A NewN,N-Dimethyl Purine from an AustralianDictyoceratidSponge

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ORIGINAL PAPER

A New *N,N*-Dimethyl Purine from an Australian *Dictyoceratid Sponge*

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Abstract N6-methyl mucronatine ($C_8H_{12}N_5O$) has been isolated from a dictyoceratid sponge collected in South East Queensland. The solid state structure of the new metabolite (I) was confirmed by X-ray crystallography, while an NMR study in d_4-MeOH reveals the presence of a minor tautomer identified as (II).

Keywords Purine · Marine sponge · Tautomer

Introduction

A number of purine derivatives have been reported from marine organisms, including marine sponges [1–12], sea anemones [13, 14], and ascidians [15–17]. Interesting biological properties have also been reported for these purines, including cytotoxicity [3, 6], antiangiogenic activity [10], cdc2 kinase inhibition [11] and antifouling activity [8]. More recently the neuroactive effects of selected purines have been described [1]. In the search for new secondary metabolites from marine sponges from South East Queensland, we recently isolated a new purine derivative whose structure was revealed as tautomer I (Scheme 1) by X-ray diffraction analysis. However, an NMR study established that the purine is a mixture of tautomers I and II in solution.

Experimental

Isolation and Purification

A single specimen (code 18-7-09-2-1a) of a pale yellow encrusting Dictyoceratid sponge was collected using SCUBA on 18th July 2009 at a depth of 10–12 m from the Caves dive site, inner Gneerings shoals, near Mooloolaba in South East Queensland, and then frozen for transport to Brisbane. Subsequent identification of the sponge specimen to genus level was not possible owing to the small size of the voucher sample. Frozen sponge (3.8 g wet wt.) was diced and extracted with DCM:MeOH (1:1, 2 × 15 mL). The DCM layer was removed, dried with anhydrous Mg_2SO_4, then evaporated to dryness under a N_2 stream to afford a viscous yellow oil (17.6 mg). The organic extract was then subjected to SiO_2 flash chromatography with gradient elution (hexanes → EtOAc) followed by recrystallization in a 4 mL vial from MeOH using the vapor diffusion technique (with a small volume of EtOAc in an outer chamber) to give the new purine (7.5 mg, m.p. 226–228 °C). The metabolite can be named as either N3, N6-dimethyl-2-methoxyadenine or, less systematically, as the N6-methyl derivative of the known sponge metabolite mucronatine [8].

HRESIMS $(M + H)^+$ calcd. for $C_8H_{12}N_5O$, 194.1036. Found: 194.1045. Gradient-enhanced HSQC (900 MHz, $^1J_{CH}$ 145 Hz) and HMBC (900 MHz, $^nJ_{CH}$ 8 Hz) were used in NMR structure analysis. The C-atom numbering is as shown for I in Fig. 1: for tautomer I ^1H NMR (MeOH-d_4) δ 3.17 (3H, s, N6-CH_3), 3.76 (3H, s, N3-CH_3), 4.18

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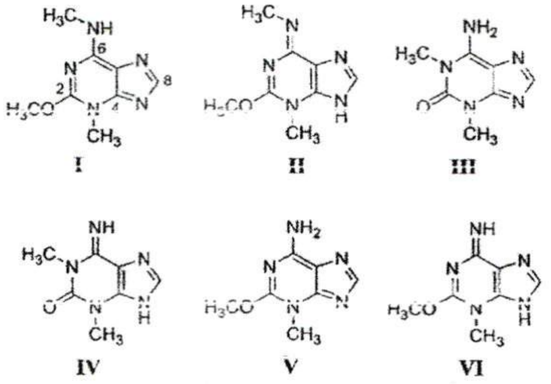

Scheme 1 The two tautomeric forms ((I) and (II)) of N6-methyl mucronatine and the equivalent tautomeric forms for 1,3-dimethyl-isoguanine ((III) and (IV)) and for mucronatine ((V) and (VI))

