

The Cymopols, a Group of Prenylated Bromohydroquinones from the Green Calcareous Alga *Cymopolia barbata* †

By Hans-Erik Högberg and R. H. Thomson,* Department of Chemistry, University of Aberdeen, Meston Walk, Old Aberdeen AB9 2UE, Scotland

Trevor J. King, Department of Chemistry, The University, Nottingham NG7 2RD

Seven new hydroquinones have been isolated from the green alga *Cymopolia barbata*. These are cymopol [2-bromo-5-(3,7-dimethylocta-2,6-dienyl)hydroquinone] and its monomethyl ether, cyclocymopol [1-bromo-3-(4-bromo-2,5-dihydroxybenzyl)-2,2-dimethyl-4-methylenecyclohexane] and its monomethyl ether, cymopolone [(4-bromo-2,5-dihydroxyphenyl) *trans*-(2,6-dimethylhepta-1,5-dienyl) ketone], and its *cis*-isomer, and cymopochromenol [7-bromo-6-hydroxy-2-methyl-2-(4-methylpent-3-enyl)-2*H*-1-benzopyran]. The structure and absolute stereochemistry of cyclocymopol monomethyl ether acetate were established by *X*-ray crystallography.

NUMEROUS halogenated metabolites have been found¹ in red and brown algae but hitherto not in green algae. We report here the presence of a number of prenylated bromohydroquinones in lipid extracts of the green calcareous alga, *Cymopolia barbata* (L.) Lamx. (Dasycladaceae), collected in Bermuda. Ether extracts from this alga have been shown² to possess antibiotic and anti-fungal properties, but no specific compounds were isolated and characterised.

Repeated chromatography of the extracts from dried and fresh seaweed gave cymopol (1) (0.7%; only in

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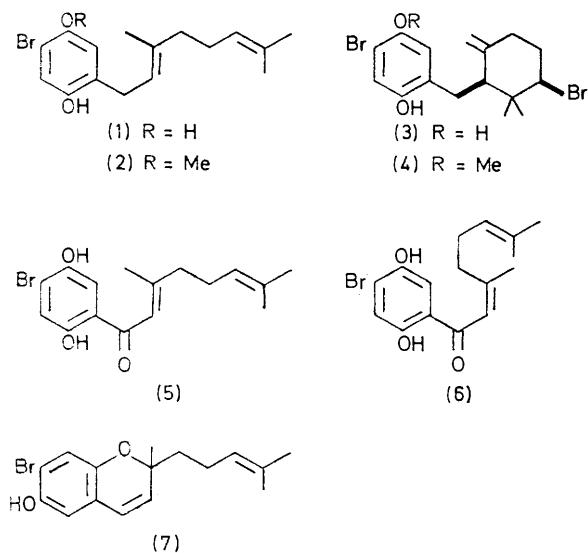
fresh material) and its monomethyl ether (2) (only in fresh material), cyclocymopol (3) (*ca.* 0.2%; only in fresh material) and its monomethyl ether (4) (present in fresh; 0.06% of dried material), cymopolone (5) (present in fresh; 0.03% of dried material), isocymopolone (6) (0.005% of dried material), and cymopochromenol (7) (0.2% of dried alga; only traces in fresh). Very little fresh alga was available (\cong 6 g dried).

Cymopol, C₁₆H₂₁BrO₂, λ_{\max} 299 nm, is a crystalline

¹ See *e.g.* J. F. Siuda and J. F. DeBernardes, *Lloydia*, 1973, **36**, 107; D. J. Faulkner and R. J. Andersen, in 'The Sea,' vol. 5, 'Marine Chemistry,' ed. E. D. Goldberg, Wiley, New York, 1974.

² N. G. Martínez, L. V. Rodríguez, and C. Casillas, *Antimicrobial Agents and Chemistry*, 1964, 131.

phenol whose n.m.r. spectrum in the range $\delta < 5.5$ closely resembles that of geranylhydroquinone dimethyl ether³ except that the two methoxy-singlets



are replaced by a broad two-proton hydroxy-singlet at δ 5.1. The low-field region showed two 1 H singlets at δ 6.79 and 6.92 arising from two *para*-protons on an aromatic ring. These data suggested the bromogeranylhydroquinone structure (1) for cymopol, which was established by synthesis. This was achieved by alkylation of bromohydroquinone with geraniol (boron trifluoride-ether as catalyst). The low yield (11%) of 2-bromo-5-geranylhydroquinone, in comparison with those reported for similar condensations between geraniol and hydroquinone or toluhydroquinone,³⁻⁵ seems to be due to the deactivating effect of the bromine on the aromatic ring. Higher yields could not be obtained.

Cymopol monomethyl ether (2), $C_{17}H_{23}BrO_2$, was isolated only from fresh seaweed and the amount available did not permit detailed spectral analysis. The most significant parts of the mass spectrum are identical with those of cymopol displaced by 14 mass units, and the two spectra include important peaks at m/e 253/255 and 239/241 attributable to ions (a) and (b), respectively. [The molecular formulae of (a) and (b) were confirmed by accurate mass measurement.] This evidence, and the analogy with cyclocymopol and its monomethyl ether, discussed below, strongly support the proposed structure (2) for cymopol monomethyl ether.

