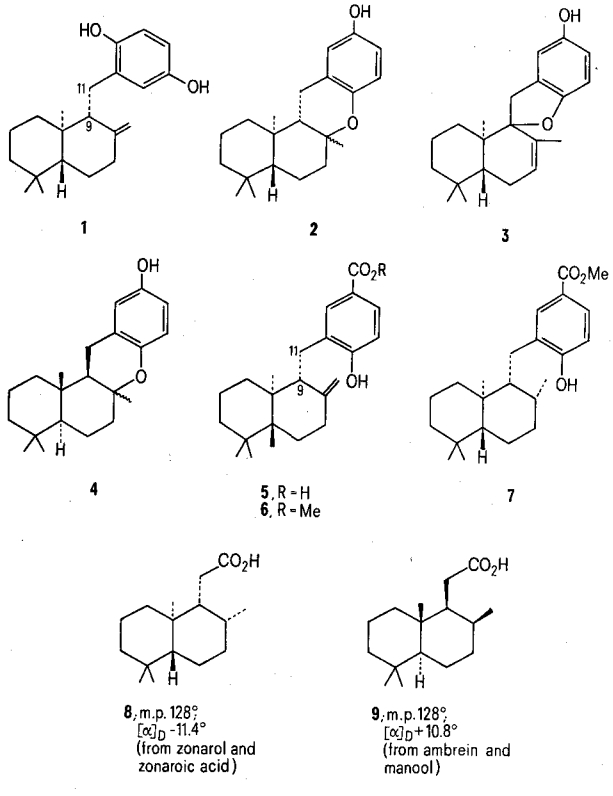
## Zonaroic Acid from the Brown Seaweed *Dictyopteris undulata* (= *zonarioides*)

The brown seaweed *Dictyopteris undulata* (= *zonarioides*) was previously shown to contain a sesquiterpene-substituted hydroquinone zonarol (**1**)[1] accompanied by minor amounts of the derived chromazonarol (**2**) and isochromazonarol (**3**)[2]. Interestingly, the enantiomeric chromazonarol (**4**) has also been shown to occur in the sponge *Disidea pallescens*[3].

We now report the occurrence in *Dictyopteris undulata* of a further sesquiterpenoid component, zonaroic acid (**5**), in which the bicyclic isoprenoid moiety is attached to a 4-hydroxybenzoic acid. During the structural work, we have also obtained evidence which defined the absolute stereochemistry in zonarol-zonaroic acid-chromazonarol series (10 α-series; 5R, 9R, 10S) and accordingly in *ent*-chromazonarol series (10 β-series; 5S, 9S, 10R).

Silica gel column chromatography of the chloroform extract of the air-dried alga gave zonaroic acid (**5**) on elution with 30% diethyl ether in benzene. Further chromatography by graded elution from silica gel column (benzene-20% diethyl ether in benzene) gave the acid as a gum (0.1% yield, dry wt.). Attemps to crystallize this material only gave amorphous powder with m.p. 81–85° (from cyclohexane), $\{\alpha\}_D$–5.4° (c, 4 in $CHCl_3$), M⁺/e 342. It gave a crystalline methyl ester (**6**), m.p. 182–182° (from light petroleum-ethyl ether), M⁺/e 356, δ $OCH_3$ 3.85, $\nu_{max}$ 1720 $cm^{-1}$, on treatment with ethereal diazomethane at r.t. for 1 min. The free acid showed UV-($\lambda_{max}^{MeOH}$ 257 nm, log ε 4.00; $\lambda_{max}^{MeOH\ -OH^-}$ 288 nm) and IR-($\nu_{max}$ 3400, 1670 and 1600 $cm^{-1}$) spectra clearly indicating the presence of a 4-hydroxybenzoic acid chromophore. This was supported by NMR ($CDCl_3$) which also established the location of the isoprenoid moiety at C-3; in the aromatic region signals from 3 protons were observed, 2 of which occurred at relative low field (δ 7.84, m) and are therefore assigned to the deshielded protons *ortho* to the carboxyl group, and the 3rd signal appeared as a doublet at δ 6.74 (*Jo* = 8 Hz). This aromatic NMR pattern is identical with that of 4-hydroxy-3-tetraprenylbenzoic acid[4]. Two hydroxyl protons ($D_2O$ exchangeable) are seen at δ 5.4 and 8.3 ppm. The rest of the spectrum showed signals corresponding to those assigned in the spectrum of zonarol (**1**)[1] to 3 *tert*-methyl groups (overlapping sharp singlets centred at δ 0.85), an exocyclic double bond (b singlets at δ 4.60 and 4.75 ppm) and a benzylic methylene group (δ 2.7, m). The close relationship between zonaroic acid and zonarol was further evidenced by mass spectrometry: both spectra are dominated by fragments resulting from the cleavage of $C_9$–$C_{11}$ bond: *m/e* 191 (100) and 123 (90) in the spectrum of **1** and 191 (100) and 151 (60) in the spectrum of **5**.




