Aust. J. Chem., 1981, **34**, 1633–44

Quinones and Quinone Methides. VIII* Oxidation Products of the Screwworm Chemosterilant, 2,4-Bis(1,1-dimethylethyl)-6-(4-methoxyphenylmethyl)phenol

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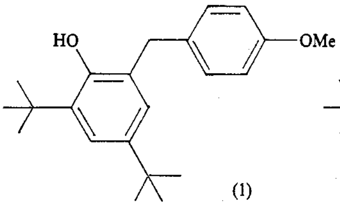
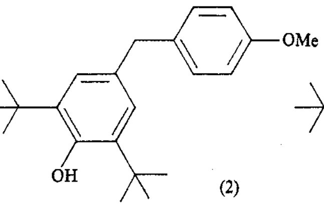
Abstract

The title compound is oxidized by silver oxide in acetone to a complex mixture of products, including the benzophenone derivative (7), a benzylic alcohol, isolated as its methyl ether (15), and two spiro cyclohexadienone benzopyran dimers (17) and (19). A colourless dimer was shown by single-crystal X-ray diffraction measurements to be a 2,3-dihydrobenzofuran derivative (22).

2,4-Bis(1,1-dimethylethyl)-6-(4-methoxyphenylmethyl)phenol (1) effectively sterilizes the female housefly[1] and screwworm fly[2]† when applied topically or fed in the diet of these insects. The ability of (1) and similar butylated phenols to sterilize these flies appears to depend on the presence of benzyl or cinnamyl substituents *ortho* to the phenolic hydroxy group, since isomeric *para* benzyl or cinnamyl compounds, e.g. (2), are generally devoid of sterilant activity. On the basis of these and other structure–activity correlations, it has been suggested[1,4] that the mode of action of effective benzylphenols may involve their initial, microsomal oxidation in the fly to unstable, highly reactive *ortho*-quinone methide intermediates, e.g. (3), which then inactivate a cell constituent(s) that is important in the reproductive process.



(1)



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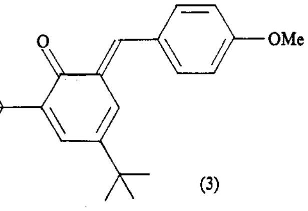

(3)

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* Part VII, *Aust. J. Chem.*, 1980, **33**, 1603.

† The screwworm, *Cochliomyia hominivorax*, is a serious livestock pest which at one time almost brought cattle raising to a standstill in Texas and other southern areas of the United States. A related screwworm species now infests Papua New Guinea. If it should cross the Torres Strait, it could pose a similar potentially devastating threat to the Australian livestock industry.[3]

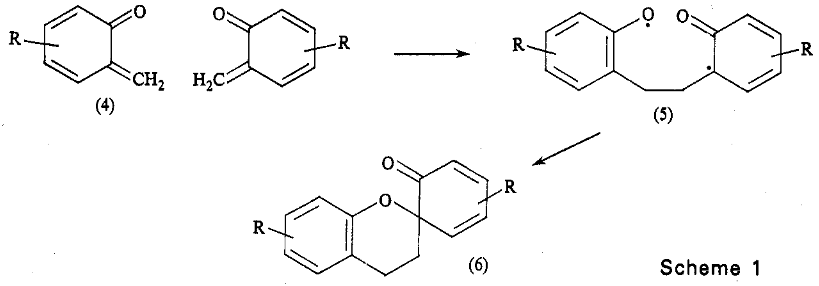
[1] Jurd, L., Fye, R., and Morgan, J., *J. Agric. Food Chem.*, 1979, **27**, 1007.

[2] Rawlins, S. C., Jurd, L., and Snow, J. W., *J. Econ. Entomol.*, 1979, **72**, 674.

[3] Anon., *Rural Research* (*CSIRO*), 1979, No. 102, 4.

[4] Jurd, L., and Manners., G. D., *J. Agric. Food Chem.*, 1980, **28**, 183.

Previous studies have shown that oxidation of substituted *o*-alkylphenols leads[5-7] to dimerization (or trimerization) with the formation of benzopyran derivatives of type (6), which are substituted at position 2 by a spiro cyclohexadienone ring. These dimers are thought[5] to result from initial oxidation to an *ortho*-quinone methide, two molecules of which then undergo a Diels–Alder reaction, (4) → (5) → (6) (Scheme 1).



Scheme 1

In connection with the proposed biochemical mode of action, the oxidation of benzylphenol insect sterilants, alone and in the presence of nitrogen bases, is now being investigated in some detail. These studies have demonstrated that, in addition to monomeric products and 2-substituted benzopyran dimers of type (6), oxidation of *o*-benzylphenols in hydroxylic and non-hydroxylic solvents can lead to the formation of a variety of dimers, the structures of which may differ markedly from the type previously recognized.

This communication describes the major products formed by reaction of the chemosterilant (1) with silver oxide in acetone. Chromatographic separation of the complex mixture of products, followed by crystallization of the major fraction from methanol, has given a brightly yellow, monomeric compound $C_{22}H_{28}O_3$ (m.p. 116–117°), a colourless phenol $C_{23}H_{32}O_3$ (m.p. 113°), two slightly yellow, isomeric ($C_{44}H_{56}O_4$) dimers A (m.p. 227–228°) and B (m.p. 189–190°), and traces of a third isomeric colourless dimer C (m.p. 168–169°). In addition, minor amounts of an unidentified, colourless dimer D $C_{44}H_{54}O_4$ (m.p. 243–245°), and an unidentified yellow dimer E $C_{44}H_{56}O_4$ (m.p. 169–170°) were also isolated. The structures of these two dimers will be determined by X-ray diffraction methods at a later date.

