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Aplidiasphingosine, an Antimicrobial and Antitumor Terpenoid from an *Aplidium* sp. (Marine Tunicate)[1]

Sir:

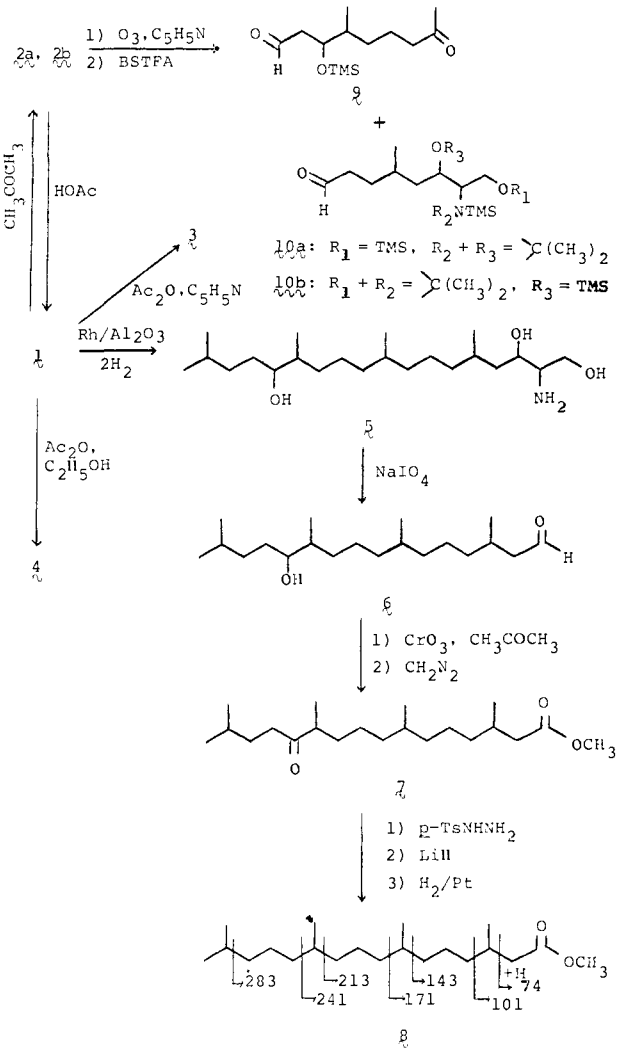
The orange-flecked compound tunicate identified as an *Aplidium* species[2] was originally collected from the Gulf of California during the Illini-Trojan Baja Expedition of June 1976 (ITBE 2-VI-76-1-3)[3] and subsequently recollected in March 1977 (IBE 13-III-77-2-5). Extracts of the tunicate were shown in our mobile laboratory to possess inhibitory activity toward Gram-positive and Gram-negative bacteria and fungi and were subsequently shown to be cytotoxic to tumor cells (KB[4a] and L1210[4b]) and monkey kidney cells[4c] and to inhibit Herpes virus type I.[4c] Aplidiasphingosine (**1**), isolated from the tunicate, gives the zones of inhibition indicated vs. the following microorganisms at 80 μg/12.7-mm disk:[4d] *Bacillus subtilis* (24 mm), *Klebsiella pneumoniae* (21 mm), *Bacteroides fragilis* (21 mm), *Mycobacterium avium* (21 mm), *Sarcina lutea* (20 mm), *Clostridium perfringens* (14 mm), *Candida albicans* and *Penicillium oxalicum* (both, trace). Cytotoxicity toward KB[4a] and L1210[4b] tumor cells in tissue culture is also shown by **1** (ED_{50} 8.3 μg/mL and ID_{50} 1.9 μg/mL, respectively).

A sample (500 g) of the tunicate[5] was homogenized in methanol-toluene (3:1) and the extract was partitioned by addition of 1 M sodium nitrate. Extraction of the aqueous phase with chloroform yielded 1.88 g of oil, which was subjected to repeated chromatography on silica gel developed with chloroform-acetone-methanol-concentrated ammonia (71:23:4.5:1.5) to give 400 mg of a mixture of the two acetone adducts, **2a** and **2b** ($C_{25}H_{47}NO_3$).[6,7a] Treatment of the mixture of **2a** and **2b** with 50% aqueous acetic acid cleaved the acetonide, affording **1** ($C_{22}H_{43}NO_3$)[7a] as an oil.