The structure **5** for zonaroic acid was confirmed by chemical interrelation with zonarol, using a method analogous to that employed by some of us in structural proof of zonarol itself[1]. The ester **6** was hydrogenated in diethyl ether over 10% Pt-C at r.t. and 2.5 atm. to the dihydroderivative **7**, m.p. 178–179° (from light petroleum-ethyl ether), M⁺/e 358, $\lambda_{max}$ 261 (log ε 4.00) mm, which was then oxidized with alkaline $KMnO_4$ to the acid **8** (10% yield), single epimer, m.p. 128° (from acetonitrile), $[\alpha]_D$–11.4° (c, 2.8 in $CHCl_3$), δ $^{CDCl_3}_{Me}$ 0.68 (s), 0.77 (s), 0.84 (s) and 0.93 (d; J 7 Hz) ppm. A sample of this acid was converted to its methyl ester and gave a single peak in GLC (3% SE-30 at 190° and 1% OV-1 at 160°). The acid **8** was identical (m.p., $[\alpha]_D$, NMR and GLC of its methyl ester) with dihydrotauranic acid derived in 40% yield from the degradation of zonarol[5]. The dihydrotauranic acid (**9**) obtained from ambrein and manool[6,7] had m.p. 128° but rotation of +10.8°[6]. Since the absolute configuration of ambrein and manool is established[6,8,9] (10 β-series; 5S, 9S, 10R), the algal metabolites zonarol, chromazonarol and zonaroic acid must derive from the antipodal 10 α-series (5R, 9R, 10S). Accordingly, the sponge-derived enantiomeric chromazonarol must have the absolute configuration shown in **4**.

The co-occurrence of zonaroic acid and the hydroquinone zonarol in *Dictyopteris undulata* strongly suggests that 4-hydroxybenzoic acid is the ring precursor as in ubiquinone biogenesis[10]. An analogous pair of biogenetically related compounds, i.e. 4-hydroxy-3-tetraprenylbenzoic acid-2-tetraprenyl-1,4-dihydroxybenzene, has also been shown to occur in the sponge *Ircinia muscarum*[4]


[1] W. FENICAL, J. J. SIMS, R. M. WING and P. RADLIK, J. org. Chem. *38*, 2383 (1973).

[2] W. FENICAL and O. MCOLNNELL, Experientia *31*, 1004 (1975).

[3] G. CIMINO, S. DE STEFANO and L. MINALE, Experientia *31*, in press (1975).

[4] G. CIMINO, S. DE STEFANO and L. MINALE, Experientia *28*, 1401 (1972).

[5] Hydrogenation of zonarol was carried out as described for the ester *6*. FENICAL et al. (ref.[1]) on hydrogenation ($PtO_2$ as catalyst) of zonarol followed by oxidative cleavage of the hydroquinone moiety obtained an epimeric mixture at C-8 (60:40) of dihydrotauranic acid.