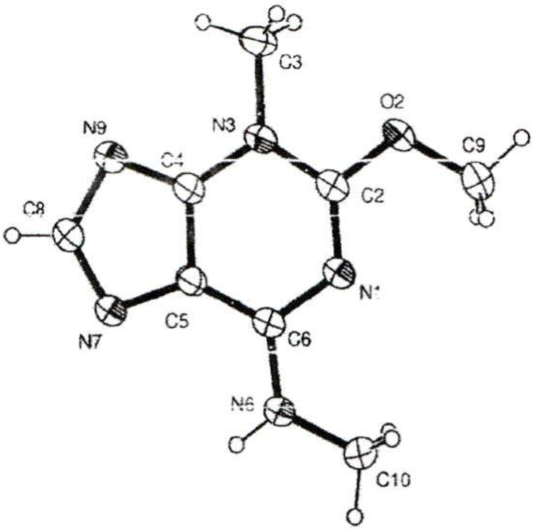

Fig. 1 ORTEP plot of compound (I) (30% probability ellipsoids). The C-atom numbering is the same as that used in the NMR assignments

(3H, s, OCH_3), 7.73 (1H, br s, H8); ^{13}C NMR (MeOH-d_4) δ 28.0 (N6-CH_3), 32.0 (N3-CH_3), 57.2 (2-OCH_3), 116.4 (C5), 152.0 (C8), 154.2 (C4), 154.6 (C2), 155.3 (C6). HMBC: -OCH_3 to C2, N3-CH_3 to C2, N6-CH_3 to C6, H8 to C4 and C5. For tautomer II, partial data ^{1}H NMR (MeOH-d_4) δ3.42 (3H, s, N6-CH_3), 3.72 (3H, s, N3-CH_3), 4.08 (3H, s, OCH_3). ^{13}C NMR (MeOH-d_4) δ31.0 (N6-CH_3), 31.8 (N3-CH_3), 56.9 (2-OCH_3), 153.3 (C2), 153.7 (C4), 155.7 (C6). HMBC: N3-CH_3 to C2 and C4, N6-CH_3 to C6. Signals for H8 and for C5 and C8 were not observable.

Physical Methods

1D and 2D NMR spectra were acquired on a Bruker AV III-900 instrument fitted with a TCI triple resonance cryoprobe (5 mm) at room temperature. Spectra were measured in MeOH-d_4 and chemical shifts (δ) were referenced internally to MeOH (δ_H 3.30 or δ_C 49.0). Positive ion electrospray mass spectra (LRESMS) were determined using a Bruker Esquire HCT instrument or (HRESMS) using a MicroTOF Q instrument each with a standard ESI source. Samples were introduced into the source using MeOH as solvent Table 1.

Structure Determination and Refinement of (I)

Intensity data were acquired on a non-merohedrally twinned specimen of (I) on an Oxford Diffraction Gemini CCD diffractometer with Cu-Kα radiation and operating in the ω scan mode. Data reduction was performed resolving both twin components with the CrysAlisPro package (Oxford Diffraction vers. 171.33.42). The structure was solved with data taken from the major twin component and then refinement of both twins was carried out with SHELXL [18]. All non-H atoms were refined anisotropically whereas H-atoms were included in calculated positions and constrained using a riding model. All calculations were performed with the WinGX package [19]. The thermal ellipsoid diagram was drawn with ORTEP3 [20] while packing diagrams were produced with PLUTON [21].

Results and Discussion

The new purine was isolated as a colourless powder which was further recrystallised from MeOH using the vapor diffusion method. The HRESIMS exhibited a molecular ion at m/z 194.1045 (M + H) corresponding to the molecular formula $C_8H_{12}N_5O$. Inspection of the ^{1}H NMR revealed the presence of two *N*-methyl signals (δ_H 3.17 and 3.76), a methoxy group (δ_H 4.18) and an isolated methine signal (δ_H 7.73, br s), which suggested a purine derivative [8, 17]. NMR assignments were made by comparison with data for other purines [5, 8, 12], and from 2D NMR data. In both the ^{1}H and ^{13}C NMR spectra, a second set of purine signals were observed. For this minor component, unobserved resonances for H8, C5 and C8 presumably overlap with corresponding signals of the major species. The NMR data suggested that the metabolite exists as a mixture of tautomers in solution, inferred to be (I) and (II) (Scheme 1), in a ratio of ~8:1 in solution. No N–H ^{1}H NMR signals were observed due to exchange with the solvent (MeOH-d_4). ^{15}N NMR work, not pursued here, could also provide a way of resolving the two tautomers.

