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ISOLATION AND SYNTHESIS OF APLYSINADIENE, A NEW REARRANGED DIBROMOTYROSINE DERIVATIVE FROM APLYSINA AEROPHOBA

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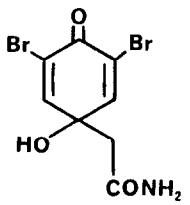
Summary: From the sponge Aplysina aerophoba a new rearranged dibromotyrosine derivative aplysinadiene (9) was isolated. The structure was solved by spectral properties and synthesis.

Phenolic substances have been reported from a number of marine plants and animals. Among marine animals, sponges and echinoderms exceed other animal phyla in the reported number of phenolic metabolites[1]. Sponges of the order Verongida, genus Aplysina, have proved to be a rich source of bromophenolic metabolites derived from dibromotyrosine, antimicrobial activity being the most common biological property observed for these substances. In the majority of them, the tyrosine side-chain has either been changed into different groupings or it has been oxidatively removed, while the central nucleus has been retained, rearranged or reduced at a double bond (1-6)[2-6].



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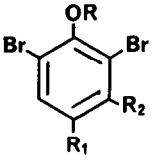
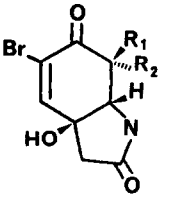
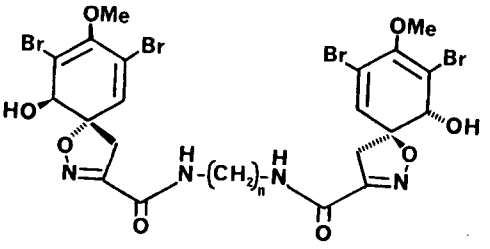


2 R = Me R_1=CH_2CONH_2 R_2=OH
3 R = H R_1=OH R_2=CH_2CONH_2



4 R_1 = Br R_2 = H
5 R_1 = H R_2 = Br



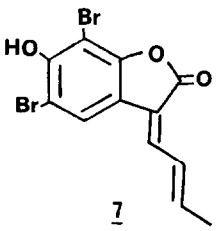
6 n = 4,5

In this communication we wish to report the isolation and synthesis of another sponge metabolite of this family of compounds. Our compound (9) is a second example of a rearranged dibromotyrosine metabolite, the first being the simple homogentisic amide (2) isolated from Aplysina fistularis[3].

Samples of Aplysina aerophoba were collected near Graciosa Island (Canary Islands). The fresh sponge was extracted with acetone. The solvent was evaporated "in vacuo" to an aqueous solution which was partitioned between water and ethyl acetate. The ethyl acetate extract (89 gr.) was chromatographed on a silica gel column using mixtures of n-hexane/ethyl acetate of increasing polarity. Selected fractions were combined and chromatographed on Sephadex LH-20 using mixtures of $CHCl_3$/MeOH (1:1) and $CHCl_3$/MeOH/n-hexane (1:1:2) as mobile phase.

Together with other related metabolites, an amorphous, optically non-active, yellow compound, was isolated (mp. 218-220 ºC.). The high resolution mass spectrum of this compound indicated an elemental composition of $C_{12}H_8O_3Br_2$, M^+ at m/z 358, 360, 362; high resolution 361.8794 ($C_{12}H_8O_3{}^{81}Br_2$; Δ=0.2). The I.R. spectrum contained bands at 3500, 1775 and 1630 $cm.^{-1}$. In the U.V. λ_{max}^{EtOH}=335 nm.(ε=47222) and 209 nm.(ε=64000). The ^{1}H-NMR ($CDCl_3$) spectrum contained signals at 2.07 (dd, 3H, J=7.4 and 1.6 Hz.); 6.59 (dq, 1H, J=14.3 and 7.4 Hz.); 7.30 (s, 1H); 7.74 (ddq, 1H, J=14.3, 11.4 and 1.6 Hz.); 8.21 (d, 1H, J=11.4 Hz.). The ^{13}C-NMR($CDCl_3$) spectrum showed the presence of a methyl at 19.78; four methines at 109.12; 128.12; 144.66 and 148.85 and five fully substituted carbon atoms at 103.75; 113.68; 146.35; 147.16 and 165.91.

