MODEL EXPERIMENTS FOR ACETYLATION OF THE MARINE SPONGE PURINES AGELASIMINE-A AND AGELASIMINE-B

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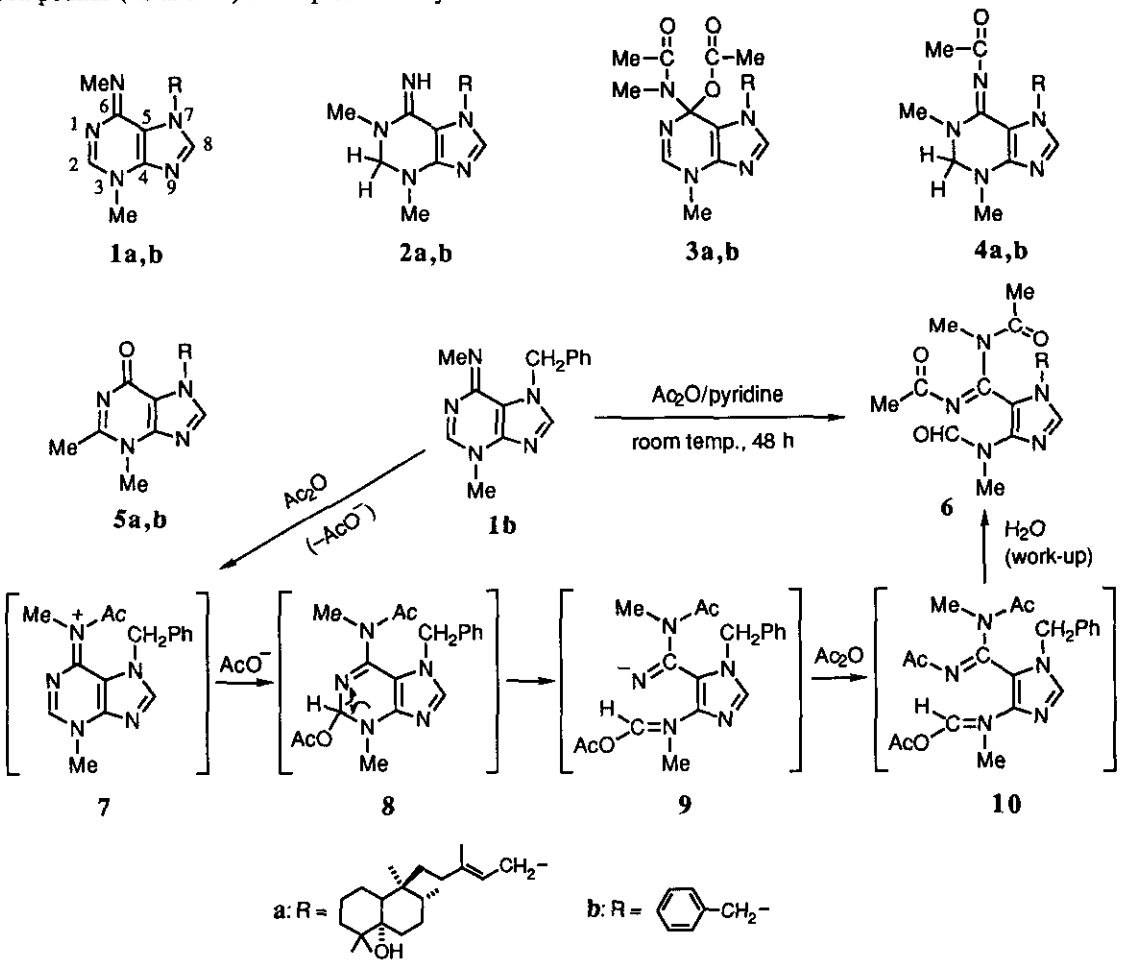
Abstract——Reactions of 7-benzyl-N^6,3-dimethyladenine (**1b**) and 7-benzyl-1,2-dihydro-1,3-dimethyladenine (**2b**), selected as models for the marine sponge alkaloids agelasimine-A (**1a**) and agelasimine-B (**2a**), with acetic anhydride in pyridine have been studied. The product from **1b** was the imidazole derivative (**6b**), whose structure was determined by an X-ray crystallographic analysis. The product from **2b** was the N^6-acetyl derivative (**4b**). On treatment with boiling H_2O, **4b** gave 7-benzyl-2,3-dimethylhypoxanthine (**5b**) and a compound presumed to be **11**.

