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Macrodasine A, a novel macroline derivative incorporating fused spirocyclic tetrahydrofuran rings containing a spiroacetal moiety

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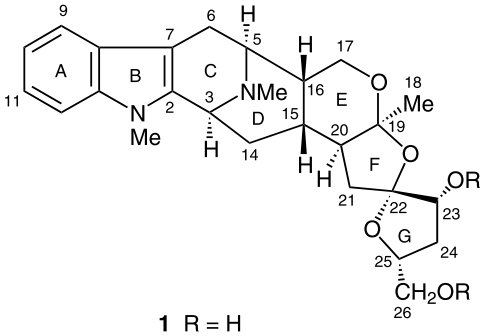
Abstract—A novel indole alkaloid, viz., macrodasine A, incorporating fused spirocyclic tetrahydrofuran rings onto a macroline-like moiety, was obtained from a Malayan *Alstonia* species. The structure, which is also notable for the presence of an unprecedented spiroacetal moiety in an indole alkaloid, was established by spectroscopic analysis.

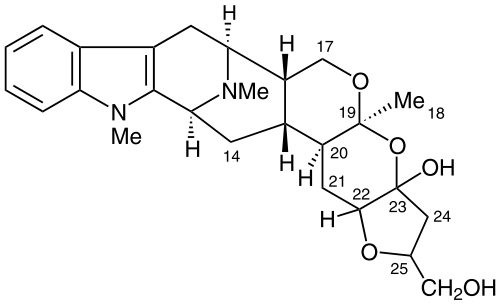
The genus *Alstonia* is characterised by a preponderance of the macroline-type indole and oxindole alkaloids.[1–8] We have previously reported the presence of new macroline indoles as well as oxindoles from the Malayan species, *A. angustifolia* var. *latifolia*.[3,4] We now wish to report the structure of a novel macroline derivative isolated from *A. macrophylla* Wall.[9]

Macrodasine A **1** was obtained from *A. macrophylla* (ca. 22 mg from 5.6 Kg dry bark), as a colourless oil, with $[\alpha]_D$ +36 (*c* 0.36, $CHCl_3$). The UV spectrum was characteristic of an indole chromophore with absorption maxima at 230 and 287 nm (log ε 3.88 and 3.17, respectively), while the IR spectrum showed a broad band at 3411 cm^{-1} suggesting the presence of hydroxyl functions. The EIMS of **1** showed a molecular ion at *m*/*z* 454, which analyzed for $C_{26}H_{34}N_2O_5$, requiring 11 degrees of unsaturation (HREIMS found *m*/*z* 454.2462, calcd for $C_{26}H_{34}N_2O_5$, 454.2468), while the mass fragments which were observed at *m*/*z* 197, 182, 181, 170, and 144 are typical of macroline derivatives[10] and provided early indication that 1 contained a macroline core. The ^{13}C NMR spectrum (Table 1) gave a total of 26 separate carbon resonances (three methyls, six methylenes, eleven methines, and six quaternary carbons) in agreement with the molecular formula. In addition to the eight signals associated with the indole moiety, the ^{13}C NMR spectrum is notable for the presence of two oxymethylenes (δ 63.9, 64.3), two oxymethines (δ 77.7, 79.2), and two quaternary carbons each of which are flanked by two oxygen atoms (δ 105.5, 114.8), consistent with a highly oxygenated molecule as indicated by the molecular formula. The ^1H NMR spectrum of **1** (Table 1) showed the presence of an unsubstituted indole chromophore, from the signals due to four contiguous aromatic hydrogens, the presence of three methyl groups corresponding to the *N*(1)-Me (δ 3.63), *N*(4)-Me (δ 2.33), and Me(18) (δ 1.59), and a hydroxymethyl group from the presence of a pair of doublet of doublets at δ 3.43 and 3.77 (corresponding to the carbon resonance at δ 63.9).



1 R = H

3 R = Ac



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The COSY spectrum disclosed some partial structures which are characteristic of a macroline skeleton, such as NCHCH$_2$ and NCHCH$_2$CHCHCH$_2$O, corresponding to the C(5)-C(6) and C(3)-C(14)-C(15)-C(16)-C(17) fragments.[3,4] This is further supported by the observed hydrogen chemical shifts and coupling behaviour for H(3), H(5), H(16), H(17), as well as the three characteristic methyl groups which are typical of a macroline compound (e.g. alstonerine).[3] At this stage, further analysis of the COSY spectrum was complicated by overlap of some key signals. Thus, two sets of partial structures can be proposed for the remaining fragments, viz., CHCH$_2$ and OCHCH$_2$CHCH$_2$O, versus CHCH$_2$CHO and CH$_2$CHCH$_2$O, which with the aid of the HMBC data lead to two possible structures, **1** and **2**, respectively. Structure **1** is distinguished by the incorporation of a 1,6-dioxaspiro[4.4]nonane substructure fused onto a macroline residue, while structure **2** on the other hand, is distinguished by incorporation of contiguously fused tetrahydropyran and tetrahydrofuran rings onto the same macroline unit. Both structures accommodate the observed NMR chemical shifts as well as the HMBC correlation data. To resolve the difficulty in distinguishing the two structures, acetylation (Ac$_2$O, pyridine) was carried out which yielded a single diacetylated derivative (EIMS m/z 538, M$^+$, C$_{30}$H$_{38}$N$_2$O$_7$), providing cogent support for structure **1**. Furthermore, the acetylated derivative had a better resolved ^{1}H NMR spectrum (Table 1), which removed the earlier ambiguity associated with some of the key signals. Specifically, the signals for H(21), H(23), H(24) and H(25) are now sufficiently clear and well resolved in the acetate derivative **3** {whereas H(24) and H(21) were overlapping multiplets in 1}, and indicated the presence of the key OCHCH$_2$CHCH$_2$O fragment, corresponding to the C(23)-C(24)-C(25)-C(26) partial structure in **1**. In addition, the observed carbon resonance of δ 114.8 for the spirocyclic centre is in good agreement with that previously noted for the spirocarbon in compounds containing a 1,6-dioxaspiro[4.4]nonane unit.[11–14]