The oxygens and nitrogen of aplidiasphingosine were shown to be present in three hydroxyl groups and a primary amine by the formation of its tetraacetyl derivative, **3** ($C_{30}H_{51}NO_7$),[7b] whose IR spectrum ($CHCl_3$) contains bands corresponding to ester (1740 cm^{-1}) and secondary amide (1682, 1518 cm^{-1}) groups. A mono-*N*-acetyl derivative, **4** ($C_{24}H_{45}NO_4$:[7a] IR ($CHCl_3$) 1665, 1521 cm^{-1}), was obtained by reaction of **1** with acetic anhydride in ethanol. The ^{13}C NMR spectrum (CD_2Cl_2) of **4** clearly shows >CH-O- carbons at 76.5 (d) and 70.0 (d) ppm, a $-CH_2O-$ carbon at 64.6 (t), and a >CH-N< carbon at 54.7 ppm (d).

The two elements of unsaturation required by the molecular formula of **1** were determined to be double bonds from the four olefinic carbon absorptions in the ^{13}C NMR spectrum of **4** (CD_2Cl_2) at 135.6 (s), 135.0 (s), 125.5 (d), and 121.8 (d) ppm, and by formation of a tetrahydro derivative, **5** ($C_{22}H_{47}NO_3$),[7b] upon catalytic hydrogenation of **1** (Scheme I). Periodate oxidation[8] of **5** gave aldehyde **6** ($C_{20}H_{40}O_2$),[7b] which was converted to the phytanic acid methyl ester **8**[9] by the reactions shown in Scheme I. The characteristic series of fragment ions observed in the spectrum of **8** (Scheme I) identify it as methyl 3,7,11,15-tetramethylhexadecanoate, a conclusion confirmed by comparison with the published mass spectrum.[9a]

Scheme I. Derivatives and Degradation Products of Aplidiasphingosine (**1**)



The loss of C_2H_6NO from **5** during periodate oxidation, taken with the ^{13}C NMR data for **4**, indicated hydroxyl or amino substitution at C-1, C-2, and C-3 of **5** (and **1**), i.e., $-CHX-CHY-CH_2OH$, where X = OH, Y = NH_2, or vice versa. The formation of two acetone adducts (**2a, 2b**) involving adjacent hydroxyl and amino groups argues for the former arrangement, and this was confirmed by the abundant $C_5H_{10}NO$ peak in the mass spectrum of **2b**, as shown.[10] In addition, the ions at *m/e* 340 and 310 locate the third hydroxyl at C-14 and restrict one double bond to the C-15–C-18 region, argued also by the *m/e* 69 ion.

It was noted above that **1** contains two =CH- and two =C< carbons. Of the five methyl groups observed in the ^1H NMR spectrum of **1**, three are olefinic methyl singlets, at 1.73, 1.63 and 1.58 ppm, requiring a $\Delta^{16,17}$ double bond. The position of the $\Delta^{16,17}$ unsaturation was confirmed and the position of the other olefinic bond was established as $\Delta^{8,9}$ by ozonolysis

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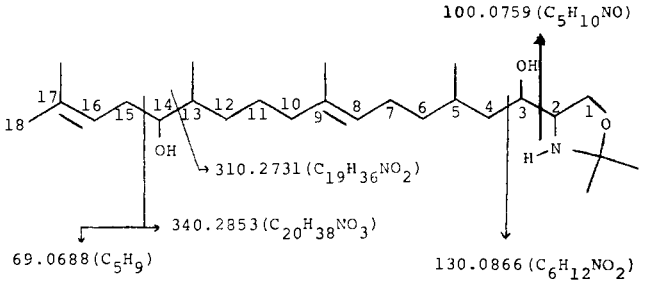
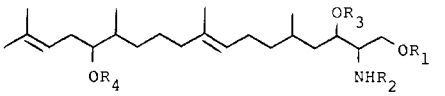
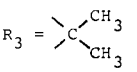
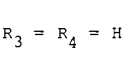


(Scheme I) of acetonides **2a** and **2b** (−78 °C, CH_2Cl_2/C_5H_5N) followed by gas chromatography/mass spectrometry of the trimsylated products, which identified the aldehydes **9** and **10** by their molecular weights, 258 and 343, respectively.[11]



