Pergamon

Tetrahedron Letters 39 (1998) 5823–5826

TETRAHEDRON LETTERS

# Danuphylline, a novel pentacyclic indole from *Kopsia*

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Received 3 April 1998; revised 26 May 1998; accepted 1 June 1998

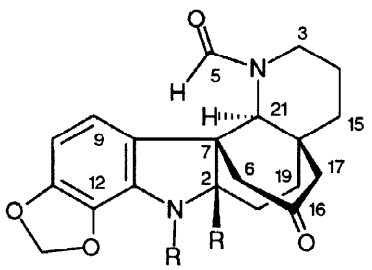
***Abstract*** : A novel pentacyclic indole alkaloid, danuphylline, was obtained from the leaf-extract of *Kopsia dasyrachis* and its structure elucidated by spectral analysis.


In the course of an investigation of the alkaloidal composition of the North Borneo species, *Kopsia dasyrachis*,[1] we obtained minor amounts of a new indole alkaloid, danuphylline, which possesses a novel pentacyclic carbon framework.

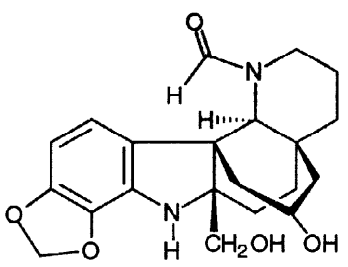
Danuphylline **1** was obtained in amorphous form, $[\alpha]_D$ -30° ($CHCl_3$, *c* 0.067). The UV spectrum showed absorption maxima at 214, 225, 248, 283 and 293 nm (log ε 3.95, 4.13, 3.66, 3.03 and 2.99 respectively) typical of a dihydroindole chromophore, while the IR spectrum showed bands due to various carbonyl functions (1720 $cm^{-1}$, broad; 1669 $cm^{-1}$). The EIMS of **1** showed a molecular ion at *m/z* 470 with other significant fragment peaks at *m/z* 411 (M - $CO_2Me$, base) and 383 (M - $CO_2Me$ - $CH_2{=}CH_2$). HREIMS measurements[2] gave the formula $C_{24}H_{26}N_2O_8$. The $^{13}C$ NMR spectrum showed a total of 24 carbon resonances, in agreement with the formula derived from the molecular ion. The $^1H$ and $^{13}C$ NMR spectral data (Table 1) showed the presence of a methylenedioxy substituent at carbon-11 and -12 (an AB doublet at $\delta_H$ 6.02, 5.97, *J* 1.5 Hz, $\delta_C$ 100.9), a $CO_2Me$ substituent at $N_1$ ($\delta_C$ 153.4), a ketonic carbonyl ($\delta_C$ 206.7), an ester function ($\delta_C$ 170.2) and another carbonyl function associated with a formamide group ($\delta_H$ 6.68, $\delta_C$ 165.7; IR 1669 $cm^{-1}$).[3] COSY and HMQC experiments revealed the presence of the following partial structures, *viz.*, 2 isolated methylene groups, a $CCH_2CH_2C$ unit and a $CCH_2CH_2CH_2N$ fragment. The NMR data indicate that compound **1** possesses some of the features common to a basic aspidofractinine skeleton and is in some respects similar to that of the methylchanofruticosinate **2** (see Table 1) which is the major

0040-4039/98/$19.00 
*PII:* S0040-4039(98)01150-2

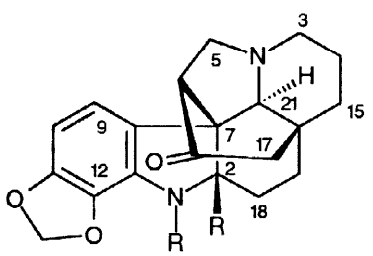
alkaloid present in the leaves, and which has been obtained previously from various *Kopsia* species.[4,5] There are however some notable differences. One major difference is the absence of signals due to the C(5)-C(6) unit and the appearance instead of an additional isolated methylene which is adjacent to a carbonyl function ($\delta_H$ 2.40, 2.74). That this methylene (C-6) is bridged by a ketonic function (C-16) to another isolated methylene (C-17) is indicated by the observation in the COSY spectrum of long range coupling ($^4J$, W) from one of the H-6 to one of the H-17. Except for this long range coupling, and the expected geminal coupling, the hydrogens of both the C-6 and C-17 methylenes show no other coupling to any adjacent proton, providing confirmation that they are linked to quaternary centres. The direct attachment of the C-6 methylene to C-7 is supported by the correlation from C-7 to H-6 in the HMBC spectrum. Likewise, a similar correlation from