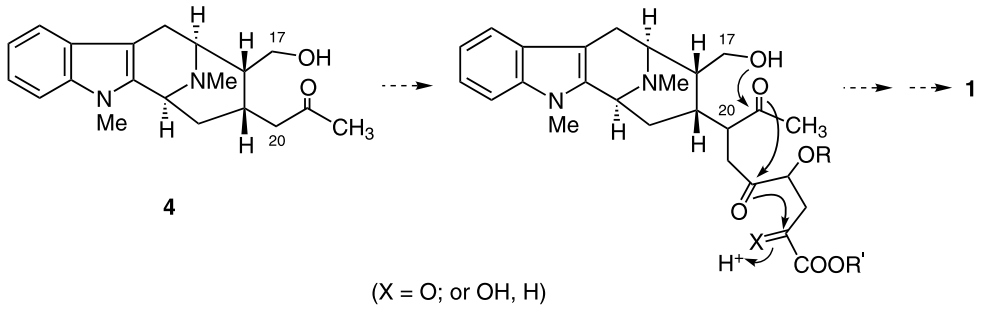
The ring junction stereochemistry between rings C, D, and E, is assumed to follow that in the known macroline compounds (e.g. alstonerine)[3] from the similarity of the chemical shifts and coupling patterns observed for the ring junction hydrogens, a supposition which is also in agreement with the NOE and NOESY data. The observed NOE between 18-methyl and H(17α) as well as H(20), fixes the E/F ring junction stereochemistry as *cis* {18-Me and H(20) both α}. The resonance for H(20) was a doublet of doublet with J 12 and 8 Hz. Decoupling experiments indicated that the splittings were due to coupling with the two C(21) protons. Since the stereochemistry of H(20) has been fixed as α, the 12 Hz coupling must be due to coupling to H(21β). Irradiation of H(23) causes NOE enhancement of H(25) and vice versa, indicating that they are *syn* to each other. Aside from these, further assignment of the remaining stereochemistry, such as that of the spirocyclic centre at C(22), were precluded by the unresolved signals of H(21) in **1**, which were fortuitously well resolved in the diacetate derivative **3**. Thus the observation of a key NOE interaction between H(23) and H(21β) in **3**, not only allowed assignment of the configuration at the spirocarbon as *R*, but also fixes the stereochemistry of C(23) and C(25), respectively, as *R*, *R*.

Macrodasine A **1**, represents an unusual macroline derivative which has incorporated additional novel structural features, in the form of fused spirocyclic tetrahydrofuran rings, incorporating an unprecedented spiroacetal moiety. The spiroketal unit has previously been encountered in insect pheromones,[15–17] marine

Table 1. ^{1}H and ^{13}C NMR spectral data of **1** and **3**[a]

Position	**1**	**3**		Position	**1**	**3**	
	δ_C	δ_H	δ_H		δ_C	δ_H	δ_H
2	132.8	–	–	17β	–	3.70 dd (12, 5)	3.75 dd (12, 5)
3	53.3	3.95 t (3)	4.79 br s	18	24.2	1.59 s	1.72 s
5	54.8	2.98 d (7)	3.56 d (7)	19	105.5	–	–
6	22.5	2.39 m	3.04 d (18)	20	44.3	2.01 dd (12, 8)	2.07 m
		3.27 dd (17, 7)	3.45 dd (18, 7)	21α	34.7	1.85 m	1.85 dd (13, 8)
7	106.4	–	–	21β	–	2.39 m	2.17 t (13)
8	126.4	–	–	22	114.8	–	–
9	118.0	7.50 br d (8)	7.56 br d (8)	23	77.7	4.13 d (5)	5.21 d (4)
10	118.9	7.12 br t (8)	7.23 td (8, 1)	24	33.0	1.85 m	2.03 m
11	121.0	7.21 td (8, 1)	7.35 td (8, 1)			2.39 m	2.14 td (9, 4)
12	108.0	7.31 br d (8)	7.40 br d (8)	25	79.2	4.42 m	4.37 dtd (9, 7, 4)
13	136.9	–	–	26	63.9	3.43 dd (12, 3)	3.98 dd (12, 7)
14	31.9	1.55 ddd (13, 5, 3)	1.78 br d (14)			3.77 dd (12, 2)	4.21 dd (12, 4)
		2.39 m	3.33 td (14, 4)	N(1)Me	29.0	3.63 s	3.69 s
15	26.5	1.85 m	1.92 dt (14, 5)	N(4)Me	41.6	2.33 s	2.88 s
16	36.9	2.03 dt (12, 5)	2.33 dt (12, 5)	23-OAc	–	–	2.02 s
17α	64.3	4.04 t (12)	4.82 t (12)	26-OAc	–	–	2.06 s

[a] CDCl$_3$, 400 MHz; assignments based on COSY, HMQC and HMBC.



Scheme 1.

natural products,[11–14,18,19] microbial compounds,[15,20–24] plant steroidal derivatives[15] and various other plant secondary metabolites.[15] It has however not been been found as a substructure in alkaloids. Macrodasine A **1**, thus represents the first instance of the incorporation of a spiroketal unit in an indole alkaloid.

A possible pathway to macrodasine A **1** is from the ring-opened form of alstonerine **4**,[4] which on alkylation by a six-carbon fragment at C(20), followed by tandem intramolecular hemiketal formation (Scheme 1), yields the ring system of **1**.

Acknowledgements

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