Tetrahedron Vol. 29, pp. 1605 to 1609. Pergamon Press 1973 Printed in Great Britain

MARINE NATURAL PRODUCTS OF THE ATLANTIC ZONE—V[1]

THE STRUCTURE AND CHEMISTRY OF TAONDIOL AND RELATED COMPOUNDS

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(*Received in the UK* 4 *December* 1972; *Accepted for publication* 8 *January* 1973)

Abstract—The structure of taondiol (**1**), a new aromatic terpenoid compound isolated from the marine alga *Taonia atomaria* (Dyctiotaceae) is elucidated and its biogenesis discussed. 11'-Desoxy-taondiol methyl ether (**7**) has been synthesized.

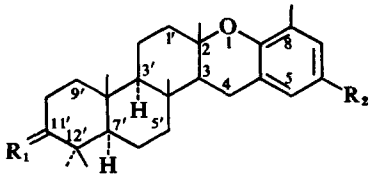
In a preliminary communication[2] we reported the isolation from the marine alga *Taonia atomaria* of the tocopherol-like compound taondiol, for which we proposed structure **1** based on spectroscopic analyses, chemical transformations and biogenetic considerations. The present paper details the chemistry and spectral properties of taondiol and its transformation products as well as the synthesis of the taondiol derivative **7**.

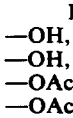
RESULTS AND DISCUSSION

Analytical values and mass spectrometry fit for taondiol the empirical formula $C_{27}H_{40}O_3$ (M^+ at *m/e* 412·292), m.p. 283–284°, $[\alpha]_D$ −76°. In the IR it shows bands at 3540, 3340, 1620, 1500, 860 and 800 cm^{-1} and in the UV at 298 nm. The PMR spectrum† (Table 1) exhibits two *meta*-coupled aromatic protons at 3·56 and 3·62, a singlet at 5·76 (1 H, exchangeable with D_2O) assigned to the phenolic hydroxyl proton, two broad signals at 6·8 ($W_{1/2}$ = 14 Hz, >CHOH) and 7·40 (two benzyl protons), and two singlets at 7·89 (aromatic Me) and 8·86 (Me group on carbon bearing oxygen). In the upfield region appear four tertiary Me groups at 9·00, 9·10, 9·12 and 9·18. Upon methylation with CH_2N_2 the compound affords in very low yield the methoxy derivative **2**, $C_{28}H_{42}O_3$ (M^+ at *m/e* 426), m.p. 203–204°, $[\alpha]_D$ −67°, which confirms the phenolic structure of **1**.

The spectral data of **1** are very similar to those of δ-tocopherol[3] and provide good evidence for the 8-methyl-6-chromanol nature of the chromophore. Examination of the mass spectra of **1** and **2** lends support to this implied taondiol-δ-tocopherol relationship. The base peak at *m/e* 137·0599 ($C_8H_9O_2$ requires 137·0602) in **1** (base peak at *m/e* 151 in **2**) occurs by cleavage with hydrogen transfer giving the fragment A (Scheme 1).[4] Further peaks at *m/e* 275·236 [$C_{19}H_{31}O$ requires 275·2374; m 183·5 ($M^+-C_8H_9O_2$)] and *m/e* 257·2290 [$C_{19}H_{29}$ requires 257·2269; m* 240·2 ($M^+-C_8H_9O_2-H_2O$)] in the mass spectrum of **1**, shown also in that of **2**, in addition to the other peaks which are in good agreement with the structures assigned, are due to the tricyclic diterpene entity of the molecule as shown below; their particularly high intensity is probably due to the great stability of the fragment A.[4]

Acetic acid treatment of taondiol gives the monoacetate **3**, of empirical formula $C_{29}H_{42}O_4$; its PMR spectrum shows a singlet at 7·92 (OAc) and a broad multiplet at 5·50 ($W_{1/2}$ = 14 Hz) corresponding to



