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PANACENE: AN AROMATIC BROMOALLENE FROM A SEA HARE (APLYSIA BRASILIANA)

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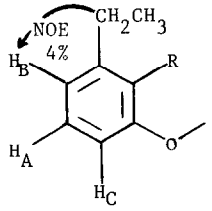
We have found the marine mollusk Aplysia brasiliana, a so-called sea hare, to be distasteful to fish and rejected by sharks. By means of bioassays we showed distastefulness to be attributable to chemical factors located in the body wall, digestive gland, and other parts of the animal. We have isolated several of these fish antifeedants. One of the more interesting from a chemical point of view (although not one of the most potent antifeedants) is the novel aromatic bromoallene, panacene. We here give the details leading to the determination of its structure.

Digestive glands (45.2 g wet weight) of 8 full-grown A. brasiliana, taken in coastal waters near Panacea, Florida, were extracted with 95% ethanol, and the crude extract (11 g) purified chromatographically to give 98 mg (0.2%) of a colorless, optically active oil, $C_{15}H_{15}O_2Br$ (m/e 306.0245, 308.0233; calcd.: 306.0256, 308.0236), which showed no carbonyl or hydroxyl absorption in its infrared spectrum. In the ultraviolet, this compound shows an isolated anisole chromophore (λ_{max}^{EtOH} 224, log ε 3.54; 279, log 3.40).[1]

In the ^{13}C magnetic resonance (cmr) spectrum of panacene, six benzenoid carbon atoms were clearly discerned; off-resonance decoupling, together with consideration of signal intensities indicated that the aromatic ring is trisubstituted. The fingerprint region of panacene's infrared spectrum suggested a 1,2,3 substitution pattern, which was confirmed by a characteristic doublet-triplet-doublet pattern (δ 6.77, 7.19, 6.64 ppm) in its ^1H magnetic resonance (pmr) spectrum. Both the pmr and cmr spectra show an ethyl group (δ 2.75, q, J = 7-8 Hz, 2H; δ 1.26 ppm, t, J = 7-8 Hz, 3H) attached to an sp^2 carbon. Spin decoupling experiments revealed small couplings between the methylene protons and the aromatic protons ortho (J = 0.3 Hz) and para (J < 0.1 Hz) to it.



The accompanying part-structure can be written on the basis of the above argument and the close agreement of the experimental and calculated chemical shifts for H_A, H_B, H_C, and the benzenoid carbon atoms.[2a,b] The proximity of H_B to the CH_2 group is also supported by an NOE experiment.

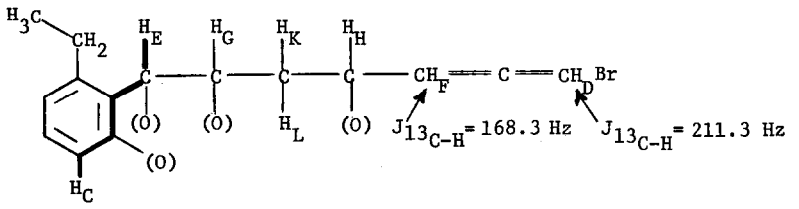
A cmr peak at δ 202 ppm, initially considered to correspond to a carbonyl carbon atom, provided the key evidence for the most interesting feature of the panacene structure; in the absence of infrared evidence for the presence of a carbonyl group, it could be ascribed only to the central carbon atom of an allene.[2a] Observation of a weak allenic stretching band at 1945 cm^{-1} in the infrared and a similar band in the Raman spectrum supported the assignment. Two allenic protons [δ 6.07(d,d), 5.45(t)] in the pmr spectrum show couplings expected for a disubstituted allene (see Table), and the cmr chemical shifts (as well as the ^{13}C-H coupling) of the two remaining allenic carbon atoms are compatible with expectations for a bromoallene moiety.

	δ (ppm)	Multiplicity	J
H_D	6.067	d of d	J_{DF} = -5.88, J_{DH} = 1.47
H_E	5.801	d of d	J_{GE} = 5.98, J_{CE} = 0.7
H_F	5.455	t	J_{DF} = -5.88, J_{FH} = 5.7 - 5.8
H_G	5.29	t, broadened sl.	J_{GL} = 5.65, J_{GE} = 5.98, J_{GK} = 0.8
H_H	4.360	d,d,d,d,	J_{HL} = 10.0, J_{HK} = 5.0, J_{HF} = 5.8, J_{HD} = 1.47
H_K	2.478	d of d	J_{KL} = -13.24, J_{KH} = 5.0, J_{KG} = 0.8
H_L	2.013	d of d of d	J_{LK} = -13.24, J_{LH} =10.0, J_{LG} = 5.65

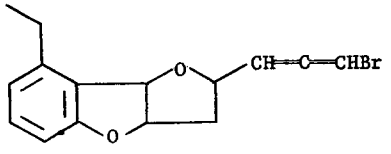
Table: Selected 270 MHz pmr spectral data obtained for panacene ($CDCl_3$).

