ACETYLATIONS OF (+)-AGELASIMINE-A AND (+)-AGELASIMINE-B: A RACEMIC SYNTHESIS OF PURINO-DITERPENE DERIVED FROM ANTIMICROBIAL METABOLITES OF AGELAS MAURITIANA

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Abstract —— The reaction of (+)-agelashine-A [(±)-3a] with acetic anhydride in pyridine yielded the imidazole derivative [(±)-5a], which was found to correspond to “diacetylagelasimine-A”. A similar acetylation of (+)-agelasimine-B [(±)-4a] provided (±)-7a and (±)-2a. On treatment with boiling 50% aqueous EtOH, (±)-7a gave (±)-2a and the dihydrohypoxanthine derivative [(±)-8a]. It is suggested that purino-diterpene (2a), isolated from the acetylated mixture of the crude extract of the sponge *Agelas mauritiana*, might have originated from agelasimine-B (4a) through N6-acetylagelasimine-B (7a).

Since the isolation and partial structural elucidation of agelasine (1), a novel quaternary 9-methyladenine derivative of an unidentified diterpene from the sponge *Agelas dispar*, were reported by Cullen and Devlin in 1975,1 a number of adenine-related diterpenoids have been isolated from certain genera of marine sponges.2,3 In 1984, Faulkner and co-workers announced the structure of purino-diterpene (2a), an artifact separated from the acetylated mixture of the crude extract of the Enewetak sponge *Agelas mauritiana*, on the basis of an X-ray crystallographic analysis.4 Thereafter Fathi-Afshar and Allen isolated agelasimine-A and agelasimine-B from the same sponge (*A. mauritiana*) and deduced that their structures are 3a and 4a, respectively, possessing the same diterpene portion as that of 2a, as a result of extensive spectral studies.3 The correctness of these structures and relative stereochemistries has been unequivocally confirmed by our recent success in synthesizing the racemic candidate structures [(±)-3a and (±)-4a].5 In
this communication, we wish to describe the acetylations of (±)-3a and (±)-4a, the latter of which have led to the formation of purino-diterpene [(±)-2a].

In connection with the structure determination of the above two marine sponge diterpenoids, Fathi-Afshar and Allen further described the reactions of 3a and 4a with acetic anhydride in pyridine to form diacetyl-agelasimine-A and N6-acetylagelasimine-B (7a), respectively. On the basis of ms fragmentation and 1H nmr spectral data, they applied structure (6a) to diacetyl-agelasimine-A, although its exact nature has not been firmly established (mixture of isomers). In order to check the structure of diacetyl-agelasimine-A, (±)-3a was first treated with an excess of acetic anhydride in pyridine at room temperature for 44 h according to the reported procedure, affording a 1 : 1 adduct of (±)-3a and acetic anhydride in 54% yield as a glassy material. The 1H nmr spectrum of the adduct in CDCl₃ at 27°C showed two sets of signals, all with a 3 : 1 ratio of relative integral intensities, for many different species of protons. Similar two sets of signals observed in Me₂SO-d₆ at 27°C coalesced into one set at 100°C. We have already reported that the acetylation of the N(7)-benzyl analogue (3b) produced the imidazole derivative (5b), whose structure was definitely determined on the basis of an X-ray crystallographic analysis, and that 5b exhibited a similar 1H nmr spectral behavior, presumed to be a result of cis-trans equilibration of the N-methylformamide group at C(4). Therefore, structure [(±)-5a] was assignable to the adduct. A set of signals arising from the major geometrical isomer in the 1H nmr spectrum (CDCl₃) of (±)-5a was found to be virtually identical with the data reported for diacetyl-agelasimine-A. Thus, the structure of “diacetyl-agelasimine-A” prepared by a similar acetylation of agelasimine-A (3a) should be represented not by the proposed purine form (6a), but by the monocyclic imidazole form (5a).

