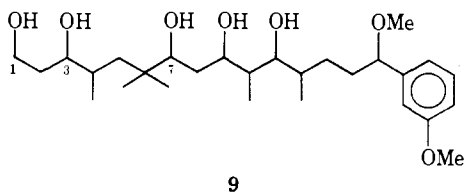
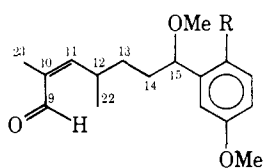


longed LAH treatment of **8**. The resulting pentaol **9**

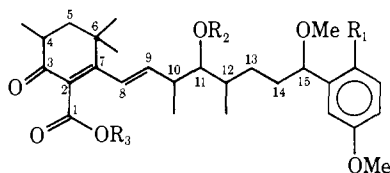


(pentaacetate, m/e 708), $C_{28}H_{50}O_7$, failed to react with periodate, but formed a diacetonide (m/e 578), which in turn was converted to a monoformate (m/e 606). LAD reduction of **8** yielded a tetra-deuteriopentaol, consistent with deuterium incorporation at C-1 (D_2), C-3, and C-7.

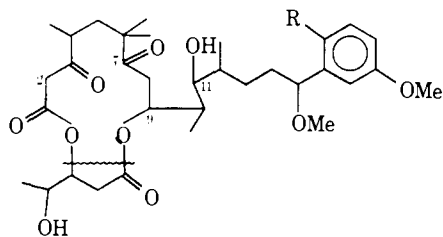
The manner in which the polyoxy chain of **9** is fashioned into the bicyclic hemiketal-spiroketal function of the aplysiatoxins (**1**, **2**) became manifest by treating mixed **7** and **8** with 0.5 *N* KOH in aqueous MeOH for 5 hr, resulting in two aldehydes **10** and **11**



10, R = Br
11, R = H



12, $R_1 = Br$; $R_2 = R_3 = H$
13, $R_1 = R_2 = R_3 = H$
14, $R_1 = H$; $R_2 = Ac$; $R_3 = Me$



15, R = Br
16, R = H

and two oxyacids **12** and **13**. If **1** and **2** are rewritten as the chain tautomer (**15**, **16**) of the hemiketal-spiroketal system, degradation products **12** and **13** involve loss of valeric acid (wiggly line) by β -elimination of the resulting C-9 hydroxyl and base catalyzed ring closure from C-2 to C-7. If the C-9 hydroxyl participates in a retroaldol reaction facilitated by the C-7 carbonyl with concomitant β -elimination of the C-11 hydroxyl, aldehydes **10** and **11** are the products. Evidence for **10** includes: m/e 356 (13%, $M^+ + 2$), 354 (13% M^+), 229 (100%, $Bz(MeO)_2Br$); uv 225 (15700), 280 (1920) nm; ir 2710, 1685 cm^{-1} ; nmr ($CDCl_3$, δ) H-9 9.41 s, H-11 6.25 (br d, $J = 10$ Hz), H-12 2.75 (br m), H-13, H-14 1.7 (4 H br), H-15 4.50 (br t), H_3-22 1.13 (d, $J = 6.5$ Hz), H_3-23 1.80 (br s). All assignments were confirmed by appropriate double resonance experiments. Aldehyde **10** autoxidized on silica gel tlc plates to the corresponding acid, characterized as its methyl ester.

Oxyacids **12** and **13** were isolated as their methyl ester acetates, of which **14** was rigorously characterized. The m/e 528 was evidence for composition $C_{31}H_{44}O_7$ and a prominent peak at m/e 151 confirmed the intact benzyl methyl ether: $uv(EtOH)$ 268 nm (29,500); ir 1730, 1675 cm^{-1} ; nmr ($CDCl_3$, δ) H-4 \sim 2.5, H₂-5 \sim 1.7, H-8 6.00 (br d, $J = 16.0$ Hz), H-9 5.80 (dd, 16.0, 3.0), H-10 2.5 (m), H-11 4.77 (t, $J = 6.0$ Hz), H-12, H₂-13, H₂-14 1.7 (m), H-15 4.05 (t, 6.0), H_3-22 0.88 (d, $J = 7.0$ Hz), H_3-23 0.98 (d, $J = 7.0$ Hz), H_{9-24,25,26} 1.2. Assignments were corroborated by double resonance experiments, and **14** was fully confirmed by catalytic hydrogenation, ozonation, and $LiAlH_4$ reduction followed by acetylation and hydrogenation. All resulting transformation products were isolated and characterized.