	R_1	R_2
1	—OH, ---H	—OH
2	—OH, ---H	—OMe
3	—OAc, ---H	—OH
4	—OAc, ---H	—OAc
5	=O	—OMe
6		—OMe
7	—H, ---H	—OMe

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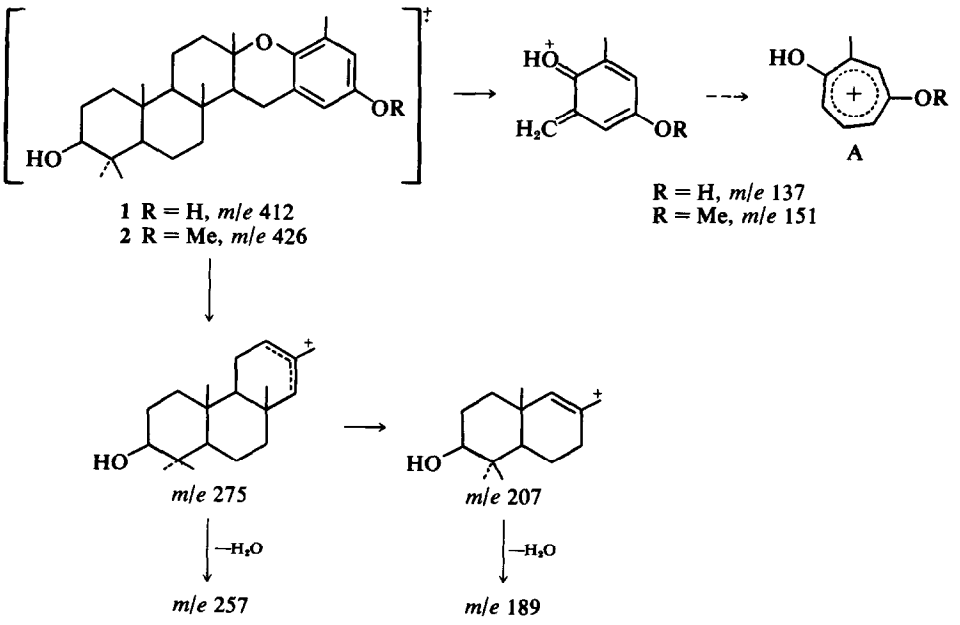
†τ-scale (100 MHz).



Scheme 1

the proton geminal to the acetate group. By refluxing **1** with acetic anhydride the diacetate **4** is obtained, $C_{31}H_{44}O_5$ (M^+ at *m/e* 496), the PMR spectrum of which exhibits two singlets at 7·75 (ϕ–OAc) and 7·95 (R–OAc). Upon oxidation with Jones reagent at 0° the OMe derivative **2** yields the ketone V which is indicative of a secondary OH group in **1**. The absence of further unsaturations besides the chromanol moiety, and the elucidation of the chemical nature of the remaining O atom, indicate the presence of three additional rings in **1**.

In order to clarify the structure and stereochemistry of **1** the OH group was removed by conversion of **2** to the thioketal **6**, via the ketone **5**, followed by Raney nickel desulfurization, thus obtaining 11′-desoxytaondiol methyl ether (**2**), $C_{28}H_{42}O_2$ (M^+ at *m/e* 410).

Examination of the PMR spectra of **1** and derivatives in the Me region, the study of the changes observed in the chemical shifts of the Me groups and critical comparison with literature data on these groups in ring A of 3(equatorial)-hydroxy-4,4-dimethyl terpenoids with A/B-*trans*-fused rings[5] suggested the presence of this same cyclic system in taondiol and led to the assignment of the Me peaks (Table 1). Of the four Me groups in the diterpene entity of **1** only the Me–$C_{4'}$ is affected by the anisotropy of the aromatic ring and therefore is found at a different magnetic field than the corresponding Me group in saturated terpenoids; the singlet at 9·12 is attributed to the Me–$C_{4'}$ because upon changing the solvent from $CDCl_3$ to C_6D_6 it is strongly moved upfield (28 Hz) whereas the other three Me resonances, which appear at the same position as in saturated triterpenes, remain almost unchanged.