From the spectroscopic data three structures (7), (8) and (9) were considered for this compound. Structure (10) is precluded due to the interaction of the bromine atom with the butenylide moiety. The structure of the natural compound was established by total synthesis of the isomers.



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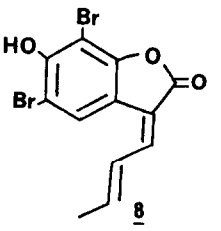

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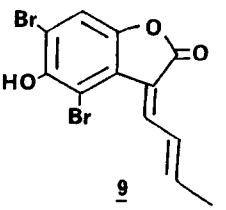

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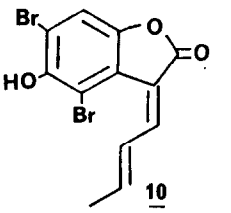

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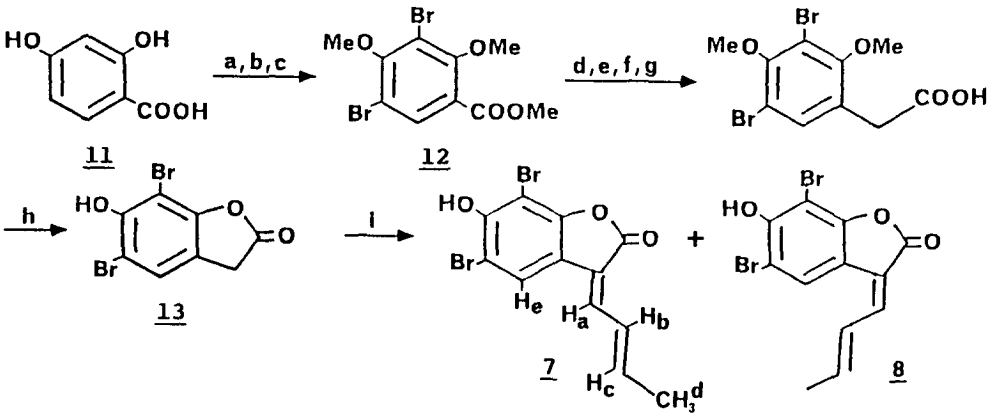
The dibromotyrosine derivatives (7) and (8) were synthesized according to **Scheme I**. The appropriately substituted lactone (13) was obtained from resorcylic acid (11). Bromination under acidic conditions and protection of the phenolic groups by a methyl group gave (12). Side chain homologation

and lactonization gave (13) and the condensation of this compound with (E)-crotonaldehide gave a mixture (4:1) of (7) and (8). Both compounds were isolated by preparative t.l.c..