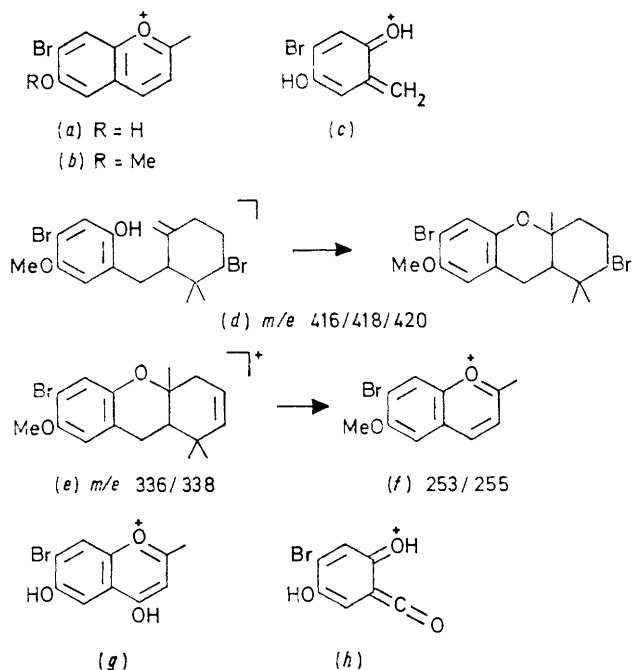
Cyclocymopol monomethyl ether (4), λ_{max} 309 nm, was an optically active viscous gum, and from its formula, $C_{17}H_{21}Br_2O_2$, appeared to be a methylated bromocymopol. The i.r. spectrum shows maxima at 1648 and 898 ($>C=CH_2$), 3450 (OH), and 1390 and 1370 cm^{-1} (CMe_2). In the mass spectrum the base

³ M. Moir, Ph.D. Thesis, University of Aberdeen, 1972, pp. 99, 100.

⁴ H. Inouye, K. Tokura, and S. Tobita, *Chem. Ber.*, 1968, **101**, 4057.

peak appears at m/e 215/217, attributable to the ion (c) (or the tropylium equivalent), which indicates that there is one bromine atom in each 'half' of the molecule, the two 'halves' being separated by a benzylic methylene group.

The n.m.r. spectrum of cyclocymopol monomethyl ether showed signals from a hydroxy-, a methoxy-, *gem*-dimethyl, two isolated aromatic, and terminal methylene protons. As no other vinyl protons are present the compound must be bicyclic to accommodate the molecular formula. Resonances from the two benzylic protons, indicated by the mass spectrum, appear as a broadened doublet at δ 2.91. A doublet of doublets at δ 4.22 is consistent with a methine proton which is attached to a carbon atom bearing bromine and coupled to only two protons. The coupling constants suggest an axial-axial (J 10.5 Hz) and an axial-equatorial (J 4.8 Hz) interaction in a six-membered ring, leaving the bromine in an equatorial position.^{6,7} A group of complex overlapping multiplets at δ 1.95–2.50 from five protons all attached to saturated carbon atoms completes the spectrum. Double-resonance experiments showed that the benzylic protons were coupled to a proton resonating at δ 2.35 and the methine proton at δ 4.22 was coupled to protons resonating at δ 2.23.



Biogenetic considerations (see below) and all the spectral data support the proposed structure (4) for cyclocymopol. The only problem remaining is the relative positions of the methoxy- and hydroxy-groups, and this was resolved in the following way.

⁵ A. R. Burnett and R. H. Thomson, *J. Chem. Soc. (C)*, 1968, 857.

⁶ S. M. Waraskiewicz and K. L. Erickson, *Tetrahedron Letters*, 1974, 2003.

⁷ M. Suzuki, E. Kurosawa, and T. Irie, *Tetrahedron Letters*, 1974, 821.

Cyclocymopol monomethyl ether forms an acetate whose n.m.r. spectrum is very similar to that of the parent phenol (apart from the acetate signal); however, a small but significant change was observed in the aromatic region. The sharper low-field singlet of the two was shifted downfield (δ 6.93 \rightarrow 7.19), whereas the broader high-field peak was scarcely affected (δ 6.68 \rightarrow 6.69) by acetylation. On irradiation at the frequency of the benzylic doublet (δ 2.80 in the acetate) a significant sharpening of the broader singlet was observed. Therefore the sharper singlet must be due to a proton *ortho* to the acetoxy- (phenolic) group which does not interact with the benzyl group, and the broader singlet to a proton *ortho* to the benzyl group. This is only compatible with structure (4). Minor support for the relative position of the methoxy-group may be deduced from some weak fragmentations observed in the mass spectrum of cyclocymopol monomethyl ether. These are most easily explained by cyclisation involving a free phenolic group *ortho* to the benzyl group as shown in the sequence (d) \rightarrow (f). Finally structure (4) was confirmed and the absolute stereochemistry established by an X-ray crystallographic study of the acetate (see Experimental section).