In 1988, Fathi-Afshar and Allen reported the isolation of the novel adenine-related bicyclic diterpenoids agelasimine-A (**1a**) and agelasimine-B (**2a**), along with three bromine-containing alkaloids, from the orange sponge *Agelas mauritiana*.[1] Agelasimine-A and -B exhibit a wide range of interesting biological activities,[1,2] and their chemical structures have been proposed on the basis of interpretation of their spectral data.[1] We recently synthesized 7-benzyl-N^6,3-dimethyladenine (**1b**) and 7-benzyl-1,2-dihydro-1,3-dimethyladenine (**2b**), selected as models for **1a** and **2a**, respectively, *via* four-step routes starting from 3-methyladenine.[3] The model compounds (**1b** and **2b**) were found to bear similarity in ^{1}H and ^{13}C nmr spectra[4] to agelasimine-A and agelasimine-B, respectively, supporting the correctness of the substitution patterns of the adenine moieties in structures (**1a**) and (**2a**) proposed for these marine alkaloids.[3]

The Canadian authors further described the reactions of **1a** and **2a** with acetic anhydride in pyridine to form diacetylagelasimine-A and N^6-acetylagelasimine-B (**4a**), respectively.[1] On the basis of ms and ^{1}H nmr spectral

data, they assigned structure (**3a**) to diacetylagelasimine-A, although its exact nature has not been firmly established (mixture of isomers).[1] Since structure (**3a**) is unique in that it corresponds to a very reactive tetrahedral intermediate, presumably difficult to isolate, in the acetolysis of the C(6)=NMe group in **1a**, the correctness of their assignment should be verified. This led us to investigate similar acetylations of our model compounds (**1b** and **2b**) in the present study.



Scheme 1

The model compound (**1b**) was first treated with an excess of acetic anhydride in pyridine at room temperature for 48 h (Scheme 1). The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. Purification of the CH_2Cl_2-soluble product by means of flash chromatography[5] [silica gel, CH_2Cl_2–EtOH (20:1, v/v)] gave a 1:1 adduct ($C_{14}H_{15}N_5 \cdot C_4H_6O_3$) of **1b** and acetic anhydride in 10% yield as almost colorless prisms, mp 152–153.5°C.[6,7] Provided the addition of acetic anhydride has occurred only in the pyrimidine moiety, the isomeric structures (**3b**), (**8**), and (**6b**) would be candidates for the

adduct. However, it was difficult to determine which structure is correct on the basis of the spectral data alone. We therefore subjected the adduct to an X-ray crystallographic analysis and were able to establish its structure to be the monocycle (**6b**).

For the X-ray analysis, colorless transparent prisms of the above adduct (**6b**) were grown from AcOEt–tetrahydrofuran. A crystal measuring 0.20 × 0.20 × 0.10 mm was selected out of them and used for all data collection. Unit cell constants and intensity data were obtained with a Rigaku AFC-5R automatic diffractometer using graphite-monochromated Cu $K\alpha$ radiation (λ = 1.5418 Å). The unit cell dimensions were determined from angular settings of 25 2θ-values in the range of 85–90°, affording the following crystal data: a = 7.921(2) Å; b = 20.281(2) Å; c = 11.537(2) Å; α = 90.00(0)°; β = 99.31(2)°; γ = 90.00(0)°; U = 1829.1(5) Å^3; space group $P2_1/n$; Z = 4; D_x = 1.290 g/cm^3; $F(000)$ = 752; μ(Cu $K\alpha$) = 0.756/mm. Out of 2717 unique reflections ($0° \le 2\theta \le 120°$) measured by using the $\omega/2\theta$ scan technique at a rate of 16°/min, 1907 without $|F_{obs}| = 0$ were considered unique and observed. No absorption corrections were applied. The structure was solved by a direct method using the program SHELXS-86[8] and the difference Fourier method. Refinement of atomic parameters was carried out using the full-matrix least-squares method with anisotropic temperature factors. All hydrogen atoms were clearly located on difference Fourier maps and refined with isotropic temperature factors. Throughout the refinement, the function $\sum w(|F_o| - |F_c|)^2$ was minimized, and the weight used during the final refinement stage was $\sqrt{w} = 1/\sigma(F_o)$; the final R value, 0.0680 (R_w = 0.0660). The atomic scattering factors were taken from the literature.[9] Figure 1 shows a computer-generated[10] drawing of the final X-ray model and