Acknowledgment. We are grateful to Hoffmann-La Roche, Inc., and to PHS Grant 15198 for financial support.

(13) From the Ph.D. Thesis of Y. K., University of Hawaii, 1973.

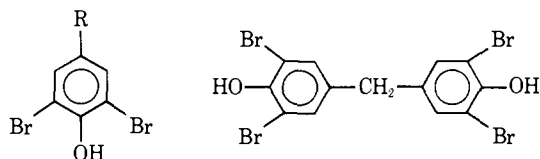
Yoshinori Kato,¹³ Paul J. Scheuer*
Department of Chemistry, University of Hawaii
Honolulu, Hawaii 96822
Received December 14, 1973

Thelepin, a New Metabolite from the Marine Annelid *Thelepus setosus*

Sir:

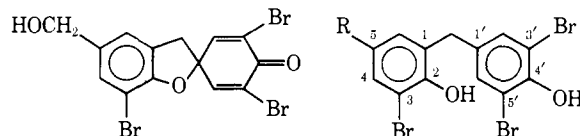
Marine annelids (segmented worms) are unfamiliar invertebrates, particularly the sedentary polychaetes which live in self-constructed tubes or permanent burrows. Unsurprisingly, the chemical constituents of these animals have remained unexplored with few exceptions, notably nereistoxin,¹ hallachrome,² and arenicochrome.³

We wish to report the isolation and structural elucidation of five brominated metabolites (**1-5**) from the tube-



1, R = CH_2OH
2, R = CHO

3

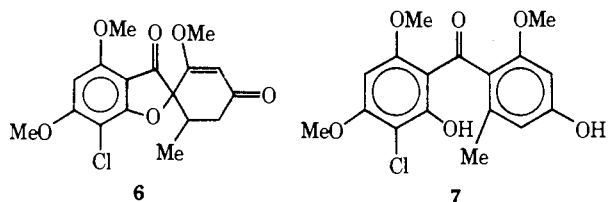


5

4, R = CH_2OH
10, R = CHO

dwelling polychaete *Thelepus setosus* (Quatrefages, 1865), Family Terebellidae, of which spirodienone **5**, which we have named thelepin, bears a striking structural resemblance to the antimycotic agent griseofulvin (**6**), first isolated from the microorganism *Penicillium*

(1) T. Okaichi and Y. Hashimoto, *Agr. Biol. Chem.*, **26**, 224 (1962).
(2) G. Prota, M. D'Agostino, and G. Misuraca, *J. Chem. Soc., Perkin Trans. 1*, 1614 (1972).
(3) I. Morimoto, M. I. N. Shaikh, R. H. Thomson, and D. G. Williamson, *Chem. Commun.*, 550 (1970).



griseofulvum.⁴ Significantly, another worm constituent, **4**, appears to be the immediate biogenetic precursor of thelepin (**5**), in full analogy with the isolation of **7** from *P. patulum*.⁵

Annelids (1 kg) were collected in Kaneohe Bay, Oahu, in June 1973 and freeze-dried. The dry residue (375 g) was treated with chloroform in a Waring blender. Solvent removal left dark brown oil (24 g) which was chromatographed on Bio-Sil A. Elution with petroleum ether-chloroform (2:1) furnished solid material, from which compounds **2** and **3** were isolated by tlc (silica gel, acetone-chloroform, 1:10). Compound **2**, R_f 0.18, after sublimation and recrystallization from chloroform, was obtained in a yield of 4.5 mg, mp 182–186°. The structure of **2**, 3,5-dibromo-4-hydroxybenzaldehyde, was deduced from spectral data and confirmed by comparison with a synthetic sample prepared by bromination of *p*-hydroxybenzaldehyde, mp 186–187°, lit.⁶ 181°. A second band, R_f 0.72, was recrystallized from benzene, 12.4 mg, mp 230–232°. Its structure, bis(3,5-dibromo-4-hydroxyphenyl)methane (**3**), was deduced on the basis of spectral data⁷ and confirmed by synthesis. Bis(*p*-hydroxyphenyl)methane was prepared from phenol and formaldehyde as previously described.⁸ The bisphenol was brominated in aqueous EtOH and the product was recrystallized from benzene, mp 230–232° (lit.⁹ 224–226°), completely identical with the natural product.

