Agelasine: A Novel Quaternary 9-Methyladenine from the Sponge *Agelas dispar*

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The isolation of a novel quaternary 9-methyladenine from the sponge *Agelas dispar* is described. The constitution (**1**) is assigned on the basis of degradative and spectroscopic data.

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On décrit la méthode de séparation d'un nouveau sel quaternaire de la méthyl-9 adénine provenant de l'éponge *Agelas dispar*. On attribue la structure (**1**) en se basant sur les données spectroscopiques et les résultats obtenus par dégradation de la molécule.

[Traduit par le journal]

We have examined the pharmacological behavior of the extractives of a large number of marine organisms with the aim of uncovering novel directives for drug design. We herein report the isolation and characterization of a major constituent, agelasine (**1**), of the sponge *Agelas dispar* Duchassaing and Michelotti.

The residue on evaporation of the ethanol extract of a freeze-dried preparation of *A. dispar* was triturated with benzene. The insoluble portion on recrystallization from acetonitrile yielded **1**[1] (2% on dry weight basis) as colorless plates, m.p. 190–195° dec.; ν_{max} (KBr) 3320, 3140, 1652, 1610 cm^{-1}; and λ_{max} (CH_3OH) 271 nm (log ε 3.91). Elemental analyses indicated the empirical formula $C_{26}H_{40}N_5Cl \cdot \frac{1}{2}H_2O$. Recrystallization from 2-butanone–dimethylformamide provided the anhydrous form ($C_{26}H_{40}N_5Cl$), m.p. 197–200° dec. While a molecular ion was not observed in the mass spectrum, principle ions were found at *m/e* 421 ($C_{26}H_{38}N_5$), 308/310 ($C_{20}H_{33}Cl$), 273 ($C_{20}H_{33}$), 272 ($C_{20}H_{32}$), 191 ($C_{14}H_{23}$), and 149 ($C_6H_7N_5$). The n.m.r. spectrum ($CDCl_3$) exhibited a complex group of signals at δ 0.5–2.3 (29H); the remaining signals were as follows: δ 4.12 (s, 3H, —N—CH_3), 5.3–5.9 (m, 4H), 7.67 (broad s, 2H, —NH_2, disappeared on addition of D_2O), 8.47 (s, 1H), and 10.84 (s, 1H).

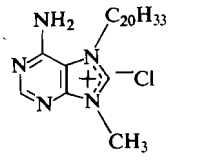
When agelasine was heated under reflux in xylene and the reaction mixture cooled a crystalline solid separated, m.p. 300–302° (from CH_3OH); ν_{max} (KBr) 3280, 3110, 1672, 1600, 1575 cm^{-1}; and λ_{max} (H_2O) 261 nm (log ε 4.03) (at p*H* 2, 7, and 11). The n.m.r. and mass spectra identified this substance as a mono-*N*-methyladenine. The i.r. and u.v. absorptions were in agreement with those reported (1, 2) for 9-methyladenine (**2**). This assignment was confirmed by a comparison with synthetic **2** prepared by the direct methylation of adenine (3).

The aforementioned mass spectral data and the thermal behavior described above suggested that agelasine was a quaternary derivative of 9-methyladenine. The quaternary iodide ($C_{26}H_{40}N_5I$), m.p. 171–173°, was readily obtained by treatment of an aqueous solution of **1** with KI. The nitrate ($C_{26}H_{40}N_6O_3$), m.p. 174–175°, was similarly formed.