On the basis of the above results the most plausible alternative for the structure and stereochemistry of taondiol seemed to be **1**. This stereostructure has now been established definitely by the X-ray analysis of methoxy taondiol iodoacetate.[6]

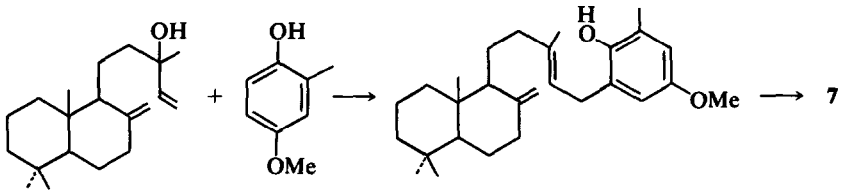
The structure of taondiol has also been confirmed by the synthesis of 11′-desoxytaondiol methyl ether.[7] Condensation of commercial manool (**8**) with toluquinol-4-methyl ether (**9**) at room temperature in dry dioxane with the aid of BF_3[8] afforded a mixture of products from which the desired "prenyl phenol" **10** was isolated as an oil. Its PMR spectrum in the low-field region exhibits signals for five protons: a two-protons singlet at 3·33 (aromatic H), a one-proton triplet centred at 4·63 ($J = 8$ Hz, H–C_3) and two broad singlets at 5·10 and 5·40 (1 H each, exocyclic $=CH_2$). Further it shows a broad doublet at 6·65 (2 H, $J = 8$ Hz, benzyl protons) and three singlets (3 H each) at 6·24 (OMe), 7·77 (aromatic Me) and 8·23 (Me–C_2). In the up-field region appear signals for three tertiary Me groups at 9·13, 9·20 and 9·32. Treatment of **10** with 98% HCOOH at 70° gave, in 85% yield, the crystalline compound **7** which proved to be identical with the taondiol degradation product obtained above.

The structure **1** for taondiol is also well explained from the standpoint of biogenesis. The pathway proposed for the biosynthesis of plastoquinones and tocopherols in higher plants[9] outlined in Scheme 2 could account also for the biosynthesis of taondiol. Tetraprenylation of homoarbutin

Table 1. Chemical shifts in $CDCl_3$ (100 MHz, τ-values)[a]

Compound	H—C_5, H—C_7	R—C_6	H—$C_{11'}$	2H—C_4	AcO—$C_{11'}$	Me—C_8	Me—C_2	Me—$C_{4'}$	Me—$C_{8'}$	αMe—$C_{12'}$	βMe—$C_{12'}$
Taondiol (1)	3·56 d(2·3)	5·76[b]	6·80	7 40	—	7·89	8·86	9·12	9·10	9·00	9·18
	3·62 d(2·3)	s	m[14]	d(8)		s	s	s	s	s	s
Taondiol methyl	3·47 d(2·4)	6·28[c]	6·77	7 40	—	7·88	8·86	9·13	9·11	9·01	9·19
ether (2)	3·57 d(2·4)	s	m[14]	d(8)		s	s	s	s	s	s
Taondiol	3·54 d(2 4)		5 50	7 40	7·93	7 89	8 88	9·12	9·12	9·12	9·12
monoacetate (3)	3·61 d(2·3)		m[14]	d(8)	s	s	s	s	s	s	s
Taondiol	3 38	7·75[d]	5 51	7·42	7·95	7·89	8·85	9·12	9·12	9 12	9·12
diacetate (4)	s	s	m[14]	d(8)	s	s	s	s	s	s	s
11′-Ketotaondiol	3·44 d(2·4)	6 26[c]	—	7·40[e]	—	7·86	8·83	9·05	9·02	8 88	8·92
methyl ether (5)	3·56 d(2·4)	s		*m*		s	s	s	s	s	s
11′-Desoxytaondiol	3 32 d(2 3)	6 20[c]		7·39	—	7·85	8·86	9·13	9·13	9·13	9·13
methyl ether (7)	3·43 d(2·3)	s		d(8)		s	s	s	s	s	s

[a]Coupling constants J in parentheses, $W_{1/2}$ in brackets (both in Hz).
[b]R = OH
[c]R = OMe
[d]R = OAc
[e]2H—C_4 + 2H—$C_{10'}$