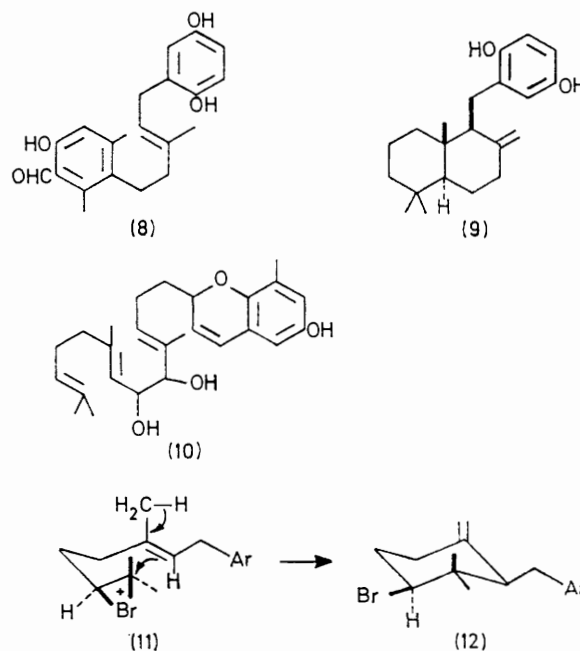
The molecular formula, $C_{16}H_{20}Br_2O_2$, of cyclocymopol (3) suggests that it is the parent hydroquinone corresponding to (4). The mass spectrum is virtually identical with that of the methyl ether (4) displaced by 14 mass units, and the n.m.r. spectrum differs from that of the methyl ether only in the absence of the methoxy-signal, which is replaced by a hydroxy-resonance. The close relationship between the methyl ether (4) and cyclocymopol (3) was also established by oxidising the ether with chromic acid to a quinone which gave cyclocymopol on reduction with sodium dithionite.

Cymopolone (5) is a yellow crystalline compound and its formula, $C_{16}H_{19}BrO_3$, suggests that it is an oxidation product of cymopol. The i.r. spectrum shows chelated aromatic carbonyl absorption at 1645 cm^{-1} , shifted to 1665 cm^{-1} in the diacetate, and the u.v. spectrum, λ_{max} 280 and 380 nm, is consistent with a 4-bromo-2,5-dihydroxyphenone chromophore.⁸ The n.m.r. spectrum of cymopolone confirms the presence of two hydroxy-groups (one chelated), and two *para*-aryl protons, and a broadened singlet at δ 6.64 corresponds to a vinyl proton α to a carbonyl group. The rest of the spectrum is identical (by direct comparison) with that part of the spectrum of commercial citral (except for the aldehyde proton) assigned to the major (*trans*) isomer (commercial citral, as judged by its n.m.r., contains a 65 : 35 mixture of the *cis*- and *trans*-isomers). The spectral evidence is fully consistent with structure (5) for cymopolone, and in addition the base peak of the mass spectrum falls at m/e 255/257 ($C_{10}H_8BrO_2$ by mass measurement) which can be assigned to the ion (g), a less important peak at

m/e 215/217 corresponding to (h) ($C_7H_4BrO_3$ by mass measurement).

Isocymopolone (6) is a minor component of the dried extract isomeric with cymopolone. The mass spectrum is similar to that of cymopolone, and the low-field portion of the n.m.r. spectrum is identical with that of cymopolone. However the high-field region is identical (by direct comparison) with that assigned to the minor, *cis*-isomer of commercial citral. It follows therefore that isocymopolone is the *cis*-isomer (6) of cymopolone (5).

Cymopochromenol (7), an optically inactive, colourless oil, is the major component in the extracts from the dried alga. The u.v. spectrum closely resembles those of 6-hydroxychromenols.^{9,10} The n.m.r. spectrum includes signals from a hydroxy- and a tertiary methyl group and two *para*-aromatic protons, and an AB quartet centred



at δ 5.6 and 6.3 (J 10 Hz) characteristic of a chromenol.^{10,11} A vinyl proton multiplet at δ 5.1, multiplets for four methylene protons at δ 1.75 and 2.05, and two broadened vinylic methyl singlets at δ 1.57 and 1.68 complete the spectrum. In the mass spectrum the base peak at m/e 239/241 ($C_{10}H_8BrO_2$) arises from the ion (a). Cymopochromenol therefore has structure (7) and is probably mainly an artefact derived from cymopol (1) by oxidation to the corresponding quinone followed by cyclisation during the drying procedure.

The cymopols are probably of mixed biogenetic origin, arising by bromination and geranylation of a shikimate-derived quinol moiety (or equivalent). Related meroterpenoids have been found in other marine organisms; examples are the paniceins [*e.g.* (8)]¹² and

¹⁰ D. McHale and J. Green, *J. Chem. Soc.*, 1965, 5060.

¹¹ A. Arnone, G. Cardillo, L. Merlini, and R. Hondelli, *Tetrahedron Letters*, 1967, 4201.

¹² G. Cimino, S. De Stefano, and L. Minale, *Tetrahedron*, 1973, 29, 2565.