Subsequent elution of the silicic acid column with chloroform furnished 20 fractions, 200 ml each. From the early fractions we isolated by tlc (silica gel, acetone-chloroform, 1:10), after recrystallization from chloroform, 3,5-dibromo-4-hydroxybenzyl alcohol (**1**), 500 mg, mp 115–116°. Synthetic **1**, prepared from synthetic **2** (*vide supra*) by NaBH₄ reduction in EtOH, mp 116–117° (lit.¹⁰ 116–117°), was identical with the natural product in all respects.

The middle fractions furnished a major band on tlc, R_f 0.36. After two recrystallizations from methanol, we isolated 130 mg of pale yellow crystals, mp 202–203° dec: uv, $\lambda_{\max}^{\text{EtOH}}$ 247 sh (4.09), 257 (4.12), 280 sh (3.72), 288 sh (3.59) nm; $\lambda_{\max}^{\text{EtOH-NaOH}}$ 285, 292 nm; ir, ν_{\max}^{KBr} 3430, 1685, 1605, 1468, 1312, 963, 690 cm⁻¹; nmr (δ , acetone-*d*₆), 2.87 (br, s), 3.73 (2 H, m), 4.56 (2 H, s), 7.26 (1 H, m), 7.36 (1 H, m), 7.75 (2 H, s); mass spectral, m/e 468 (39), 466 (100), 464 (98), 462 (35), 387 (6), 385 (11), 383 (6), 369 (6), 367 (11), 365 (6), 278 (12), 277 (12), 276 (32), 275 (12), 274 (20), 197 (11), 196 (10),

(4) J. F. Grove, *Quart. Rev., Chem. Soc.*, **17**, 1 (1963), and literature cited therein.

(5) W. J. McMaster, A. I. Scott, and S. Trippet, *J. Chem. Soc.*, 4628 (1960).

(6) J. K. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," 4th ed, Eyre and Spottiswoode, London, 1965, p 926.

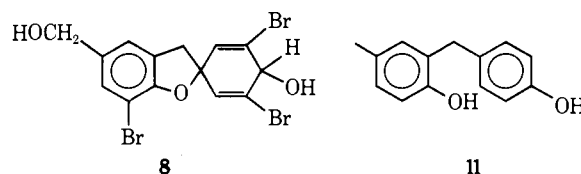
(7) Compounds **3**, **4**, and **5** were subjected to elemental microanalysis with satisfactory results.

(8) Y. Ishikawa, T. Ando, and S. Kataoka, Japanese Patent 26844 (1964); *Chem. Abstr.*, **62**, 9064 (1965).

(9) H. Kämmerer and H. Lenz, *Kunststoffe*, **51**, 26 (1961); *Chem. Abstr.*, **55**, 14369 (1961).

(10) See ref 6, p 927.

169 (11), 168 (12), 152 (11), 139 (29 rel %). These data strongly suggested structure **5**, which we confirmed as follows. NaBH₄ reduction of thelepin (**5**) in EtOH furnished **4** and **8** in equal amounts. Compound **4**