We next investigated the acetylation of (±)-agelasimine-B [(±)-4a]. On treatment with an excess of acetic anhydride in pyridine at room temperature for 1 h, (±)-4a provided (±)-7a in 48% yield. The ms and 1H
nmr spectra (CDCl₃) of (+)-7a were in agreement with those of N⁶-acetylagelasimine-B described in the literature.³ Elongation of the reaction time from 1 h to 50 h led to the formation of (+)-2a (mp 178.5–180.5°C)⁹ in 60% yield together with (+)-7a in 15% yield. A parallel result was also obtained from the acetylation of (+)-4a in the absence of pyridine. When treated with boiling 50% aqueous EtOH, (+)-7a was converted to (+)-2a and the dihydrohypoxanthine derivative [(+)8a] in 22% and 39% yields, respectively.⁸ The ¹H nmr spectral data for (+)-2a thus synthesized were virtually identical with those reported selectively for purino-diterpene⁴ (isolated from the acetylated mixture of the crude extract of the sponge Agelas mauritiana).

Finally, oxidation of (+)-4a⁵ with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CHCl₃ at room temperature for 1 h, followed by successive treatment with 10% aqueous HCl and 10% aqueous NaOH, provided (+)-3a in 43% yield. This transformation may imply the possibility of a biosynthetic pathway from agelasimine-B (4a) to agelasimine-A (3a).

In conclusion, the present results have emphasized the propriety of our previous suggestion⁷ that purino-
diterpene (2a) might have been derived from agelasimine-B (4a) through N6-acetylagedasimine-B (7a). They have also disclosed that the “diaacetylagelasimine-A” has the imidaiole structure (5a) instead of 6a.

REFERENCES AND NOTES


6. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.


8. For the reaction mechanism proposed for the benzyl analogue, see ref. 7.

9. Recrystallized from AcOEt. Selected spectral data: uv λ_{max}^\text{MeOH} 267 nm (ε 11700); λ_{max}^{95\% \text{aq. EtOH}} 268 (11900); λ_{max}^{\text{solvent A}} 256 (10600); λ_{max}^{\text{solvent N}} 267 (12000); λ_{max}^{\text{solvent B}} 266 (11800);^1 \text{ir ν_{max}^\text{Nujol} cm}^{-1}: 3400 (OH), 1638 (CO); ^1\text{H nmr (CDCl}_3): 0.80 [3H, d, J = 7 Hz, C(8)-Me], 0.83, 0.86, and 0.97 [3H each, s, C(4)-Me’s and C(9)-Me], 1.05–2.0 [16H, m, C(1)-H’s, C(2)-H’s, C(3)-H’s, C(6)-H’s, C(7)-H’s, C(8)-H, C(10)-H, C(11)-H’s, and C(12)-H’s], 1.17 (1H, s, OH), 1.79 [3H, s, C(13)-Me], 2.58 [3H, s, C(2’)-Me], 3.83 [3H, s, N(3’)-Me], 5.08 [2H, d, J = 7.5 Hz, C(15)-H’s], 5.48 [1H, t, J = 7.5 Hz, C(14)-H], 7.62 [1H, s, C(8’)-H];^1\text{C nmr (CDCl}_3): 16.0 (q), 16.8 (q), 17.4 (q), 21.7 (t), 21.7 (q), 22.1 (t), 24.1 (q), 24.4 (q), 26.3 (t), 32.0 (t), 32.9 (t), 33.1 (q), 36.0 (t), 36.5 (d), 36.9 (t), 38.8 (s), 38.9 (s), 40.9 (d), 44.4 (t), 76.3 (s), 114.2 (s), 117.6 (d), 139.7 (d), 144.0 (s), 148.8 (s), 155.9 (s), 162.2 (s); hrmr Calcd for C_{27}H_{42}N_{4}O_{2}: 454.3308, Found: 454.3324.

10. Solvent A stands for 80% (v/v) aqueous EtOH containing HCl at 0.1 M concentration; solvent N, 80% (v/v) aqueous EtOH; solvent B, 80% (v/v) aqueous EtOH containing NaOH at 0.1 M concentration.

11. For convenience, each position of the purine ring is indicated by a primed number.

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