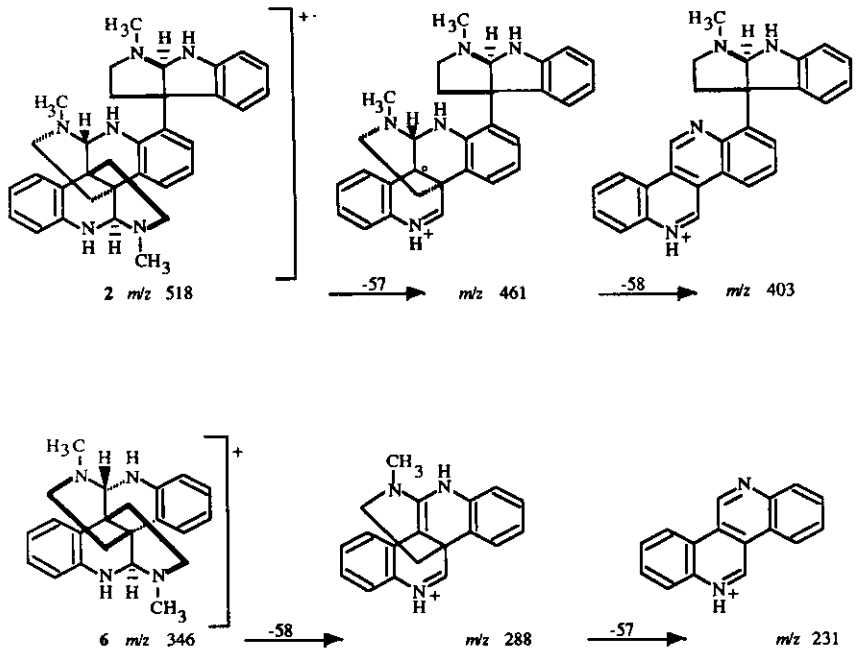


Figure 2

Recently, we have demonstrated the diagnostic value of ^{13}C-nmr chemical shifts of carbon 8a for pyrrolidinoindoline alkaloids [1, 2]. While C-8a of racemic chimonanthine **5** has a chemical shift value of $\delta = 85.2$, the corresponding resonances of the three carbon atoms of hodgkinsine **1** occur at δ = 87.0, 83.2 and 82.5 (Table 1). In contrast the 8a and 8a' carbon atoms of racemic calycanthine **8**, which are part of six membered rings, show a signal at $\delta = 71.0$. The ^{13}C-nmr spectra of calycosidine **2** were analyzed on the basis of these results and exhibit three (N-CH-N) methine carbon signals at δ = 88.2 ,74.5 and 70.9 respectively. While the first of this signal corresponds to a chimonanthine type structure, the latter two are analogous to the corresponding resonances of carbon 8a of racemic calycanthine **8**. The same remarks are valid for the majority of carbon atoms in Table 1 (7a, 4a,3a, 2, 3 and N-CH_3). Dramatic differences of diagnostic value are observed for type 3a carbon atoms, which resonate in the range of δ = 60-65 in the case of pyrrolidinoindoline skeletons while there chemical shift range is about δ = 30-40 for piperidinoquinolines .

Finally, both hodgkinsine **1** and calycosidine **2** show only two aromatic methine signals at high field ($\delta = 110$) in their ^{13}C-nmr spectrum. Since these signals must belong to a carbon atom of type 7, the third one must therefore form a bond between two subunits.

Table 1

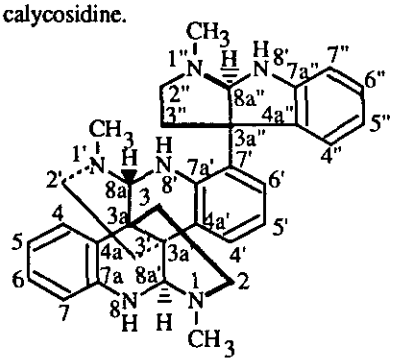
^{13}C- and ^{1}H-Nmr data *: δ *ppm* / TMS

n°	hodgkinsine **1**		calycosidine **2**		chimonanthine **5**		calycanthine **8**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
7a (C)	150.8		148.1 147.3 144.5		150.6		145.3	
4a (C)	132.4		133.3 128.7 124.7		133.4		125.0	
4 (CH)					127.9	7.17	124.3	6.99
5 (CH)					118.5	6.65	116.3	6.53
6 (CH)					124.3	6.97	126.5	6.79
7 (CH)	108.7 108.7	6.43** 6.57	112.2 110.4	6.58 6.70	109.1	6.53	112.0	6.27
8a (N-CH-N)	87.0 83.2 82.5		88.2 74.5 70.9	5.57 4.36 4.17	85.2	4.25	71.0	4.31
3a (C)	63.8 63.1 60.7		59.8 33.4 33.1		63.3		36.0	
2 ($N-CH_2$)	52.3 52.2 52.1		47.7 46.2		52.6	2.50	46.5	2.59 2.27
3 (CH_2)	38.1		38.2 38.1		35.7	2.07 2.50	31.7	3.12 1.27
($N-CH_3$)	35.4 35.1	2.34 2.44	43.2 42.1 36.4	2.23 2.25 2.33	37.2	2.29	42.5	2.42

*Only unambiguous data or values confirmed by correlation experiments are given.
** Attributed by selective proton decoupling experiment.