(2,4'-dihydroxy-5-hydroxymethyl-3,3',5'-tribromodiphenylmethane) was synthesized by preparing 3-bromo-4-hydroxybenzaldehyde (**9**) from *p*-hydroxybenzaldehyde.¹¹ Compounds **9** and **1** were condensed in the presence of polyphosphoric acid and yielded **10**. Aldehyde **10**, mp 205–208°, was characterized spectrally and reduced to **4** with NaBH₄ in EtOH, mp 183–184°. Although our attempts to prepare thelepin (**5**) itself from **4** by oxidation with ferricyanide or lead dioxide failed, the structure of thelepin was further confirmed by spectral characterization of thelepin acetate, mp 190°, pale yellow needles from CCl₄ and by Pd-C hydrogenation of **5** to the known 2,4'-dihydroxy-5-methyldiphenylmethane (**11**), mp 135–136° from chloroform-cyclohexane. Compound **11** was prepared by acid-catalyzed condensation of *p*-cresol and *p*-hydroxybenzyl alcohol, mp 137–138° from aqueous EtOH (lit. 135.5¹²), identical in all respects with the thelepin degradation product.

The second product of the NaBH₄ reduction of thelepin (**5**) was characterized as dienol **8** by its mass spectral bromine isotope peaks at m/e 470 (13), 468 (30), 466 (30), and 464 (11 rel %), and by its uv (MeOH) bands at 284 and 291 nm, unchanged in base; notably absent in the uv spectrum was the 257-nm band assigned to the cyclohexadienone chromophore. Structure **8** was confirmed by its ready conversion in MeOH-HCl to, and comparison with, synthetic **4**.

The tail fractions of the chloroform eluate were concentrated to a black tar, from which we recovered by tlc (silica gel, MeOH-chloroform, 3:100) 11 mg of a white crystalline solid, R_f 0.24, mp 180–182°. Its spectral properties led to its identification as 2,4'-dihydroxy-5-hydroxymethyl-3,3',5'-tribromodiphenylmethane (**4**), which we had prepared (*vide supra*) as a synthetic precursor of thelepin (**5**), and with which the natural product was fully identical.

Although the dibromocyclohexadienone moiety of thelepin (**5**) is reminiscent of a number of constituents of marine sponges,¹³ of the five metabolites described here only 3,5-dibromo-4-hydroxybenzyl alcohol was previously known as a natural product. It was reported as a constituent of two species of red algae.¹⁴ This phenol, or its debromo analog, may well be the biogenetic precursor of thelepin (**5**), in contrast to griseofulvin (**6**), which has been shown to be biosynthesized from acetate.¹⁵

(11) C. Paal, *Chem. Ber.*, **28**, 2409 (1895).

(12) R. Pummerer, H. Puttfarcken, and P. Schopflocher, *Chem. Ber.*, **58**, 1808 (1925).

(13) R. J. Andersen and D. J. Faulkner, *Tetrahedron Lett.*, 1175 (1973), and earlier references cited therein.

(14) P. J. Scheuer, "Chemistry of Marine Natural Products," Academic Press, New York, N. Y., 1973, p 91.

(15) A. J. Birch, R. A. Massy-Westropp, R. W. Richards, and H. Smith, *J. Chem. Soc.*, 360 (1958).

Acknowledgment. We are grateful to Drs. Y. Kato and B. J. Burreson for help with the collection of the annelids and to Dr. J. H. Brock for identification.

Tatsuo Higa, Paul J. Scheuer*

Department of Chemistry, University of Hawaii
Honolulu, Hawaii 96822

Received December 26, 1973

Single-Crystal Electron Paramagnetic Resonance and Nonparameterized Fenske–Hall Molecular Orbital Calculations Substantiating the Demise of the Ballhausen–Dahl Bonding Model for d^1 and d^2 $M(IV)$ $M(h^5-C_5H_5)_2L_2$ Complexes

Sir:

The nature of bonding in $M(h^5-C_5H_5)_2L_2$ complexes has been a subject of considerable interest. In 1961 Ballhausen and Dahl¹ formulated a qualitative description to represent the bonding in $M(h^5-C_5H_5)_2H_2$ ($M = Mo, W$) in which they proposed that the lone valence electron pair is localized in a sterically active orbital situated between the two hydrogens. This bonding model has been widely accepted² and generalized to other d^1 and d^2 $M(IV)$ $M(h^5-C_5H_5)_2L_2$ -type complexes containing nonhydridic L ligands. In 1967 Alcock,³ in rationalizing the acute $H_3C-Re-CH_3$ bond angle of 75.8 (1.3)° in dimethyl(*pentahaptocyclopentadienyl*)-(methylcyclopentadiene)rhenium, modified the B–D model by placing the lone pair in an orbital primarily directed normal to the plane bisecting the $Re(CH_3)_2$ fragment.