⁸ A. I. Scott, 'Interpretation of Ultraviolet Spectra of Natural Products,' Pergamon, London, 1964.

⁹ D. Creed, E. Werbin, and E. T. Strom, *J. Amer. Chem. Soc.*, 1971, 93, 502.

simple prenylated quinols¹³ found in sponges, and in algae the tocopherols,¹⁴ zonarol (9),¹⁵ and sargatriol (10).¹⁶ The cymopols differ in the presence of bromine and a shorter prenyl side chain. The formation of the cyclocymopols in which the side chain is cyclised and brominated is most easily explained by postulating an enzyme-catalysed attack by a bromine cation (or equivalent) on the double bond remote from the aromatic ring to form the chiral bromonium ion (11), followed by cyclisation to give (12) which has the cyclocymopol skeleton with the two bulky groups in equatorial positions.¹⁷

EXPERIMENTAL

Extraction of Dried Cymopolia barbata.—The dried alga (1.9 kg), collected at Ferry Reach, St. George's, Bermuda, in February, was extracted in a blender several times with toluene (10 l in all). Filtration followed by evaporation gave a dark green oil (18 g, 1%) which was chromatographed in toluene on a column of silica gel (150 g). A dark green band which passed rapidly down the column was discarded. Further elution with toluene gave a greenish-brown oil (8.6 g) which was rechromatographed on a column of t.l.c. grade silica gel (750 g) in toluene. The first 750 ml were discarded and then 25 ml fractions were collected. Fractions 52—68 (i) yielded a dark oil (3.3 g), mainly cymopochromenol, 69—91 (ii) gave a brownish oil (1.7 g), largely cyclocymopol monomethyl ether, 92—122 (iii) afforded a yellow semicrystalline syrup (0.7 g), essentially cymopolone, and 123—140 (iv) yielded a brown oil (0.3 g) consisting of impure isocymopolone.

Cymopochromenol (7). Fraction (i) (0.3 g) was rechromatographed (twice) on a short column of t.l.c. grade silica gel (30 g), first with dichloromethane as eluant and then with toluene-ethyl acetate (19 : 1), and finally purified by short path distillation *in vacuo* to give *cymopochromenol* as an oil (Found: C, 59.7; H, 5.8; Br, 24.4%; M^+ , 322.0568. $C_{16}H_{19}^{79}BrO_2$ requires C, 59.5; H, 5.9; Br, 24.7%; M , 322.0568), λ_{max} (EtOH) 235, 267, and 335 nm ($\log \epsilon$ 4.13, 3.48, and 3.53), δ (CDCl₃) 1.34 (3 H, s, MeC<), 1.57 and 1.68 (each 3 H, s, =CMe₂), 1.6—1.8 (2 H, m, CH₂·CH₂·CH=), 1.9—2.3 (2 H, m, -CH₂·CH₂·CH=), 5.0—5.2br (1 H, t, -CH=CMe₂), 5.1 (1 H, s, moves upfield on addition of CD₃OD, OH), 5.60 (1 H, d, J 10 Hz, ArCH=CH-), 6.26 (1 H, d, J 10 Hz, ArCH=CH-), and 6.62 and 6.88 (each 1 H, s, ArH); m/e 324(4%), 322(4), 241(100), and 239(100).

Cyclocymopol monomethyl ether (4). Fraction (ii) was rechromatographed on t.l.c. grade silica gel (200 g) four times with dichloromethane and toluene-ethyl acetate (92.5 : 7.5) in alternation as eluants. The pure product (1.2 g) (as judged by t.l.c. in several solvents) was an almost colourless glass which could not be crystallised (Found: C, 49.1; H, 5.4; Br, 38.0%; M^+ , 415.9985. $C_{17}H_{22}^{79}Br_2O_2$ requires C, 48.8; H, 5.3; Br, 38.2%; M , 415.9985), $[\alpha]_D^{25} + 32^\circ$ (in CHCl₃), λ_{max} (EtOH) 220sh and 297nm ($\log \epsilon$ 4.10 and 3.61), ν_{max} (CHCl₃) 3 450, 1 648, 1 390, 1 370, and 898 cm⁻¹, δ (CDCl₃) 1.00 and 1.24 (each 3 H, s, >CMe₂), 1.95—2.50 (5 H, m, >C·CH₂·CH₂- and ArCH₂·CH<), 2.91br (2 H, d, J 7 Hz, ArCH₂), 3.79 (3 H, s, OMe), 4.22 (1 H, dd, J 10.5 and 4.8 Hz, -CHBr-), 4.69br and 4.86br (each 1 H, s,

>C=CH₂), 6.68 and 6.93 (each 1 H, s, ArH), and 5.07 (1 H, s, moves upfield on adding CD₃OD, OH); m/e 420(8%), 418 (17), 416(8), 339(2), 338(2), 337(2), 336(2), 255(1), 253(1), 217(100), 215(100), and 121(17). The *acetate* (acetic anhydride-pyridine; cold) crystallised from ethanol in prisms, m.p. 102—104° (Found: C, 49.3; H, 5.4; Br, 34.4. $C_{19}H_{24}Br_2O_3$ requires C, 49.6; H, 5.3; Br, 34.7%), δ (CDCl₃) 1.02 and 1.22 (each 3 H, s, >CMe₂), 2.0—2.6 (5 H, m, >C·CH₂·CH₂- and ArCH₂·CH<), 2.29 (3 H, s, OAc), 2.80 (2 H, d, J 7.6 Hz, ArCH₂), 3.82 (3 H, s, OMe), 4.18 (1 H, dd, J 9.3 and 4.5 Hz, -CHBr-), 4.57br and 4.86br (each 1 H, s, >C=CH₂), and 6.69 and 7.19 (each 1 H, s, ArH).