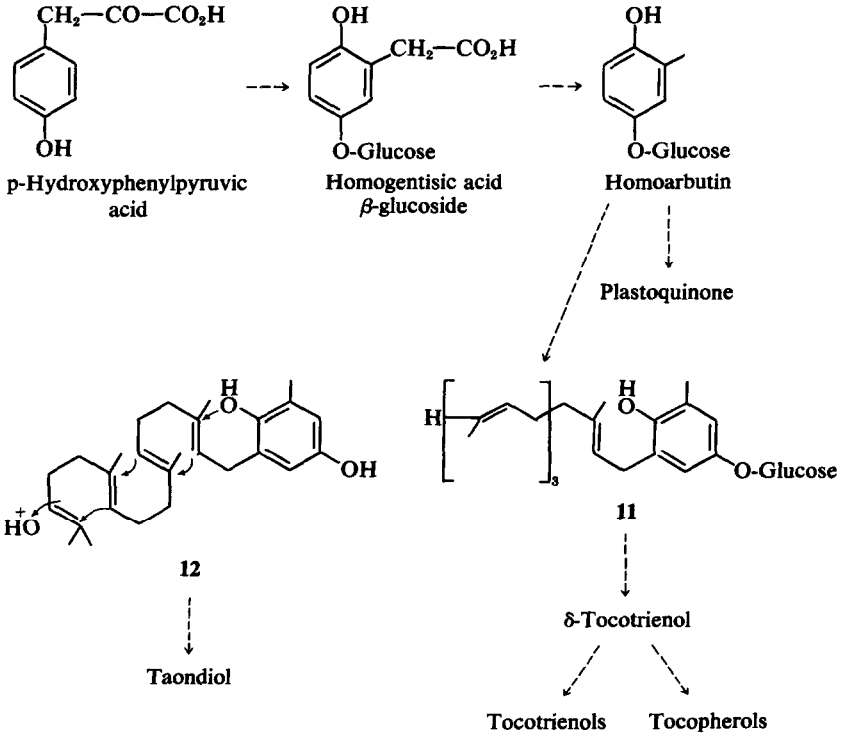
8 9 10

would give tetraprenyl-homoarbutin (**11**). Cyclisation and deglycosylation (not necessarily in this sequence) of **11** would give δ-tocotrienol, which can be regarded as the parent member of both the tocotrienol and tocopherol series, by suitable hydrogenation and methylation reactions. Taondiol might also be produced from **11**. In fact, we can imagine that **11**, or the deglycosylated intermediate **12**, undergoes an essentially synchronous process for the formation of the rings, if some oxidizing agent furnishes HO^+ at $C_{11'}$, following the same kind of rearrangement required to get most of the terpenoid compounds.

EXPERIMENTAL

The m.ps were determined on a Kofler block and are uncorrected. Solvent used for recrystallization was MeOH unless otherwise stated. Optical rotations were measured in $CHCl_3$ on a Perkin–Elmer 141 polarimeter. The UV spectra were taken with a Perkin–Elmer 137 and the IR spectra with a Perkin–Elmer R-10 (60 MHz) or a Varian HA-100D (100 MHz) in $CDCl_3$ with TMS as internal reference. Mass spectra were recorded on Hitachi Perkin–Elmer RMU-7 and AEI MS-902 instruments. Column and dry column chromatography was performed on silica gel 0·2–0·5 and 0·05–0·2 mm, respectively, and TLC as well as preparative TLC on silica gel G, all Merck products. Light petroleum refers to the fraction of b.p. 60–80°.