Table 1 Crystal data

CCDC deposition number	817620
Formula	$C_8H_{11}N_5O$
Formula weight	193.21
Temperature	293 K
Wavelength	1.54180 Å
Crystal system	triclinic
Space group	$P\bar{1}$ (no 2)
Unit cell dimensions	$a = 7.164(1)$ Å
	$b = 7.418(1)$ Å
	$c = 8.952(1)$ Å
	$\alpha = 79.71(1)°$
	$\beta = 73.47(1)°$
	$\gamma = 85.32(1)°$
Volume	448.5(1) Å^3
Z	2
Density (calculated)	1.431 g cm^{-3}
Absorption coefficient	0.845 mm^{-1}
F(000)	204
Crystal size	0.15 × 0.10 × 0.10 mm
Theta range for data collection	5.22[illegible]2.4°
Index ranges	$-8 \leq h \leq 8$, $-8 \leq k \leq 8$, $-10 \leq l \leq 10$
Reflections collected	6,159
Independent reflections	6,159 [R(int) = 0.0]
Observed reflections	3,489
Completeness to theta = 62.4°	99.7%
Goodness-of-fit	0.896
Final R indices	$R_1 = 0.0619$ (obs. data), $wR_2 = 0.1736$ (all data)
Largest difference between peak and hole	0.26 and −0.25 e.Å^{-3}

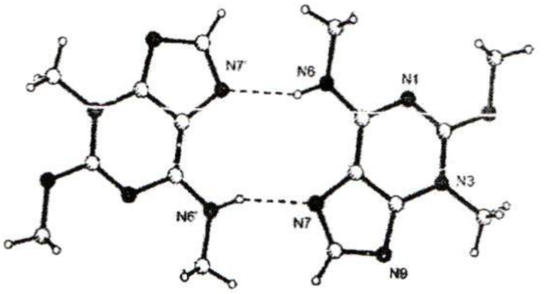

Fig. 2 PLUTON plot of the centrosymmetric H-bonded dimers of (I)

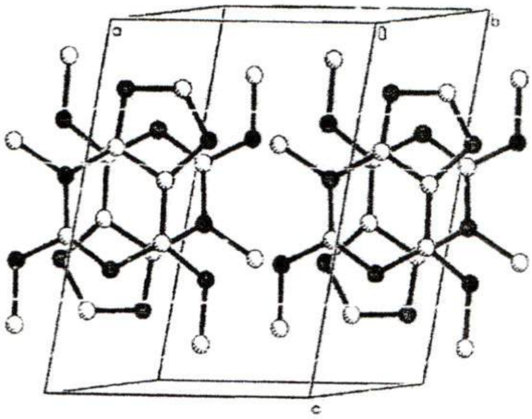

Fig. 3 PLUTON plot showing stacking of the purine rings in the structure of (I) (H-atoms omitted)

Structure determination of methylated purines by spectroscopic methods alone can often be ambiguous [1], and does not always provide insight into the tautomeric composition of the metabolite. For example, for 1,3-dimethylisoguanine (III/IV) or its trihydrate, different tautomeric forms were deduced by NMR and by X-ray crystallographic analysis; the major tautomeric form has been shown to be III by X-ray analysis [7, 12] rather than IV deduced from NMR study [4, 5]. In contrast, for mucronatine (V/VI, Scheme 1) NMR investigations have confirmed tautomer V rather than VI in solution [7, 8].

In order to confirm the solid state structure of the isolated purine, its crystal structure was determined. The ORTEP diagram of tautomer (I) is apparent in Fig. 1. This corresponds with the major tautomer identified in solution by NMR. The H-atoms were all identified during refinement thus unequivocally confirming that tautomer (I) is the form present in the solid state. The purines form centrosymmetric H-bonded dimers (Fig. 2) comprising pairs of symmetry related N6-H...N7′ contacts (N6-[illegible].N7′ 2.14 Å, N6...N7′ 2.946(2) Å, N6-H...N7′ 156.5°, symmetry operation $-x-1, -y+1, -z+1$). The purines also stack in an expected anti-parallel fashion (Fig. 3) with an interplanar separation of 3.37 Å.

Although numerous *N*-methylated purines are documented in the natural products literature, mucronatine and the N6-methyl analogue reported here represent rare examples of purines with a 2-methoxy group. Our data also indicate a preference for the amino tautomer rather than the imino tautomer in both solution and the solid state.

Supplementary Material

Crystallographic data reported in this paper have been deposited with the Cambridge Data Centre (CCDC deposition number 817620). The data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ (email deposit@ccdc.cam.ac.uk).

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