Cymopolone (5). Fraction (iii) was dissolved in hexane (1 ml), from which yellow crystals, m.p. 79—81° (0.55 g, 0.03%), were slowly deposited. Two further crystallisations gave long, colourless needles, m.p. 81.0—81.5° (Found: C, 56.4; H, 5.4; Br, 23.2%; M^+ , 338.0518. $C_{16}H_{19}^{79}BrO_3$ requires C, 56.7; H, 5.6; Br, 23.5%; M , 338.0517); λ_{max} (EtOH) 280 and 378 nm ($\log \epsilon$ 4.30 and 3.83), ν_{max} (KBr) 3 300 and 1 645 cm⁻¹; δ (CDCl₃) 1.63br and 1.74br (each 3 H, s, =CMe₂), 2.18 [3 H, d, J 1 Hz, =C(CH₃)·CH₂-], 2.2—2.3 (4 H, m, -CH₂·CH₂·CH=), 5.1 (1 H, m, -CH=CMe₂), 5.28 (1 H, s, moved upfield with CD₃OD, OH), 6.64br (1 H, s, -CO·CH=), 7.14 and 7.37 (each 1 H, s, ArH), and 12.5 (1 H, s, chelated OH). Irradiation at δ 6.64 caused the doublet at δ 2.18 to collapse to a singlet; m/e 340(3%), 338(3), 257(100), 255(100), 217(10), and 215(10). The *diacetate* formed an oil (Found: M^+ , 422.0728. $C_{20}H_{23}^{79}BrO_5$ requires M , 422.0728); λ_{max} (EtOH) 265 nm; ν_{max} 1 765 and 1 665 cm⁻¹; m/e 424(1%), 422(1), 382(2), 380(2), 340(1), 338(1), 299(48), 297(48), 257(100), and 255(100).

Isocymopolone (6). Fraction (iv) was passed down a small column of silica gel (10 g) in dichloromethane. This gave pure *isocymopolone* as an oil (40 mg), which on addition of a little hexane and cooling to -20 °C crystallised as yellow needles, m.p. 55—56° (Found: M^+ , 338.0516. $C_{16}H_{19}^{79}BrO_2$ requires M , 338.0517); λ_{max} (EtOH) 283 and 375 nm ($\log \epsilon$ 4.22 and 3.22), ν_{max} (KBr) 3 300 and 1 640 cm⁻¹, δ (CDCl₃) 1.62br (6 H, s, =CMe₂), 2.02 [3 H, d, J 1 Hz, =C(CH₃)CH₂-], 2.00—2.35 (2 H, m, -CH₂·CH₂·CH=), 2.60 [2 H, t, J 8 Hz, =C(Me)CH₂·CH₂-], 5.12 (1 H, m, -CH₂·CH=CMe₂), 5.14 (1 H, s, moves upfield with CD₃OD, OH), 6.62br (1 H, s, -CO·CH=), 7.13 and 7.38 (each 1 H, s, ArH), and 12.5 (1 H, s, chelated OH) (irradiation at δ 2.02 sharpened the broad singlet at 6.62, and conversely irradiation at δ 6.62 caused the doublet at 2.02 to collapse to a singlet; irradiation at δ 5.12 modified the multiplet at 2.00—2.35); m/e 340(4%), 338(4), 322(25), 320(25), 269(10), 267(10), 257(100), 255(100), 217(22), and 215(22).

Extraction of Fresh Cymopolia barbata.—Fresh material collected in April (47 g wet; 6 g dry) was extracted in a blender with chloroform-methanol-water (4 : 2 : 1) (3 × 150 ml), and then left overnight under fresh solvent. The combined extracts were evaporated, leaving a dark green oil (154 mg) which was passed down a column of t.l.c. grade

¹³ G. Cimino, S. De Stefano, and L. Minale, *Tetrahedron*, 1972, **28**, 1315; *Experientia*, 1972, **28**, 1401.

¹⁴ A. Jensen, *J. Sci. Food Agric.*, 1969, **20**, 449, 454.

¹⁵ W. Fenical, J. J. Sims, D. Squatrito, R. M. Wing, and P. Radlick, *J. Org. Chem.*, 1973, **38**, 2383.

¹⁶ T. Kikuchi, Y. Mori, T. Yokoi, S. Nakazawa, H. Kuroda, Y. Masada, K. Kitamura, and I. Umezaki, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 690.