The presence of a terminal bromoallene group was established unambiguously by microozonolysis of panacene at -78°C, followed by reductive workup. This degradation afforded a volatile aldehyde whose mass spectrum showed a molecular ion at m/e 218 (corresponding to the oxidative removal of a C_2HBr unit), strong M-1 and M-29 peaks characteristic of aldehydes, and peaks at 159 and 147 (also characteristic of panacene itself). It lacked the two allenic resonances at δ 6.07 and 5.45 ppm in its pmr spectrum, but showed the expected aldehydic proton as a doublet centered at δ 9.70 ppm.

Between the bromoallene moiety and the benzene ring bearing an ethyl substituent, eleven of panacene's fifteen carbon atoms and ten of its fifteen protons are accounted for. The remaining C_4H_5 moiety can be shown to have the linear arrangement given below on the basis of cmr and pmr spectral data. Three of the carbon atoms have chemical shifts which indicate that they are bound to oxygen, while the fourth is a methylene group unaffected by electron withdrawing groups.



Pmr decoupling revealed that the five hydrogen atoms are situated on adjacent carbons, and a 0.7 Hz long-range H_C-H_E coupling was apparent. Structure 1 is uniquely compatible with these data, as well as with the mass spectrum of panacene, which shows important fragment ions at



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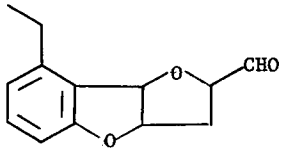

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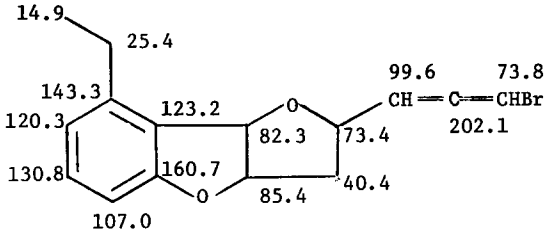
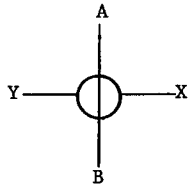
m/e 189, 159, and 147. Structure 1 is in excellent agreement with the cmr spectrum of panacene, as shown below. Finally, the aldehyde obtained by ozonolysis of panacene has pmr and mass spectra in good accord with expectations for 2.

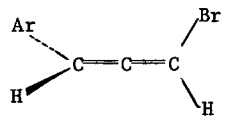


With the structure of panacene established, we turn to its stereochemistry. The fusion of the 2,6-dioxabicyclo[3.3.0]octane ring system is assumed to be cis. Pmr spectra of model systems show that the bridgehead protons of cis disubstituted dihydrobenzofurans have 5-8 Hz coupling constants;[3] in 1 the corresponding coupling constant is 5.98 Hz. Furthermore, trans fusion of the two five-membered rings would correspond to a very highly strained system, no close analog of which has been observed in nature.

The allenic side-chain in 1 can be assigned the exo configuration on the basis of the observed coupling constant between H_G and H_L (or H_K). Whether the allene is cis or trans to the bridge hydrogens H_E and H_G, ring C is able to pucker so that the side chain can assume a pseudoequatorial conformation. With the rings thus arranged, however, only an exo allene permits a nearly 90° dihedral angle between H_K and H_G, corresponding to the observed coupling constant of ca. 0.8 Hz.

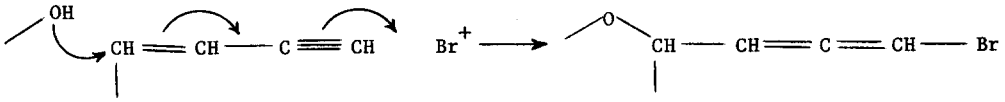
Application of Lowe's rule[4] to panacene allows tentative assignment of the absolute configuration of the allene moiety. According to this rule, unsymmetrically substituted allenes with the absolute configuration given below show positive rotations at the sodium D line when





A > B and X > Y in polarizability. The strong positive rotation observed for panacene ($[\alpha]_D^{21°}$ + 382°) corresponds to the configuration shown above.

While panacene has considerable novelty as a natural halo-allene, its structure shows it to be closely related to the large group of halogenated, acetylenic natural products of marine origin, all of which are based on an unbranched C_{15} skeleton, as is panacene itself. Representatives of this group have been found chiefly in red algae, but they also occur in sea hares.[5] It has been suggested that brominated marine terpenoids owe their biogenesis to an electrophilic bromination.[6] It seems reasonable to postulate that panacene is biosynthesized from a C_{15} algal precursor bearing the typical enyne terminus via an analogous process, as shown below. Whether this process occurs in an alga upon which A. brasiliana feeds, or whether it occurs in the sea hare itself, remains an open question.[7]



Details of the chemistry of other compounds isolated from A. brasiliana will be given elsewhere, together with data on the relative antifeedant potency of these compounds and of panacene.

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