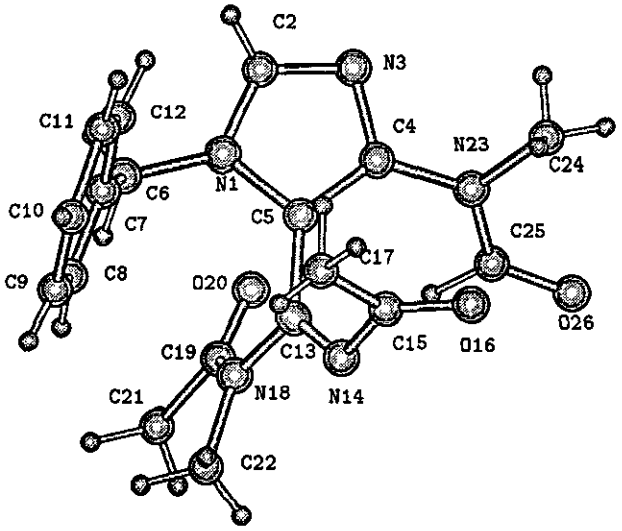
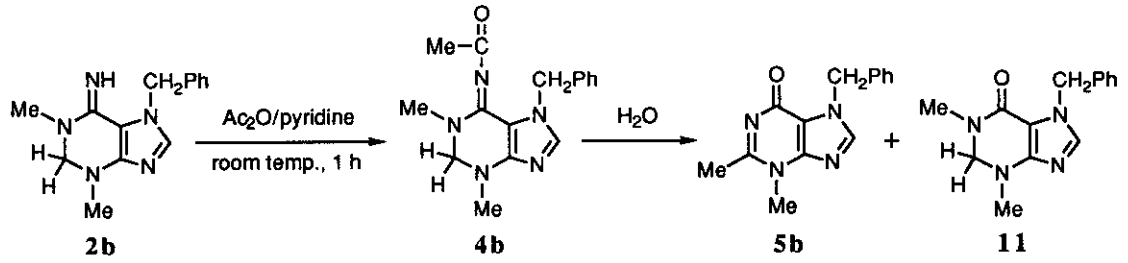


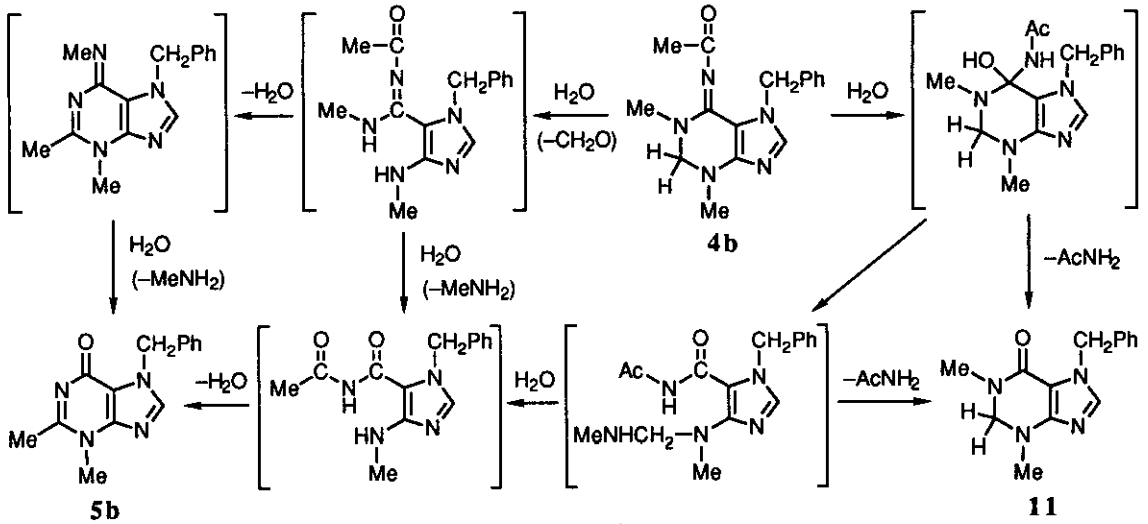
Figure 1. A Parallel View of the Molecular Structure of the Adduct (**6b**) and the Numbering Scheme Employed