¹⁷ Cf. E. E. van Tamelen and E. J. Hessler, *Chem. Comm.*, 1966, 411; A. G. González, J. M. Aguiar, J. D. Martín, and M. Norte, *Tetrahedron Letters*, 1975, 2499; A. G. González, J. D. Martín, C. Pérez, and M. A. Ramirez, *Tetrahedron Letters*, 1976, 137; W. Fenical, *J. Phycol.*, 1975, **11**, 245.

silica gel (20 g) in dichloromethane. The first 15 ml were discarded and then 2.5 ml fractions were collected.

Fractions 14—18 (i) gave a brownish oil (7 mg), which was separated by p.l.c. on silica gel in dichloromethane to give three main components, two of which were identified (t.l.c. and mass spectra) as cyclocymopol monomethyl ether (4) and cymopol (1). The third 'component', of highest R_F value, was further separated by t.l.c. into cymopolone (5) and cymopol monomethyl ether (2). The crude 'component' before t.l.c. showed peaks at m/e 322/324 and 239/241 arising from traces of cymopochromenol (7).

Fractions 19—25 (ii) gave cymopol as a colourless oil (40 mg, 0.67%) which slowly crystallised, and fractions 26—39 (iii) gave mainly cyclocymopol with a trace of cymopol.

Cymopol monomethyl ether (2). Purification by t.l.c. gave an oil (ca. 1 mg) (Found: M^+ , 338.0879. $C_{17}H_{23}^{79}BrO_2$ requires M , 338.0880); m/e 340(56%), 338(56), 255(25), 253(18), 217(59), 215(63), 190(100), 175(59), 123(95), and 109(22).

Cymopol (1). Fraction (ii) separated from hexane as crystals, m.p. 59—61°, identical (mixed m.p., t.l.c., and mass spectrum) with synthetic material (spectral details are given below).

Cyclocymopol (4). Fraction (iii) was purified on a column of t.l.c. grade silica gel (30 g) in dichloromethane to give an oil (6 mg) (Found: M^+ , 401.9828. $C_{16}H_{20}^{79}Br_2O_2$ requires M , 401.9829); δ ($CDCl_3$) 1.01 and 1.24 (each 3 H, s, $>CMe_2$), 2.0—2.5 (5 H, m, $-CH_2-CH_2-CHBr-$ and $ArCH_2-CH<$), 2.86br (2 H, d, $ArCH_2$), 4.12—4.35 (1 H, m, $-CH_2-CHBr-$), 4.71br and 4.86br (each 1 H, s, $>C=CH_2$), and 6.78 and 6.84 (each 1 H, s, ArH), m/e 405(5%), 403(10), 401(5), 326(5), 325(6), 324(6), 323(5), 241(6), 239(5), 203(100), 201(100), 149(50), 123(44), and 121(89). This compound was also derived from the monomethyl ether (4) as follows. To the ether (4) (5 mg) in acetic acid (0.5 ml) a 10% solution (0.5 ml) of chromium trioxide in aqueous acetic acid (1 : 1) was added. A precipitate formed almost immediately. After addition of water (0.5 ml) the quinone was collected, dissolved in ether, and reduced by shaking with sodium dithionite solution for 5 min. The ether was washed with water, dried (Na_2SO_4), and evaporated to give a brownish oil identical (mass spectrum and t.l.c. in several systems) with cyclocymopol.

Bromohydroquinone.—This was prepared according to the method of Sarauw,¹⁸ except that an excess of bromine was used to ensure complete consumption of starting material (t.l.c.; 20% EtOAc in C_6H_6).

2-Bromo-5-(3,7-dimethylocta-2,6-dienyl)hydroquinone (*Cymopol*) (1).—To bromohydroquinone (2 g) and freshly distilled boron trifluoride-ether complex (0.4 ml) in dry dioxan (5 ml), stirred at 55 °C under nitrogen, a solution of freshly distilled geraniol (0.76 g) in dioxan (2 ml) was added during 30 min. After stirring and heating for 2 h further the mixture was cooled, diluted with ether, shaken with saturated sodium hydrogen carbonate solution until neutral, and dried. After removal of the ether the residue, in dichloromethane, was repeatedly shaken with water until most of the starting hydroquinone was removed (t.l.c.), and then dried. Evaporation gave a brown oil (0.8 g) which was chromatographed on a column of t.l.c. grade silica gel (200 g) in dichloromethane. This afforded an oil which separated from hexane as prisms of *bromogeranylhydroquinone*, m.p. 59—61°

(0.15 g) (Found: C, 59.5; H, 6.5; Br, 24.9%; M^+ , 324.0728. $C_{16}H_{21}^{79}BrO_2$ requires C, 59.2; H, 6.5; Br, 24.6%; M , 324.0725), λ_{max} (EtOH) 299 nm (log ϵ 3.88), ν_{max} (KBr) 3 300 cm^{-1} , δ ($CDCl_3$) 1.60, 1.69, and 1.73 [each 3 H, s, $=CMe_2$ and $=C(CH_3)CH_2-$], 2.04—2.20 (4 H, m, $-CH_2-CH_2-CH=$), 3.28 (2 H, d, J 7.4 Hz, $ArCH_2-CH=$), 5.10br (2 H, moved upfield with CD_3OD , OH), 5.0—5.2 (1 H, m, $-CH=CMe_2$), 5.27 (1 H, t, J 7.4 Hz, $ArCH_2-CH=$), and 6.79 and 6.92 (each 1 H, s, ArH); m/e 326(45%), 324(45), 241(18), 239(10), 203(20), 201(20), 176(98), 161(30), 160(3), 123(100), and 109(22).