[6] L. RUZICKA, O. DÜRST and O. JEGER, Helv. chim. Acta *30*, 353 (1947).

[7] J. D. COCKER and T. G. HALSALL, J. chem. Soc. *1956*, 4262.

[8] G. BÜCHI and K. BIEMANN, Croat. chem. Acta *29*, 163 (1957); J. D. COCKER and T. G. HALSALL, J. chem. Soc. *1957*, 4401.

[9] W. KLYNE and J. BUCKINGHAM, in *Atlas of Stereochemistry* (Chapman and Hall, London 1974), p. 110 and 119.

[10] D. R. THRELFALL and G. R. WHISTANCE, in *Aspect of Terpenoid Chemistry and Biochemistry* (Ed. T. W. GOODWIN, Academic Press, London and New York 1971), p. 357.

and this further indicates that similar biosynthetic potentials exist in both marine algae and invertebrate animals.

*Summary.* A sesquiterpene-substituted 4-hydroxybenzoic acid, zonaroic acid (**5**), is described from the brown seaweed *Dictyopteris undulata* (= *zonarioides*). The absolute stereochemistry in the zonarol (**1**)-chromazonarol (**2**) and zonaroic acid (**5**) series has also been defined. The occurrence of **5** along with zonarol (**1**), the corresponding sesquiterpene-substituted hydroquinone, suggests that 4-hydroxybenzoic acid is the ring precursor as in ubiquinone biogenesis.

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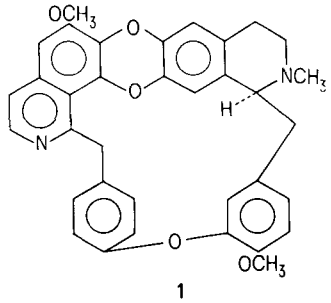
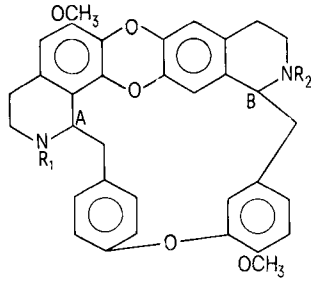
## Trigilletimine: A New *Bis*benzylisoquinoline Alkaloid from *Triclisia* Species[1]

In a previous communication[2] the isolation of an unidentified base referred to as TGS-1 from an acidic extract of the stems and roots of *Triclisia gilletii* (De Wild.) Staner and *T. patens* Oliv. was reported, along with other *bis*benzylisoquinoline alkaloids. This paper is to report the structure and stereochemistry of this base which has been named trigilletimine.

Trigilletimine (**1**), crystallized from ethanol as white needles, mp 284° (dec); $[\alpha]_D^{25}$ −285.7° (c 0.7, $CH_2Cl_2$); $\lambda_{max}^{MeOH}$ 210 nm (log ε 4.72), 232 (sh) (4.67), 273 (sh) (4.21), 311 (sh) (3.46) and 351 (3.05) with a bathochromic shift in acidic methanol; $\delta_{60\ MHz}^{CDCl_3}$ 2.40 (s) (3H) ($NCH_3$), 3.92 (s) (3H) ($OCH_3$), 3.99 (s) (3H) ($OCH_3$), 5.86–7.29 (m) (1OH) (ArH), 7.39 (d) (1H, J = 6Hz) and 8.34 (d) (1H, J = 6 Hz);




**1**




**2** $R_1$ = H, $R_2$ = $CH_3$; A = R, B = S
**3** $R_1$ = $R_2$ = $CH_3$; A = R, B = S
**4** $R_1$ = H, $R_2$ = $CH_3$; A = B = S
**5** $R_1$ = $CH_3$, $R_2$ = H; A = B = R
**6** $R_1$ = $R_2$ = $CH_3$; A = S, B = R
**7** $R_1$ = $CH_3$, $R_2$ = H; A = R, B = S
**8** $R_1$ = $CH_3$, $R_2$ = H; A = S, B = R

M+ *m/e* 558 (89%) (measured 558.2131 and calculated 558.2154 for $C_{35}H_{30}N_2O_5$), 557 (100), 543 (32), 279 (36), 211 (8), 210.5 (10) and 189 (6). The base gave a positive dibenzodioxin test with a mixture of nitric and sulfuric acids[3].