**1** R = $CO_2Me$

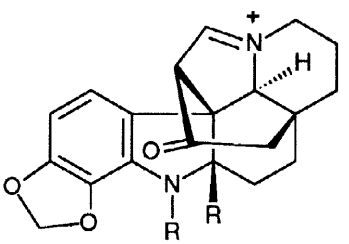


**3**



**2** R = $CO_2Me$

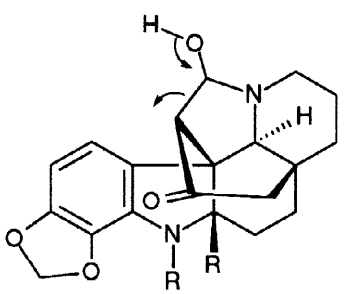
[O]



**4**

$H_2O$

$(-H^+)$



**5**

retro-aldol

$H_2O$

**1**

C-20 to H-17 confirmed the direct attachment of the C-17 methylene to the quaternary C-20. Another major difference shown by compound **1** when compared with **2** is the appearance of a formamide function ($\delta_H$ 6.68, $\delta_C$ 165.7),[3] which from the HMBC data is deduced to be at position-5 ($^3J$, C-5 to H-3, H-21). The location

of a formamide function at position-5 is also consistent with the unusual deshielding observed for H-3β ($\delta_H$ 4.57) as a result of the anisotropy due to the proximate formamide carbonyl function, which has been observed previously in other compounds.[6] These observations and other correlations from HMBC experiments (Table 1) suggest structure **1** for the new compound which represents a novel skeletal arrangement in which a new 6-membered ring incorporating C-7, -6, -16, -17, -20 and -21 has been formed by cleavage of the C-5/C-6 bond of the precursor compound **2**. Compound **1** can thus be considered a "*seco*-methylchanofruticosinate" and represents the first member of this novel group obtained as a natural product. Irradiation of the H-21 resonance causes NOE enhancement of the formamide resonance and *vice-versa*, indicating that the H-21 and the *N*-4 lone pair are now in a *trans* arrangement, in contrast to the conformation adopted in other aspidofractinine compounds such as kopsingine[7] and the methylchanofruticosinate **2**.[4]

Table 1. $^1$H and $^{13}$C NMR Spectral Data[a] for **1** and **2**[b]