Crystal Structure Determination of Cyclocymopol Monomethyl Ether Monoacetate.—*Crystal data*. $C_{19}H_{24}Br_2O_3$, monoclinic, space group $P2_1$, $a = 11.697(2)$, $b = 9.115(2)$, $c = 10.671(2)$ Å, $\beta = 116.9(1)^\circ$, $U = 1 015$ Å³, $D_m = 1.49$ g cm^{-3} , $Z = 2$, $D_c = 1.50$ g cm^{-3} , $Mo-K\alpha$ (λ 0.71069 Å), $\mu = 42.5$ cm^{-1} .

The quality of the crystals available was poor and the spots on preliminary photographs were not sharply defined, suggesting high thermal vibration and/or some disorder. The cell parameters were refined, and the reflection intensities were measured on a Hilger-Watt four-circle diffractometer out to $\theta = 20^\circ$ using $Mo-K\alpha$ radiation (graphite monochromator). The intensity of three standard reflections which were regularly monitored decreased significantly (40%) during the data collection, and an appropriate linear scaling factor was applied. A total of 812 reflections with a net count of $>3\sigma$ were measured. Lorentz and polarisation corrections were made but no correction was made for absorption.

The bromine positions were located by using MULTAN, and the light atoms were found by repeated cycles of refinement followed by difference maps. Many of the light atom peaks were weak and poorly resolved. However, in spite of the unsatisfactory quality of the data a difference map computed after all the carbon and oxygen atoms had been located did show peaks at nearly all the positions expected for hydrogen; accordingly in the final stages of refinement hydrogen atoms were included at calculated positions but were not refined. The refinement was completed by full-matrix least-squares methods with the non-hydrogen atoms treated anisotropically and using anomalous scattering for the bromine once the absolute configuration had been established (see below). In the final cycle the average shift of the positional parameters was $<0.1\sigma$ and the maximum 0.23σ . The final R value was 0.069. Table 1 lists the fractional co-ordinates of non-hydrogen atoms and Table 2 their thermal parameters. Table 3 gives the bond lengths and angles; the calculated estimated standard deviations of these quantities (0.04 Å and 3°) are about ten times that which we would normally expect for structures of this type. Figure 1 is a diagram of the molecule showing the crystallographic numbering, and Figure 2 a perspective drawing of the molecule.

Absolute configuration. In the early stages of this work it was anticipated that the data quality would render unconvincing an assignment of configuration based on small differences of R value. Thus for all planes with h from 0 to 5 the Friedel pair was measured immediately after the measurement of each reflection. When refinement was nearly complete anomalous bromine scattering factors were introduced into the computations and the reflection list was searched for those reflections which satisfied all the following

¹⁸ E. Sarauw, *Annalen*, 1881, 209, 93.

criteria: a marked difference ($>10\%$) between $I_{\text{calc.}}$ for the two enantiomers; reasonable agreement between $I_{\text{obs.}}$ and $I_{\text{calc.}}$; a significant difference ($>5\sigma$) between $I_{\text{obs.}}$ of the

TABLE 1

Fractional atomic co-ordinates $\times 10^3$ (estimated standard deviations in parentheses)

	x/a	y/b	z/c
Br(1)	929(1)	161	513(1)
C(1)	743(3)	-577(3)	-153(3)
C(3)	848(3)	-405(4)	28(4)
C(5)	650(4)	-344(4)	-163(4)
C(7)	747(3)	-157(3)	19(3)
C(9)	656(3)	-188(3)	186(3)
C(11)	736(3)	-60(4)	416(3)
C(13)	838(3)	-5(3)	252(3)
C(15)	968(3)	17(4)	250(4)
C(17)	1034(3)	-614(3)	168(4)
C(19)	408(4)	-74(4)	-393(5)
O(2)	940(2)	-641(2)	30(2)
Br(2)	733(1)	-764(1)	-235(1)
C(2)	839(3)	-544(3)	-37(3)
C(4)	743(3)	-303(3)	-42(4)
C(6)	645(3)	-488(4)	-255(3)
C(8)	773(3)	-151(3)	169(3)
C(10)	677(3)	-196(3)	334(4)
C(12)	853(3)	-15(4)	395(3)
C(14)	550(3)	-225(5)	88(4)
C(16)	755(3)	128(3)	168(3)
C(18)	532(3)	-167(4)	-335(4)
O(1)	536(2)	-257(3)	-235(2)
O(3)	611(3)	-155(3)	-370(3)

TABLE 3

Bond lengths and angles (calculated estimated standard deviations in parentheses)