The release of the 9-methyladenine moiety as the hydrochloride was rapidly effected by hydrogenation of **1** (H_2/5% Pd–C) in ethanol. A nonpolar fragment was also isolated as a colorless oil which by analysis and mass spectroscopy (M^+ 274, *m/e* 259, *m/e* 205, *m/e* 191) was assigned the molecular formula $C_{20}H_{34}$; two olefinic protons were present in the n.m.r. spectrum ($CDCl_3$) as a broad multiplet at δ 5.0–5.5. Further hydrogenation (H_2/Pt_2O/ethyl acetate – HCl) of this oil provided the tetrahydro derivative $C_{20}H_{38}$ (M^+ 278, *m/e* 263, *m/e* 193); the n.m.r. spectrum ($CDCl_3$) exhibited only a complex group of signals at δ 0.7–2.0. The nonpolar fragment can therefore be classified as a dicyclic hydrocarbon con-

[1]The i.r., n.m.r., and mass spectra of all compounds have been recorded and are in agreement with the structures assigned. Only specially relevant spectral data are reported. All crystalline compounds gave correct elemental analyses.

taining two double bonds. The fragmentation patterns observed in the mass spectra of both the nonpolar fragment and its tetrahydro derivative are similar to the patterns observed with the carbodicyclic diterpenes (4). The precise constitution of this substance is presently under investigation.



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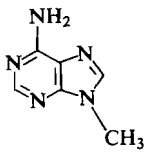

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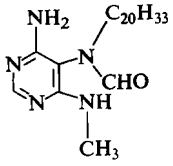

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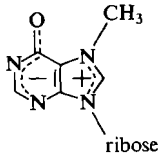

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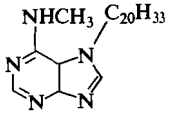

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Treatment of an aqueous solution of **1** with 2 *N* Na_2CO_3 precipitated a white crystalline solid (**3**), m.p. 105–108° (from isopropyl ether); ν_{max} (KBr) 3440 (sh), 3340, 3220, 2920, 1660, and 1590 cm^{-1}; λ_{max} (C_2H_5OH): p*H* 7, 260 nm (log ε 3.77); p*H* 2, 271 nm (log ε 3.98); p*H* 11, 260 nm (log ε 3.80). The molecular formula ($C_{26}H_{41}N_5O$) was supported by analyses and the mass spectrum (M^+ 439). The n.m.r. ($CDCl_3$) spectrum exhibited signals at δ 2.9 (d, 3H, $NHCH_3$; $+D_2O$, s, 3H), 7.9 (s, 1H, C2-H or —NC*H*O), and 8.1 (s, 1H, —N—C*H*O or C2-H). The —$NHCH_3$ signal at δ 2.9 demonstrated that the nucleophilic attack occurred at C-8, with subsequent ring cleavage. The ease with which this hydrolysis occurred, encouraged us to assign N-7 as the site of quaternization with the positive charge delocalized as shown (**1**); an assignment which was supported (5) by the rapid exchange of the C8-H (δ 10.84 in $CDCl_3$; δ 10.13 in CD_3SOCD_3; δ 11.5 in C_5D_5N) of agelasine with D_2O when the n.m.r. spectrum was run in C_5D_5N. The low-field position of this proton is in agreement with that of the C-8 proton of 7-methylinosine (6) (**4**, δ 9.64 in CD_3SOCD_3) which is in a similar environment.

The constitution **1** was therefore considered for agelasine and **3** for that obtained upon treatment with 2 *N* Na_2CO_3. This assignment was supported by the ring closure of **3** with NaH in dimethylacetamide to provide **5**, $C_{26}H_{39}N_5$ (M^+ 421), as colorless plates, m.p. 163–165° (from acetonitrile); ν_{max} (KBr) 3280, 2940, 1615, 1550 cm^{-1}. The u.v. absorption (λ_{max} (C_2H_5OH): p*H* 7 and 11, 272 (log ε 4.12); p*H* 2, 282 nm (log ε 4.17)) corresponded to that anticipated for a 7-alkyladenine (7). The n.m.r. spectrum ($CDCl_3$) exhibited signals at δ 3.50 (d, 3H, —$NHCH_3$; $+D_2O$, s, 3H), 7.85 (s, 1H, C2-H), and 8.55 (s, 1H, C8-H).

To our knowledge, agelasine is the first quaternary derivative of adenine to be found in nature. Agelasine has a very broad spectrum of pharmacological activity although many of these effects can be ascribed to its saponin-like nature. These aspects will be described in a forthcoming paper.

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