| Position | $\delta_C$(**2**) | $\delta_C$(**1**) | $\delta_H$ (**1**) | HMBC (**1**) $^2J$ | HMBC (**1**) $^3J$ |
|---|---|---|---|---|---|
| 2 | 76.0 | 79.1 | - | 18 | 6, 19 |
| 3α | 46.5 | 34.7 | 2.70 m | 14 | 5, 15, 21 |
| 3β | - | - | 4.57 dd (14.5, 9.5) | - | - |
| 5 | 52.5 | 165.7 | 6.68 s | - | 3, 21 |
| 6α | 55.5 | 39.3 | 2.40 br d (17) | - | 17, 21 |
| 6β | - | - | 2.74 d (17) | - | - |
| 7 | 58.4 | 54.5 | - | 6, 21 | 9, 18 |
| 8 | 129.1 | 125.0 | - | 9 | 6, 10, 21 |
| 9 | 116.9 | 117.0 | 6.35 d (8) | - | - |
| 10 | 103.4 | 103.6 | 6.56 d (8) | - | - |
| 11 | 149.0 | 150.4 | - | 10 | 9, $OCH_2O$ |
| 12 | 133.9 | 134.9 | - | - | 10, $OCH_2O$ |
| 13 | 124.1 | 124.9 | - | - | 9 |
| 14a | 17.5 | 19.3 | 1.73 m | 3, 15 | - |
| 14b | - | - | 1.95 m | - | - |
| 15a | 35.3 | 29.6 | 1.29 dt (13.5, 9) | 14 | 3, 17 |
| 15b | - | - | 1.65 m | - | - |
| 16 | 208.1 | 206.7 | - | 6, 17 | - |
| 17a | 43.1 | 46.1 | 2.48 d (20) | - | 6, 15, 19, 21 |
| 17b | - | - | 2.72 d (20) | - | - |
| 18a | 23.5 | 23.0 | 2.36 ddd (16.5, 12, 8) | 19 | 15 |
| 18b | - | - | 3.28 dt (16.5, 3.5) | - | - |
| 19a | 34.9 | 39.4 | 1.65 m | 18 | 17 |
| 19b | - | - | 1.65 m | - | - |
| 20 | 36.0 | 34.5 | - | 15, 17, 19, 21 | - |
| 21 | 68.5 | 61.5 | 3.38 s | - | 3, 5, 6, 15, 19 |
| $OCH_2O$ | 100.7 | 100.9 | 5.97 d (1.5); 6.02 d (1.5) | - | - |
| $NCO_2Me$ | 52.6 | 53.1 | 3.88 s | - | - |
| $NCO_2Me$ | 153.0 | 153.4 | - | - | OMe |
| $CO_2Me$ | 53.0 | 53.0 | 3.63 s | - | - |
| $CO_2Me$ | 170.9 | 170.2 | - | - | 18, OMe |

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC and NOE; [b] $^{13}$C NMR data only

Examination of models indicates that there should be considerable hindrance to free rotation about the formamide C-N bond due to the proximity of the formamide function to the aromatic ring.[8] Rotation about the C-N bond would result in severe repulsive interactions as the π-electron density of the formamide C=O as well as that of the 2 lone-pairs of the oxygen are brought into undue proximity with the π-electron density of the aromatic system. For this same reason a preferred conformation appears to have been adopted such that the formamide carbonyl is directed away from the aromatic ring, which in turn results in the formamide-H being placed within the shielding zone of the aromatic ring current, thus accounting for the unusually high field resonance observed for the formamide-H. Additional confirmation of the structure is provided by reduction ($NaBH_4$/MeOH, 3 h, 30 °C) of **1** which yielded a single product **3**. The hydroxymethyl protons of **3** are clearly seen as a pair of AB doublets (δ 3.21, 3.84; *J* 10.6 Hz) as is the H-16 oxymethine which is seen as a doublet of doublets at δ 4.32 (*J* 9, 7 Hz). The correlations observed from the hydroxymethyl protons to C-2 ($^2J$) as well as to C-7 and C-18 ($^3J$) provided confirmation for the attachment of the ester function at C-2 in danuphylline **1**. Furthermore, the three bond correlation from H-16 to C-7 and C-20 in the HMBC spectrum of **3** provided further confirmation for the location of the C-16 carbonyl function in danuphylline **1**.

A possible origin of this ring-opened alkaloid[3,9] is from the methylchanofruticosinate **2** which on oxidation provides the iminium ion **4**. Hydrolysis of this iminium ion **4** gives, the presumably unstable carbinolamine **5**, which could then undergo a retro-aldol-type reaction to provide the *seco*-compound, danuphylline **1**. We have succeeded in realising such a biomimetic conversion of **2** to **1** based on the above proposal *via* the electrochemically-generated iminium ion **3**[10] which will be reported in a forthcoming submission.

**Acknowledgements** : We would like to thank the University of Malaya and IRPA for financial support.

## References and Notes

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2. HREIMS found, *m/z* 470.1694 (calcd for $C_{24}H_{26}N_2O_8$, 470.1689).
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6. Kam, T. S., Yoganathan, K. and Chen Wei. *Tetrahedron Lett.*, **1996**, *37*, 3603.
7. Kam, T. S., Yoganathan, K., Chuah, C. H. and Chen Wei, *Phytochemistry*, **1993**, *32*, 1343.
8. In the spectrum obtained at ambient temperature there is no evidence of the presence of a second rotamer. The spectrum obtained at 55 °C was essentially unchanged indicating the barrier to rotation to be rather high.
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