Preparative and crystallographic investigations performed independently at Wisconsin⁴ and at Oxford⁵ provided operational tests by which the B–D model was rejected for $M(h^5-C_5H_5)_2L_2$ -type complexes. The former group based this conclusion from their comparison between the molecular parameters of $Ti(h^5-C_5H_5)_2(SC_6H_5)_2$ ^{4c} vs. $V(h^5-C_5H_5)_2(SC_6H_5)_2$ ^{4c} and $Ti(h^5-C_5H_5)_2S_5$ ^{4d,6} vs. $V(h^5-C_5H_5)_2S_5$ ^{4d} which showed the similar L–M–L bond angles in the d^1 $V(IV)$ complexes to be ca. 6° less than those in the corresponding isomorphous d^0 $Ti(IV)$ complexes; if the B–D model were correct, electron-pair repulsion arguments would necessitate that the S–V–S bond angle would be larger (rather than significantly smaller) than the S–Ti–S bond angle. From crystal structural data of at least seven new $M(h^5-C_5H_5)_2L_2$ complexes (with d^0 , d^1 , and d^2 $M(IV)$), Green, Prout, and coworkers⁵ at Oxford not only found an analogous correlation between the L–M–L bond angle and the number of nonbonding d electrons on the metal,

which they cited as strong evidence for the Alcock model for $M(h^5-C_5H_5)_2L_2$ molecules, but also suggested a MO bonding description (involving a blending of the B–D and Alcock models) for $M(h^5-C_5H_5)_2H_2$ and $(h^5-C_5H_5)_2M-(\mu_2-L)_2-M'L_n'$ systems.

This paper reports the outcome of epr measurements of the paramagnetic $V(h^5-C_5H_5)_2S_5$ complex doped in a single crystal of the diamagnetic $Ti(h^5-C_5H_5)_2S_5$ host. It provides for the first time a quantitative determination of the orbital character and directional properties of the previously designated nonbonding orbital (with half- or full-occupancy) in a $M(h^5-C_5H_5)_2L_2$ complex. We also present the results of nonparameterized (Fenske–Hall)-type MO calculations⁷ which give excellent agreement with the epr results.^{8,9} These studies provide concrete evidence that the B–D model applied to d^1 and d^2 $M(IV)$ $M(h^5-C_5H_5)_2L_2$ systems is incorrect.

Solution epr spectra of $V(h^5-C_5H_5)_2S_5$ and $V(h^5-C_5H_5)_2(SC_6H_5)_2$ each show eight well-resolved lines (line width, 5–8 G), due to the hyperfine interaction of the unpaired electron with the ⁵¹V nucleus ($I = 7/2$ for ⁵¹V, 99.8%). The isotropic parameters are $V(h^5-C_5H_5)_2S_5$ (in DMF), $g_{iso} = 1.9909$, $A_{iso} = (-)64.78$ G; $V(h^5-C_5H_5)_2(SC_6H_5)_2$ (in toluene), $g_{iso} = 1.9919$, $A_{iso} = (-)64.99$ G. These isotropic hyperfine constants fall within the range of 60–75 G for $V(h^5-C_5H_5)_2L_2$ complexes¹⁰ thereby indicating a similar behavior of the unpaired electron despite considerable variation in the terminal L ligands. Epr measurements were made on several crystals containing ca. 0.2% $V(h^5-C_5H_5)_2S_5$ in the diamagnetic $Ti(h^5-C_5H_5)_2S_5$ host;¹¹ experimental details are available elsewhere.¹²