1: $R_1 = R_2 = R_3 = R_4 = H$

2a: $R_1 = R_4 = H$; $R_2 + R_3 =$ 

2b: $R_1 + R_2 =$  ; $R_3 = R_4 = H$

3: $R_1 = R_2 = R_3 = R_4 = Ac$

4: $R_1 = R_3 = R_4 = H$; $R_2 = Ac$

Aplidiasphingosine (**1**, 2-amino-5,9,13,17-tetramethyl-8,16-octadecadiene-1,3,14-triol) can be regarded as a derivative of sphingosine itself, i.e., as 14-hydroxy-5,9,13,17-tetramethyl-8,16-sphingadienine, disregarding stereochemistry at C-2 and C-3. One may reasonably assume that the biosynthesis of aplidiasphingosine proceeds from the corresponding diterpenic acid (perhaps as its CoA derivative) plus serine with loss of the serine carboxyl group.[12] However, whether aplidiasphingosine serves some of the same biological functions in this urochordate that sphingosine does in higher animals (and plants) can only be speculated. Similarly, it is not yet known whether the various bioactivities of aplidiasphingosine may depend on its interference with normal sphingosine functions.

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References and Notes

(1) Presented in part at the Second International Symposium on Marine Natural Products (IUPAC–Societa Chimica Italiana), Sorrento, Italy, Sept 12–15, 1978.
(2) Identified by Dr. D. P. Abbott, Hopkins Marine Station, Pacific Grove, Calif., from a sample preserved in ethanol.
(3) *New York Times*, July 19, 1976, p 1.
(4) Biological activity data were provided by (a) Dr. L. P. Hager, Mr. J. Nemanich, and Ms. G. Williamson, University of Illinois; (b) Dr. L. H. Li and Ms. S. L. Kuentzel, The Upjohn Co.; (c) Dr. R. G. Hughes, Roswell Park Memorial Institute; (d) Dr. J. J. Vavra and Mr. G. E. Zurenko, The Upjohn Co.
(5) The samples were stored in ethanol after collection, and a proportional aliquot of the storage ethanol was included in the extraction.
(6) The 5:1 mixture of **2a** and **2b** was recognized from its ^{13}C NMR spectrum, which shows duplicate absorptions for the ketal carbon, C-1, C-2, and C-3.
(7) In accord with the molecular formulas shown were (a) high resolution or (b) low resolution mass spectral data.
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(10) Further support for this assignment was provided by the failure of **4** to undergo a similar periodate cleavage.
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Book Reviews*

Advances in Organometallic Chemistry. Volume 15. Edited by F. G. A. STONE and R. WEST. Academic Press, New York. 1977. vii + 332 pp. $33.00.

The chapters in this volume are: Recent Developments in Theoretical Organometallic Chemistry (D. M. P. Mingos); Metal Atom Synthesis of Organometallic Compounds (P. L. Timms and T. W. Turney); Metal Complexes of π-Ligands Containing Organosilicon Groups (I. Haiduc and V. Popa; Activation of Alkanes by Transition Metal Compounds (David E. Webster); Supported Transition Metal Complexes as Catalysts (F. R. Hartley and P. N. Vezey); Structures of Main Group Organometallic Compounds Containing Electron-deficient Bridge Bonds; and Organometallic Radical Anions (P. R. Jones).

It is not stated how up to date the literature coverage in these reviews is, but some references from 1976 are included, and one chapter includes a note added in proof, concerning some important work published in 1976. As is characteristic of the series, there are included extensive tables and bibliographies, a subject index, and a cumulative list of titles from previous volumes.

The Uncertainty Principle and Foundations of Quantum Mechanics. Edited by W. C. PRICE, FRS, and S. S. CHISSICK (King's College, London). John Wiley & Sons, Inc., New York, N.Y. 1977. xvii + 572 pp.

A tribute to the late Professor Werner Heisenberg (1901–1976) to commemorate the 50th anniversary of the formulation of quantum mechanics. In his dedication of the volume, Professor Sir Hermann Bondi states, "This volume brings together many illuminating phases of one of the most exciting and successful hunts in history, the formulation of the quantum theory. Not only was this hunt outstanding in the range and wealth of experimental data it covered . . . but also in its philosophical implications." The collection of 25 articles by 30 authors is organized into four parts: 1. Quantum Uncertainty Description; 2. Measurement Theory; 3. Formal Quantum Theory; 4. Applied Quantum Mechanics. The opening article is by Heisenberg himself, "Remarks on the Origin of the Relations of Uncertainty." A good portion of the contents presupposes the professional expertise of a theoretical physicist. Of chemical interest are articles by C. C. J. Roothaan and J. H. Detrich, "Relativistic Electromagnetic Interaction Without Quantum Electrodynamics", and by M. A. Ratner, J. R. Sabin, and S. B. Trickey, "Applications of Model Hamiltonians to the Electron Dynamics of Organic Charge Transfer Salts". Price

* Unsigned book reviews are by the Book Review Editor.