the atomic numbering for the adduct (**6b**). It may be seen that the adduct (**6b**) is an imidazole-5-carboxamidine derivative bearing an *N*-methylformamido group at C(4), two acetyl groups attached separately to N(14) and N(18) in the amidine moiety, and a benzyl group at N(1).

The ^{1}H nmr spectrum of **6b** in $CDCl_3$ at 27°C showed two sets of signals, all with a 3:1 ratio of relative integral intensities, for most of the different species of protons.[6] Similar two sets of signals were also observed in Me_2SO-d_6 at 27°C, but they coalesced into one set at 100°C. The complexity of these signals is probably a result of *cis–trans* equilibration of the amido groups, most likely that of the *N*-methylformamido group, as we have experienced previously in similar structures.[11] The formation of **6b** from **1b** by acetylation may be assumed to proceed through the intermediates (**7**, **8**, **9**, and **10**) as shown in Scheme 1. Thus, it is likely that "diacetylagelasimine-A" obtained by a similar acetylation of agelasimine-A (**1a**) has the analogous structure (**6a**) instead of the proposed[1] purine structure (**3a**).



Scheme 2



Scheme 3

We next studied the acetylation of **2b**, a model for agelasimine-B (**2a**). Treatment of **2b** with an excess of acetic anhydride in pyridine at room temperature for 1 h, work-up of the reaction mixture in a manner similar to that described above for the acetylation of **1b**, and purification of the CH_2Cl_2–soluble product by flash chromatography[5] [silica gel, CH_2Cl_2–EtOH (5:1, v/v)] furnished the N^6-acetyl derivative (**4b**) [mp 130–135.5°C (decomp.)][12] in 80% yield (Scheme 2). The ^1H nmr spectrum of **4b** in $CDCl_3$[12] was similar to that of **4a**,[1] except for signals arising from the N(7)-substituent. On treatment with boiling H_2O, **4b** produced 7-benzyl-2,3-dimethylhypoxanthine (**5b**) (mp 199.5–201°C)[13] and a compound inferred to be **11**[14] in 23% and 35% yields, respectively. The formation of **5b** and **11** from **4b** may be explained in terms of the sequences of reactions depicted in Scheme 3. Interestingly, **5b** was found to be a minor product in the above acetylation of **2b** and was obtained more efficiently (64% yield) when **2b** was treated with acetic anhydride in the absence of pyridine at room temperature for 50 h.

In conclusion, **4b** and **5b** correspond to N^6-acetylagelasimine-B (**4a**) and the artifact purino-diterpene (**5a**), both isolated by Faulkner and co-workers[15] from the acetylated mixture of the crude extract of the same sponge (*Agelas mauritiana*).[1] Therefore, the present results may suggest that **5a** originated from agelasimine-B (**2a**) through N^6-acetylagelasimine-B (**4a**). They also suggest that the structure of "diacetylagelasimine-A" is not **3a**, but **6a**.