Note : The nmr spectra of calycanthine and chimonanthine have been obtained with synthetic racemic compounds. The observed chemical shift values in the ^{1}H-nmr spectrum of these compounds have been shown to be different of their *meso*-isomers[7], which exhibit an other spatial arrangement .

Structure **2**, which comprises a pyrrolidinoindoline and a *meso*-calycanthine subunit derived from hodgkinsine **1**, can therefore be attributed to calycosidine.



2 calycosidine

The most important result of our work is certainly the transformation of hodgkinsine into calycosidine under mild acidic conditions. Our findings suggest that alkaloids of calycanthine type may be artefacts resulting from transformation during extraction and isolation as depicted in Figure 1. Preliminary experiments in our laboratory suggest a general behaviour of more complex pyrrolidinoindoline alkaloids like psychotridine or quadrigemines.

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EXPERIMENTAL

The nmr spectra were measured on a Bruker AM-400 spectrometer (400.1 MHz ^{1}H, 100.6 MHz ^{13}C). The mass spectra were recorded on a MS-902 spectrometer at 70 and 20 ev in the electron impact and chemical ionisation (NH_3) mode. The ir spectra were measured on a Perkin-Elmer 257. Uv spectra were recorded on a Unicam SP 1800. A Zeiss polarimeter was used for optical rotation determination.

Transformation of hodgkinsine **1** :

200 mg of hodgkinsine **1**[isolated from *C. milnei*, $[\alpha]_D$ = - 42° ($CHCl_3$, c=1)] in 5 ml of 0.1N CH_3COOH were heated to reflux under nitrogen for 8 h. The reaction mixture was poured into ice water, made alkaline with NaOH and extracted with CH_2Cl_2. The crude mixture of products was purified by preparative HPLC (Jobin-Yvon Miniprep) over alumina Merck 60 H (5-40µ) using CH_2Cl_2 with increasing amounts of MeOH (99/1 to 97/3) as solvent. 59 mg of calycosidine **2** could be isolated.

Calycosidine : $[\alpha]_D$ = - 18° ($CHCl_3$, c=1); $C_{33}H_{38}N_6$ (ms hr tr. : 518.3151; cal. : 518.3157) ; uv λ_{max} nm (log ε) : 245 (4.40), 310 (4.02); ir ν_{max} cm^{-1} : 3400, 3300, 1600; ms m/z (%) 518 ($M^{+\cdot}$) (100), 485 (15),

461 (29), 403 (19), 344 (19), 172 (27), 130 (10); ^{1}H-nmr, δ (ppm /TMS, $CDCl_3$) : 1.03 (1H, dd, J_{HH}=13Hz, 3Hz), 1.25 (1H, dd, J_{HH}=12Hz, 3Hz), 1.88 (3H, m), 2.17 (3H, m), 2.23 (3H,s), 2.25 (3H, s), 2.33 (3H, s), 2.45 (2H, m), 2.63 (2H, m), 4.17 (1H, s), 4.36 (1H, s), 5.57 (1H, s), 6.58 (1H, d, J_{HH}=9 Hz), 6.70 (1H, d, J_{HH}=9Hz), 6.73 (1H, d, J_{HH}=9Hz), 6.74 (1H, t, J_{HH}=9Hz), 6.82 (1H, t, J_{HH}=9Hz), 6.84 (1 H, t , J_{HH}=9Hz), 7.03 (1H, t, J_{HH}=9Hz), 7.08 (1H, t, J_{HH}=9Hz), 7.09 (1H, d, J_{HH}=9Hz), 7.20 (1H, d, J_{HH}=9Hz), 7.25 (1H, d, J_{HH}=9Hz); ^{13}C-nmr, δ (ppm, $CDCl_3$) : 148.1 (C), 147.3 (C), 144.5 (C), 133.3 (C), 128.7 (C), 128.1 (CH), 126.8 (CH), 124.7 (C), 124.4 (CH), 123.6 (CH), 120.1 (CH), 119.9 (CH), 118.9 (C), 117.5 (CH), 117.4 (CH), 112.2 (CH),110.4 (CH), 88.2 (CH), 74.5 (CH), 70.9 (CH), 59.8 (C), 46.2 (CH_2), 46.1 (CH_2), 38.2 (CH_2), 38.1 (CH_2), 37.5 (CH_2), 33.4 (C), 33.1 (C), N-CH_3 : 43.2, 42.1, 36.4.

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