DIPPININE C, A NEW HEXACYLIC CHIPPIINE DERIVATIVE FROM A MALAYAN *TABERNAEMONTANA*

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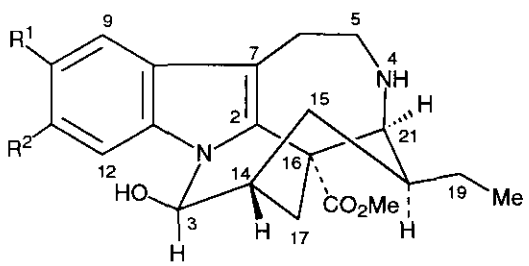
Abstract - A new indole alkaloid, dippinine C, belonging to the chippiine group but with incorporation of an additional ring, was obtained from the stem-bark extract of *Tabernaemontana corymbosa* and its structure established by spectral analysis.

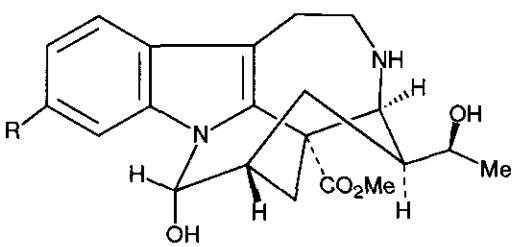
The chippine group of alkaloids comprises a small group of indoles (only two members were previously known) which can be considered as having arisen from an ibogan-type precursor *via* cleavage of the *N*(4)-C(3) bond followed by formation of a new bond between C(3) and *N*(1).[1,2] We recently reported the isolation and structure of dippinine A (**3**) from the leaf extract of *Tabernaemontana corymbosa* Roxb. and established by NOE experiments, the stereochemistry at carbon-3, which differed from that of the two known chippiine compounds belonging to this group (**1**, **2**).[3] The configuration at this center was originally assigned for chippiine based on consideration of the chemical shift of H(3) by analogy with that of H(16) in the eburnamines and 16-descarbomethoxy-tacamines.[1,4,5] We now report the structure of another chippiine derivative, dippinine C (**4**), isolated from the stem-bark, in which an additional six-membered ring has been formed *via* insertion of a formyl group between C(19) and *N*(4).

Dippinine C (**4**) was obtained as a light yellow oil, $[\alpha]_D$ +19° ($CHCl_3$, *c* 0.07). The IR spectrum showed bands due to OH (3358 cm^{-1}) and ester (1728 cm^{-1}) functions while the UV spectrum was similar to that of **3** displaying absorption maxima typical of an indole at 228, 285 and 294 nm. The MS spectrum gave a molecular ion at *m/z* 382, and HRMS measurements (*m/z* 382.1877) yielded the formula $C_{22}H_{26}N_2O_4$ (calcd 382.1892). The ^{13}C NMR spectrum showed a total of 22 carbon resonances in agreement with the formula obtained from the mass-spectrum. The ^1H NMR spectrum of **4** showed a general similarity with that of dippinine A (**3**) and chippiine (**1**). In common with these compounds, the spectrum is characterized by the

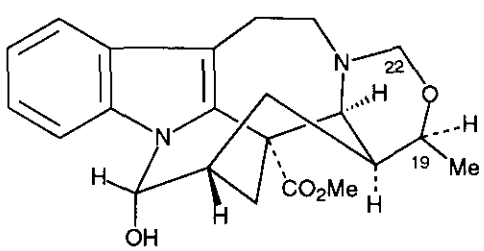
absence of any indole NH signal and the presence of a high field signal due to H(15α). There are however some distinct differences. Firstly, unlike **3** there is no signal due to any aromatic methoxy group and the aromatic region shows the presence of four aromatic hydrogens. Another prominent difference is the presence in the spectrum of **4** of a pair of low field AB doublets at δ 4.41 and 4.62 due to an oxymethylene function. This is also supported by the oxymethylene resonance at δ 88.7 in the ^{13}C NMR spectrum. The molecular formula of **4** yields a DBE value of 11 which is one more than that of chippiine (**1**) and dippinine A (**3**), indicating formation of an additional ring. The HMBC spectrum of **4** showed three-bond correlations from C(5), C(19) and C(21) to the oxymethylene hydrogens which is consistent with the oxymethylene function being part of the additional tetrahydro-1,3-oxazine ring system as shown in **4**. The configuration at C(3) is similar to that of dippinine A **3** as shown by the observed NOE interaction between H(3) and H(15β), H(12) and *vice versa*.[6]