Isolation of taondiol **1**. The air-dried seaweed (3·2 kg), collected in August at Punta del Hidalgo (Tenerife), was extracted with ether and the extract concentrated *in vacuo* to about 2 l. It was then shaken with 1 N KOH and subsequently with 1 N HCl to remove acidic and basic components. After evaporating the solvent the neutral oily residue (350 g) was chromatographed on silica gel (3 kg). The fractions (84 g) eluted with $CHCl_3$ were carefully rechromatographed to yield **1** (2·2 g), colourless crystals from dry benzene, m.p. 283–284°, $[\alpha]_D$ −76° (*c*, 0·30). (Found: C, 78·59; H, 9·88. $C_{27}H_{40}O_3$ requires: C, 78·60; H, 9·77%); λ_{max}^{EtOH} 298 nm (ε 3860); ν_{max}^{KBr} 3540, 3340, 1620, 1500, 860, 800 cm^{-1}; PMR: see



Scheme 2

Table 1, mass spectrum: *m/e* (%) 412 (M^+), 275 (25), 257 (75), 207 (12), 189 (40), 175 (63), 137 (100), 135 (50), 121 (52), 109 (43), 95 (44).

Taondiol methyl ether **2**. Taondiol (200 mg) with CH_2N_2 in ether was allowed to stand overnight at room temp. Usual work-up gave **II** in colourless crystals, m.p. 203–204°, $[\alpha]_D$ −67° (*c*, 0·94). (Found: C, 79·06; H, 10·07. $C_{28}H_{42}O_3$ requires: C, 78·83; H, 9·92%); ν_{max}^{KBr} 3400, 1620, 1495, 1240, 1160, 1070, 860 cm^{-1}; PMR: see Table 1; mass spectrum: *m/e* (%) 426 (M^+), 275 (19), 257 (69), 189 (69), 175 (31), 151 (100), 135 (41), 121 (50)

Taondiol monoacetate **3**. Taondiol (30 mg) in HOAc (10 ml) was refluxed for 7 hr. The mixture was poured into water, extracted with ether and the crude product chromatographed using benzene-$CHCl_3$ (2:1) as eluent. Recrystallization of the less polar compound (16 mg) afforded colourless crystals of **3**, m.p 254–256°, $[\alpha]_D$ −60° (*c*, 0·33) (Found: C, 76·36, H, 9·08. $C_{29}H_{42}O_4$ requires: C, 76·61, H, 9·31%), $\nu_{max}^{CCl_4}$ 3540, 1740, 1480, 1230, 1040, 940 cm^{-1}; PMR: see Table 1. Further elution with $CHCl_3$ yielded starting material

Taondiol diacetate **4**. Taondiol (100 mg) in Ac_2O (10 ml) was refluxed for 4 hr. The mixture was poured into water, extracted with ether and worked up as usual. Recrystallization gave **4**, colourless crystals, m.p. 195–197°, $[\alpha]_D$ −56° (*c*, 0·82). (Found: C, 74·96; H, 8·93. $C_{31}H_{44}O_5$ requires: C, 74·96, H, 8·98%); $\nu_{max}^{CCl_4}$ 1760, 1740, 1480, 1240, 1200, 1030, 940 cm^{-1}; PMR: see Table 1; mass spectrum: *m/e* (%) 496 (M^+), 454 (33), 436 (5), 421 (9), 394 (10), 379 (12), 351 (10), 257 (100), 189 (40), 175 (51), 137 (70), 121 (50).

11′-*Ketotaondiol methyl ether* **5**. A soln of **2** (120 mg) in acetone (20 ml) was treated with CrO_3 (180 mg)-H_2O (0·15 ml)-H_2SO_4 (0·15 ml) and the ice-cooled mixture stirred for 1 hr. After usual work-up the product was chromatographed, elution with benzene-light petroleum (2:1) yielding colourless crystals of **5** (102 g), m.p. 208–209°, $[\alpha]_D$ −31° (*c*, 0·64). (Found: C, 79·06; H, 9·60. $C_{28}H_{40}O_3$ requires: C, 79·20; H, 9·50%); ν_{max}^{KBr} 1700, 1500, 1230, 1060, 940 cm^{-1}; PMR: see Table 1; mass spectrum: *m/e* (%) 424 (M^+), 273 (33), 205 (18), 151 (100), 135 (27), 121 (40)