Br(1)-C(12)	1.99(3)	Br(2)-C(1)	1.90(3)
C(1)-C(2)	1.28(3)	C(1)-C(6)	1.33(4)
C(2)-C(3)	1.43(4)	C(2)-O(2)	1.38(3)
C(3)-C(4)	1.45(4)	C(4)-C(5)	1.32(4)
C(4)-C(7)	1.47(4)	C(5)-C(6)	1.46(4)
C(7)-C(8)	1.49(4)	C(8)-C(9)	1.50(4)
C(8)-C(13)	1.59(4)	C(9)-C(10)	1.49(4)
C(9)-C(14)	1.25(4)	C(10)-C(11)	1.50(4)
C(11)-C(12)	1.53(4)	C(12)-C(13)	1.46(4)
C(13)-C(15)	1.55(4)	C(13)-C(16)	1.57(4)
O(2)-C(17)	1.41(3)	C(5)-O(1)	1.44(4)
O(1)-C(18)	1.33(4)	C(18)-C(19)	1.55(5)
C(18)-O(3)	1.15(3)		
Br(2)-C(1)-C(2)	120(3)	Br(2)-C(1)-C(6)	115(3)
C(2)-C(1)-C(6)	125(3)	C(1)-C(2)-C(3)	121(3)
C(1)-C(2)-O(2)	122(3)	O(2)-C(2)-C(3)	117(3)
C(2)-C(3)-C(4)	118(3)	C(3)-C(4)-C(5)	117(3)
C(3)-C(4)-C(7)	120(3)	C(5)-C(4)-C(7)	123(3)
C(4)-C(5)-C(6)	124(4)	C(4)-C(5)-O(1)	121(3)
C(6)-C(5)-O(1)	115(4)	C(5)-C(6)-C(1)	116(3)
C(4)-C(7)-C(8)	117(3)	C(7)-C(8)-C(9)	112(3)
C(7)-C(8)-C(13)	116(2)	C(9)-C(8)-C(13)	111(2)
C(8)-C(9)-C(10)	115(3)	C(8)-C(9)-C(14)	125(3)
C(10)-C(9)-C(14)	120(3)	C(9)-C(10)-C(11)	113(3)
C(10)-C(11)-C(12)	110(2)	C(11)-C(12)-C(13)	119(3)
C(11)-C(12)-Br(1)	107(2)	C(13)-C(12)-Br(1)	115(2)
C(12)-C(13)-C(8)	109(3)	C(12)-C(13)-C(16)	113(3)
C(12)-C(13)-C(15)	112(3)	C(15)-C(13)-C(16)	105(3)
C(8)-C(13)-C(15)	109(2)	C(8)-C(13)-C(16)	108(2)
C(2)-O(2)-C(17)	121(2)	C(5)-O(1)-C(18)	117(2)
O(1)-C(18)-C(19)	110(3)	O(1)-C(18)-O(3)	126(4)
O(3)-C(18)-C(19)	124(4)		

reflection and that of its Friedel pair. Twenty-three pairs satisfying these criteria were found and all favoured the assignment indicated in structure (4). These reflections and

the appropriate figures are listed in Table 4. The ratio of the R values for the two enantiomorphs was also calculated as 1.015. According to Hamilton's statistical tables,¹⁹ a ratio of 1.006 would be meaningful at the 0.005 confidence level, so this method also strongly supports the assigned configuration.

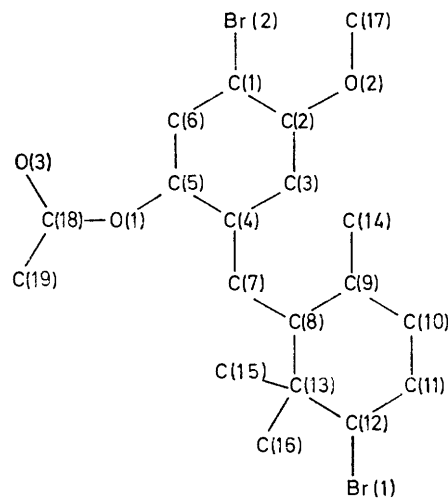


FIGURE 1 Diagram of compound (4)

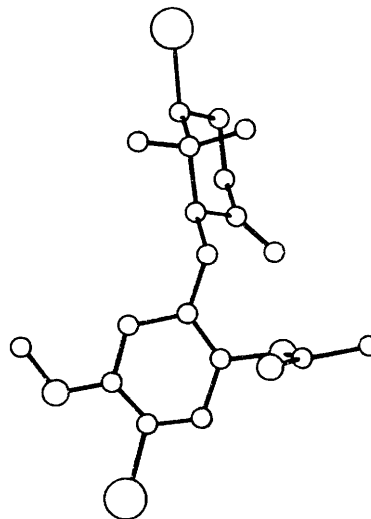


FIGURE 2 Perspective drawing of compound (4)

Tables 2 and 4 and the listing of observed and calculated structure factors are available as Supplementary Publication No. SUP 21773 (11 pp, 1 microfiche).†

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† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

¹⁹ W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.