The interpretation of the epr data (Table I) is based

Table I. Experimental g and T Tensors with Directions and Best Fit Parameters

$g_x = 1.9964$	$\phi = 59.05^\circ$	$T_x = (-)66.6$ G	$\phi = 32.41^\circ$
$g_y = 1.9997$	$\theta = 51.50^\circ$	$T_y = (-)111.3$ G	$\theta = 140.68^\circ$
$g_z = 1.9689$	$\psi = -59.52^\circ$	$T_z = (-)23.5$ G	$\psi = 27.97^\circ$
For $a = -0.963$ and $b = 0.270$			
$T_x = (-)66.6$ G	$P = 93.2 \times 10^{-4}$ cm ⁻¹		
$T_y = (-)111.3$ G	$\langle r^{-3} \rangle = 1.99$ au		
$T_z = (-)23.5$ G	$\chi = -2.11$		
$-A_{iso} = K = 65.8 \times 10^{-4}$ cm ⁻¹	$\lambda = 30$ cm ⁻¹		

upon the reasonable assumption of C_{2v} symmetry for the $V(h^5-C_5H_5)_2S_2$ fragment of the pentasulfide complex. The epr data are only compatible with an electronic ground state of a_1 representation with the unpaired electron localized mainly on the vanadium. On the basis of the computed χ value¹³ of -2.11 (almost

(1) C. J. Ballhausen and J. P. Dahl, *Acta Chem. Scand.*, **15**, 1333 (1961).

(2) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Interscience, New York, N. Y., 1966, p 766.

(3) N. W. Alcock, *J. Chem. Soc. A*, 2001 (1967).

(4) (a) L. F. Dahl, Plenary Lecture, 4th International Conference on Organometallic Chemistry, Bristol, 1969; (b) E. G. Muller, Ph.D. Thesis, University of Wisconsin (Madison), 1970; (c) E. G. Muller, S. F. Watkins, and L. F. Dahl, to be submitted for publication. (d) E. G. Muller, J. L. Petersen, and L. F. Dahl, to be submitted for publication.

(5) (a) J. C. Green, M. L. H. Green, and C. K. Prout, *J. Chem. Soc., Chem. Commun.*, 421 (1972), and references cited therein; (b) M. L. H. Green, Sectional Lecture, 5th International Conference on Organometallic Chemistry, Moscow, 1971 (*cf. Pure Appl. Chem.*, **30**, 373 (1972)); (c) W. E. Douglas and M. L. H. Green, *J. Chem. Soc., Dalton Trans.*, 1796 (1972).

(6) E. F. Epstein, I. Bernal, and H. Köpf, *J. Organometal. Chem.*, **26**, 299 (1971).

(7) *Cf.* M. B. Hall and R. F. Fenske, *Inorg. Chem.*, **11**, 768 (1972).

(8) While this investigation was in progress, Bakalik and Hayes⁹ reported a single-crystal epr study of $V(h^5-C_5H_5)_2Cl_2$ together with MO calculations. Although they concluded that the unpaired electron is in an a_1 -type MO primarily composed of $3d_{z^2}$ and $3d_{x^2-y^2}$ $V(IV)$ character (since the crystal structure of the diamagnetic $Ti(h^5-C_5H_5)_2Cl_2$ host is unknown), they did not know the orientation of the hyperfine tensor in $V(h^5-C_5H_5)_2Cl_2$ and hence were not able to choose a unique set of coefficients specifying the metal orbital character. In addition, their MO calculations are in disagreement with their conclusions (and with our MO calculations).

(9) D. P. Bakalik and R. G. Hayes, *Inorg. Chem.*, **11**, 1734 (1972).

(10) G. Doyle and R. S. Tobias, *Inorg. Chem.*, **7**, 2479 (1968).

(11) The red, air-stable $V(h^5-C_5H_5)_2S_5$ -doped crystals of $Ti(h^5-C_5H_5)_2S_5$ are monoclinic, $P2_1/n$, $a = 9.019$, $b = 13.089$, $c = 11.294$ Å, $\beta = 93.62^\circ$, $Z = 4$.

(12) See paragraph at end of paper regarding supplementary material.

(13) B. R. McGarvey, *J. Phys. Chem.*, **71**, 51 (1967).