11′-*Desoxytaondiol methyl ether* **7**. A mixture of **5** (22 mg), ethane-dithiol (0·5 ml) and BF_3-etherate (0·5 ml) was set aside at room temp for 1 hr. Then $NaHCO_3$ aq was added and the whole extracted with ether. The ether soln was washed with 2 N NaOH and water, dried over Na_2SO_4 and the solvent evaporated. Chromatography of the crude thioketal (24 mg) with benzene-light petroleum (1:2) as eluent yielded **6** (20 mg), m.p. 200–202°; PMR (60 MHz, τ): 3·44 (1 H, d, J = 2·4 Hz), 3·56 (1 H, d, J = 2·4 Hz), 6·23 (3 H, s), 6·77 (ethylene thioketal protons), 7·86, 8·85, 8 88 and 8·96 (each 3 H, s), 9·12 (6 H, s). The thioketal **6** (20 mg) was dissolved in EtOH (15 ml) and heated at 70° with Raney-Ni (W-2) for 12 hr under stirring. After cooling and removal of the catalyst and solvent, the oily residue was taken up with ether and the ether soln washed with water, dried and evaporated. The resulting oily product was purified by preparative TLC, developing the plates with benzene-light petroleum (1:1), to give the crystalline compound **7** (12 mg), m.p. 158–160°, $[\alpha]_D$ −69° (*c*, 0·40) (Found: C, 82·00; H, 9·97. $C_{28}H_{42}O_2$ requires: C, 81·95; H, 10·24%); ν_{max}^{KBr} 1620, 1500, 1070, 860 cm^{-1}; PMR: see Table 1; mass spectrum: *m/e* (%) 410 (M^+), 259 (92), 206 (30), 191 (50), 151 (84), 135 (30), 121 (30).

Synthesis of **7**. To a soln of **9** (3·08 g, 0·0220 moles) and BF_3 etherate (2·0 ml) in freshly distilled dioxane (30 ml) was added dropwise, with stirring at room temp and under N_2, a soln of manool **8** (6·47 g, 0·0223 moles) in dioxane (30 ml). After the addition was complete, stirring at room temp was continued overnight. The mixture was poured onto crushed ice and extracted 3 times with 100 ml portions of ether. The ether soln was washed with water, 5% $NaHCO_3$ aq and water and dried over Na_2SO_4 After removing the solvent, the oily residue (9·2 g) was chromatographed on silica gel (500 g). The benzene-light petroleum fractions (7·9 g) were carefully rechromatographed to yield the "prenyl phenol" **10** (5 7 g, 65% yield) as an oil; PMR (60 MHz, τ): 3 33 (2 H, s), 4·63 (1 H, t, J = 8 Hz), 5·10 and 5 40 (each 1 H, s), 6·24 (3 H, s), 6·65 (2 H, d, J = 8 Hz), 7·77, 8·23, 9·13, 9·20 and 9·32 (each 3 H, s). To **10** (1·06 g) 98% HCOOH (15 ml) was added with stirring under N_2. After the addition was complete, stirring was continued for 15 min at 25°, upon which the mixture was gradually heated to 50° obtaining a clear soln. Then it was refluxed for 1 hr After cooling it was poured into water and extracted with ether. The ether soln was washed with water, 5% $NaHCO_3$ aq and water, dried over Na_2SO_4 and the solvent evaporated. The oily residue was chromatographed on silica gel (30 g), elution with benzene-light petroleum (1:2) affording **7** (840 mg, 85% yield), m.p. 158–159°, $[\alpha]_D$ −69° (*c*, 0 80). (Found: C, 82 06; H, 9 98. $C_{28}H_{42}O_2$ requires: C, 81·95; H, 10·24%). The physical and spectroscopic data (m m.p , TLC, IR, PMR, MS) were identical with those of the chromane derived from naturally occurring taondiol.

Acknowledgement—The authors wish to thank Dr. W. Vetter, Hoffmann-La Roche, Basel, for realizing the high resolution mass spectra, Dr. J. L. Bretón for his helpful suggestions and encouragement, and the Oceanographic Institute for valuable help One of us (J.D.) thanks the Ministerio de Educación y Ciencia for the fellowship granted from "Formación de Personal Investigador". This work was performed within the Programme 1971 conceded by the Foundation Juan March.

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