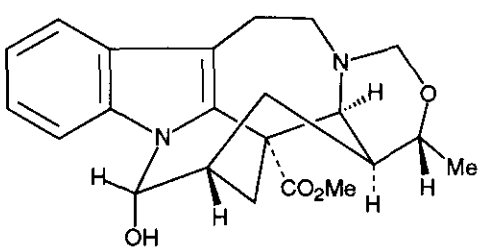
1 $R^1 = R^2 = OMe$
2 $R^1 = R^2 = H$



3 R = OMe
3a R = H



4



4a

The hexacyclic chippiine derivatives, as exemplified by the first member reported herein, can be envisaged to have arisen by condensation of formaldehyde onto *N*(4) of a suitable precursor, such as the

11-demethoxy derivative of dippinine A (**3a**), followed by intramolecular cyclization.[7] The configuration of C(19) is deduced to be *S* as shown in **4**, which is consistent with the observed NOE interactions between H(19) and H(21), H(22). Had the C(19) configuration been *R*, as in the alternative structure (**4a**), the pseudoequatorially oriented H(19) would then be directed away from both H(21) and H(22) and would therefore not be expected to show NOE's with these hydrogens. Since the hexacyclic, tetrahydrooxazine containing derivatives (*e.g.* **4**) are probably derived from the pentacyclic precursors such as **3**, this allows us to in turn, fix the configuration of C(19) in dippinine A (**3**)[3] as *S*. Dippinine C represents the first isolation of a chippiine-type compound which has incorporated an additional tetrahydrooxazine ring.

Table 1. ^{1}H and ^{13}C NMR Spectral Data for **3** and **4**[a]

	3		**4**	
Position	δ_H	δ_C	δ_H	δ_C
2	-	132.0	-	132.6
3	5.47 m	79.1	5.58 m	79.4
5	2.70 td (14, 1.5)	42.0	2.79 m	47.6
5	2.79 dt (14, 3)		2.93 m	-
6	2.54 td (14, 3)	25.2	2.74 m	23.2
6	2.66 ddd (14, 3, 1.5)		2.79 m	-
7	-	112.9	-	113.9
8	-	122.1	-	128.1
9	7.32 d (8)	119.0	7.56 dd (7, 1.5)	109.9
10	6.84 dd (8, 2)	110.1	7.20 td (7, 1.5)	120.8
11	-	156.1	7.23 td (7, 1.5)	121.8
12	7.00 d (2)	93.9	7.53 dd (7, 1.5)	118.7
13	-	136.8	-	136.8
14	2.34 m	35.7	2.46 m	36.0
15	1.17 ddd (14, 12, 6)	30.0	1.23 ddd (14, 11, 6)	31.3
	1.64 ddt (14, 6, 2.5)		1.67 ddt (14, 5.5, 2.5)	-
16	-	50.5	-	47.7
17	1.74 br dd (13, 4)	29.7	2.02 brdd (13, 4)	29.0
	2.56 dt (13, 2.5)		2.68 dt (13, 2.5)	-
18	0.92 d (6)	20.6	0.93 d (6)	18.5
19	3.50 dq (7, 6)	75.1	3.27 dq (9, 6)	79.4
20	0.89 dddd (12, 11, 7, 2.5)	36.4	0.67 tdd (11, 9, 5.5)	33.1
21	3.19 d (11)	60.8	3.44 d (11)	64.6
22	-	-	4.41 d (10.5), 4.62 d (10.5)	88.7
CO_2Me	3.77 s	52.6	3.80 s	52.6
CO_2Me	-	174.8	-	173.5
11-OMe	3.87 s	55.7	-	-

[a] $CDCl_3$; 400 MHz; assignments based on COSY, HMQC and HMBC.

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