ACKNOWLEDGMENT

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3. T. Saito, J. Chikazawa, Y. Nakamura, and T. Fujii, *Heterocycles*, 1993, **35**, 143.
4. Except for signals arising from the N(7)-substituent.
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6. Recrystallized from AcOEt. Selected spectral data: ms *m/z*: 355 (M^+); uv $\lambda_{max}^{95\%\ aq.\ EtOH}$ 241 nm (sh) (ε 11300); $\lambda_{max}^{H_2O}$ (pH 1) 266 (4900); $\lambda_{max}^{H_2O}$ (pH 7) 240 (sh) (10300); $\lambda_{max}^{H_2O}$ (pH 13) 245 (9700); ir ν_{max}^{Nujol} cm^{-1}: 1692, 1670, and 1615 (amide CO's); ^1H nmr ($CDCl_3$) [major and minor peaks (3:1 in relative integral intensity)] δ: 2.03 and 2.10 (or 1.96) (3H, s each, COMe), 2.07 and 1.96 (or 2.10) (3H, s each, COMe), 2.96 and 2.95 (3H, s each, NMe), 3.25 and 3.37 (3H, s each, NMe), 5.23 and 5.16 (2H, s each, CH_2Ph), 7.2–7.5 (6H, m, CH_2Ph and imidazole ring proton), 8.25 and 8.17 (1H, s each, HCON).
7. Satisfactory analytical and/or spectroscopic data have been obtained for all of the new compounds reported herein.

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9. J. A. Ibers and W. C. Hamilton (eds.), 'International Tables for X-ray Crystallography,' Vol. IV, Kynoch Press, Birmingham, 1974.
10. A Sony NEWS-3860 computer was employed.
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12. Selected spectral data for **4b**: uv λ_{max}^{MeOH} 226 nm (sh) (ε 11100), 258 (7700), 347 (6800); $\lambda_{max}^{95\%\ aq.\ EtOH}$ 225 (sh) (11700), 258 (7900), 347 (7300); $\lambda_{max}^{H_2O}$ (pH 1) 229 (sh) (7500), 272 (7700), 377 (6500); $\lambda_{max}^{H_2O}$ (pH 7) 227 (sh) (10000), 257 (8600), 355 (6800); $\lambda_{max}^{H_2O}$ (pH 13) 224 (sh) (10000), 256 (8400), 354 (6500); ir $\nu_{max}^{CHCl_3}$ 1600 cm^{-1} (amide CO); ^1H nmr ($CDCl_3$) δ: 2.14 (3H, s, COMe), 2.97 and 3.04 (3H each, s, NMe's), 4.41 [2H, s, C(2)-H's], 5.40 (2H, s, CH_2Ph), 7.2–7.4 [6H, m, CH_2Ph and C(8)-H]; hrms calcd for $C_{16}H_{19}N_5O$: 297.1589, found: 297.1585.
13. Selected spectral data for **5b**: ms *m/z*: 254 (M^+); uv λ_{max}^{MeOH} 221 nm (sh) (ε 14000), 268 (11900); $\lambda_{max}^{H_2O}$ (pH 1) 257 (11200); $\lambda_{max}^{H_2O}$ (pH 7) 267 (12300); $\lambda_{max}^{H_2O}$ (pH 13) 267 (12200); ir ν_{max}^{Nujol} 1640 cm^{-1} (CO); ^1H nmr (Me_2SO-d_6) δ: 2.46 [3H, s, C(2)-Me], 3.74 [3H, s, N(3)-Me], 5.57 (2H, s, CH_2Ph), 7.2–7.4 (5H, m, CH_2Ph), 8.30 [1H, s, C(8)-H].
14. Selected spectral data: ms *m/z*: 256 (M^+); ir ν_{max}^{Nujol} 1640 cm^{-1} (CO); ^1H nmr ($CDCl_3$) δ: 2.92 and 2.98 (3H each, s, NMe's), 4.30 [2H, s, C(2)-H's], 5.42 (2H, s, CH_2Ph), 7.2–7.4 [6H, m, CH_2Ph and C(8)-H].
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