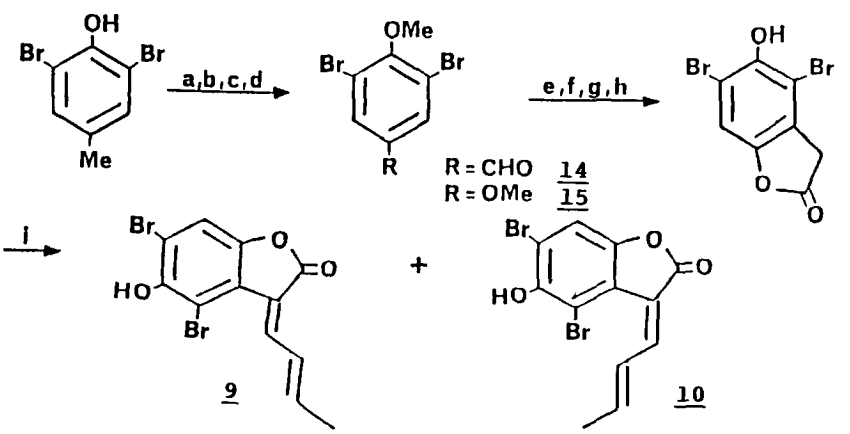
SCHEME I



a) Br_2, AcOH, 40ºC., 80%; b) CH_2N_2, ether, 0ºC., 90%; c) Me_2SO_4, K_2CO_3, acetone reflux, 98%; d) DIBAL, ether, - 40ºC., 90%; e) ClMs, Py, 0ºC., 90%; f) KCN, DMSO, 0ºC., 90%; g) H^+, reflux, 90%; h) F_3B, CH_2Cl_2, r.t., 85%; i) HNa, E-CH_3CH:CHCHO, THF, -40ºC., 60%.

The synthesis of the rearranged dibromotyrosine derivatives is shown in Scheme II. The 2,6-dibromo-1,4-dimethoxybencene (15) was obtained from the methoxybenzaldehyde (14) by Bayer-Villiger oxidation. The compound obtained by chloromethylation of (15) was trated as in Scheme I to give (9) and traces of (10).

SCHEME II



a) CrO_3, Ac_2O, 0ºC., 89%; b) H_3O^+, r.t., 90%; c) MCPBA, H_2SO_4, CH_2Cl_2, r.t., 60%; d) Me_2SO_4, K_2CO_3, acetone, reflux, 90%; e) HCOH, HCl, 100ºC., 85%; f) KCN, DMSO, 0ºC., 90%; g) H^+, reflux, 90%; h) F_3B, CH_2Cl_2, r.t., 85%; i) HNa, E-CH_3CH:CHCHO, THF, -40ºC., 60%.

The ^{1}H-NMR spectra of compounds (7), (8) and (9) are shown in **Table I**. The structure (9) was assigned to our compound on the basis of the spectroscopic data of the compounds synthesized.

TABLE I: ^{1}H-NMR spectra of compounds (7), (8) and (9)

Compound	Chemical shifts and multiplicities[a,b]
(7)	H_a 7.1(d) H_b 7.57(ddq) H_c 6.43(dq) H_d 2.03(dd) H_e 7.49(s) J_{ab}= 11.6; J_{bc}= 14.2; J_{cd}= 7.02; J_{db}= 1.6
(8)	H_a 7.28(d) H_b 6.8(ddq) H_c 6.56(dq) H_d 2.08(dd) H_e 7.69(s) J_{ab}= 10.1; J_{bc}= 13.67; J_{cd}= 6.7; J_{db}= 1.51
(9)	H_a 8.21(d) H_b 7.74(ddq) H_c 6.59(dq) H_d 2.07(dd) H_e 7.3(s) J_{ab}= 11.4; J_{bc}= 14.3; J_{cd}= 7.4; J_{db}= 1.6

a) The spectra were recorded at 200 MHz. in $CDCl_3$ solution.
b) Chemical shifts are reported in PPM relative to TMS (0).

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References

1.- T. Higa. **Mar. Nat. Prod.** Ed. P.J.Scheuer Ac. Press. 1981, **Vol. IV**, 93
2.- G.M. Sharma and P.R. Burkholder. **Tetrahedron Lett.** 1967, **42**, 4147.
3.- A.A. Tymiak and K.L. Rinehart Jr.. **J. Am. Chem. Soc.** 1981, **103**, 6763
4.- C.W.J. Chang and A.J. Weinheimer. **Tetrahedron Lett.** 1977, 4005
5.- M. D'Ambrosio, A. Guerriero, P. Traldi and F. Pietra. **Tetrahedron Lett.** 1982, **23**, 1091.
6.- J.A. Mc.Millan, I.C. Paul, Y.M. Goo, K.L. Rinehart Jr., W.C. Krueger and L.M. Pschigoda. **Tetrahedron Lett.** 1981, **22**, 39.

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