Catalytic reduction of trigilletimine in ethanol over 5% Pd-C for 12 h afforded tetrahydrotrigilletimine (**2**), mp starts decomp. at 187°; $[\alpha]_D^{17}$ −160° (c 1.0, $CH_3OH$); $\lambda_{max}^{CH_3OH}$ 211 nm (log ε 4.15), 238 (sh) (4.05), 280 (3.23), 307 (sh) (3.05); $\delta_{60\ MHz}^{CD_3OD}$ 2.88 (s) (3H) ($NCH_3$), 3.89 (s) (6H) (2 $OCH_3$), 6.04–7.17 (10H) (ArH); M+ *m/e* 562 (57%) for $C_{35}H_{34}N_2O_5$, 561 (41), 547 (5), 363 (6), 349 (16), 336 (27), 335 (100), 321 (28) and 168 (16).

Treatment of **2** with $CH_2O$ and $NaBH_4$ gave N-methyltetrahydrotrigilletimine (**3**) mp 178–182° dec; $[\alpha]_D^{20}$ −209° (c 0.45, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 210 nm (log ε 4.10), 235 (sh) (4.01), 275 (sh) (3.54), 288 (sh) (3.49), 345 (sh) (3.00); $\delta_{60\ MHz}^{CDCl_3}$ 2.50 (s) (3H) ($NCH_3$), 2.56 (s) (3H) ($NCH_3$), 3.89 (s) (3H) ($OCH_3$), 3.93 (s) (3H) ($OCH_3$), and 6.00–7.50 (10H) (ArH); M+ *m/e* 576 (56%) for $C_{36}H_{36}N_2O_5$, 350 (37), 349 (100), 335 (59) and 175 (84).

The NMR-spectrum of trigilletimine showed a pair of doublets characteristic of *ortho* aromatic protons at δ 8.34 (1H, J = 6 Hz) and 7.39 (1H, J = 6 Hz), each of which collapsed to a singlet upon irradiation of the other. The same behavior is exhibited by the C-3 (δ 8.33 [d, 1H, J = Hz]) and C-4 (δ 7.36 [d, 1H, J = 6 Hz]) protons of papaverine. The molecular ion appeared at *m/e* 558 which is 4 mass units less than that of some secondary amino alkaloids of this group such as trilobine[4] (**4**) and *O*-methylmicranthine[5] (**5**). The large M, M-1 and M-15 ions were suggestive of an isoquinoline system similar to papaverine[6]. All of these data, along with the bathochro-

[1] Part XII in the series 'Constituents of West African Medicinal Plants'. For Part XI see D. Dwuma-Badu, J. S. K. Ayim, A. N. Tackie, J. E. Knapp, D. J. Slatkin and P. L. Schiff, jr., Phytochemistry, in press (1975).
[2] A. N. Tackie, D. Dwuma-Badu, T. Okarter, J. E. Knapp, D. J. Slatkin and P. L. Schiff, jr., Lloydia *37*, 1 (1974).
[3] I. R. C. Bick and A. R. Todd, J. chem. Soc. *1950*, 1606.
[4] Y. Inubushi and K. Nomura, Tetrahedron Lett. *1962*, 1133.
[5] I. R. C. Bick, J. B. Bremner, H. M. Leow and P. Wiriyachitra, J. chem. Soc. Perkin I *1972*, 2884.
[6] M. Shamma, *The Isoquinoline Alkaloids* (Academic Press, New York 1972), p. 81.