The yellow monomeric product has $\lambda_{\max}$ 354 nm and contains a conjugated, hydrogen-bonded carbonyl group ($\nu_{\max}$ 1615 cm^{-1}). This was confirmed by its ^1H n.m.r. spectrum in which a strongly bonded hydroxyl proton appeared well downfield at δ 12·60. In addition to the signals of two t-butyl and one 4-methoxyphenyl groups, two coupled olefinic protons appear at δ 7·44 and 7·55. These data may be accounted for by the simple benzophenone structure (7), although the bright yellow colour of the compound in organic solvents suggests that it may in fact be better represented as the tautomer with a quinone methide structure (8). In this connection it is noteworthy that, in contrast to the intensely yellow oxidation product,

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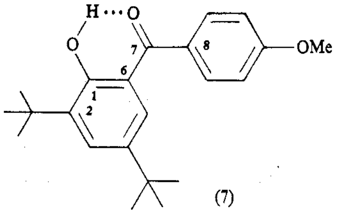
[5] Turner, A. B., *Q. Rev., Chem. Soc.*, 1964, **18**, 347.

[6] Schleigh, W. R., *Eastman Org. Chem. Bull.*, 1971, **43**, 1.

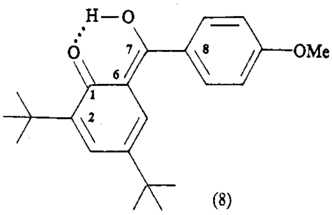
[7] Wagner, H.-U., and Gompper, R., in 'The Chemistry of the Quinonoid Compound' (Ed. S. Patai) p. 1145 (John Wiley: New York 1974).

the isomeric *p*-benzoylphenol (9) is completely colourless; it cannot form a quinone methide stabilized by intramolecular hydrogen bonding.

The ^{13}C n.m.r. spectrum of the oxidation product is also in good accord with structure (8). Thus, it has previously been noted[8] with *ortho*-substituted phenols that $^{3}J_{C,OH}$ differs depending on whether the ^{13}C and ^{1}H atoms are '*syn*' or '*anti*' with respect to each other, with $^{3}J_{anti}$ *c.* 7–8 Hz and $^{3}J_{syn}$ *c.* 4 Hz; e.g. for (10) coupling for C(6),OH is 8·3 Hz (*anti*) and for C(2),OH 4·4 Hz (*syn*). This pattern is consistent with that also found[9] for the $^{3}J_{C,H}$ in substituted alkenes where $^{3}J_{trans} > {^{3}J_{cis}}$.



(7)



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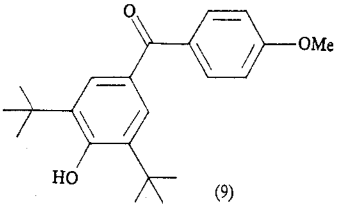

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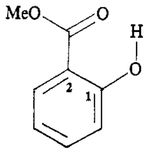

(10)

arbitrary numbering

The following detailed analysis of the ^{13}C n.m.r. spectrum of the oxidation product in relation to the two alternative structures (7) and (8) was kindly prepared by M. Benson: with structure (7) one would expect to observe $^{3}J_{C(6),OH}$ *c.* 4 Hz (*syn*) and $^{3}J_{C(2),OH}$ *c.* 8 Hz (*anti*). For structure (8) one would observe only $^{3}J_{C(6),OH}$ *c.* 4 Hz (*syn*) and $^{5}J_{C(2),OH} = 0$. Examination of the proton-coupled ^{13}C n.m.r. spectrum of the fully protonated oxidation product and of the D_2O-exchanged product shows, by changes of the coupling upon deuteration, that only the carbons at 160·2 and 118·4 ppm are coupled to the OH proton. The signal at 160·2 ppm is due to an oxygen-substituted carbon and is, therefore, C(1) in (7) or C(7) in (8). Of the quaternary carbons in the aromatic region at 139·5, 137·7, 131·7 and 118·4 ppm, only the last shows coupling to OH with $J_{C,OH}$ 4 Hz. Selective irradiation of the peak at 131·1 ppm, which is hidden in the proton-coupled spectrum, shows a triplet, $J_{C,H}$ 8 Hz, which remains unchanged on deuteration. This peak is C(8), showing typical long-range coupling to the two *meta* protons. A coupling of 7–8 Hz is not seen to either of the peaks at 139·5 or 137·7 ppm, one of which must be C(2) of (7) or (8). These data, therefore, indicate that the oxidation product has structure (8) rather than (7), the peak at 118·4 ppm being due to C(6) of (8) with $^{3}J_{C(6),OH}$ 4 Hz.

Not surprisingly, attempts to prepare stable derivatives of the oxidation product with retention of a quinone methide structure were unsuccessful. Colourless derivatives of the benzophenone form (7) were obtained. Thus, methylation gave (11)

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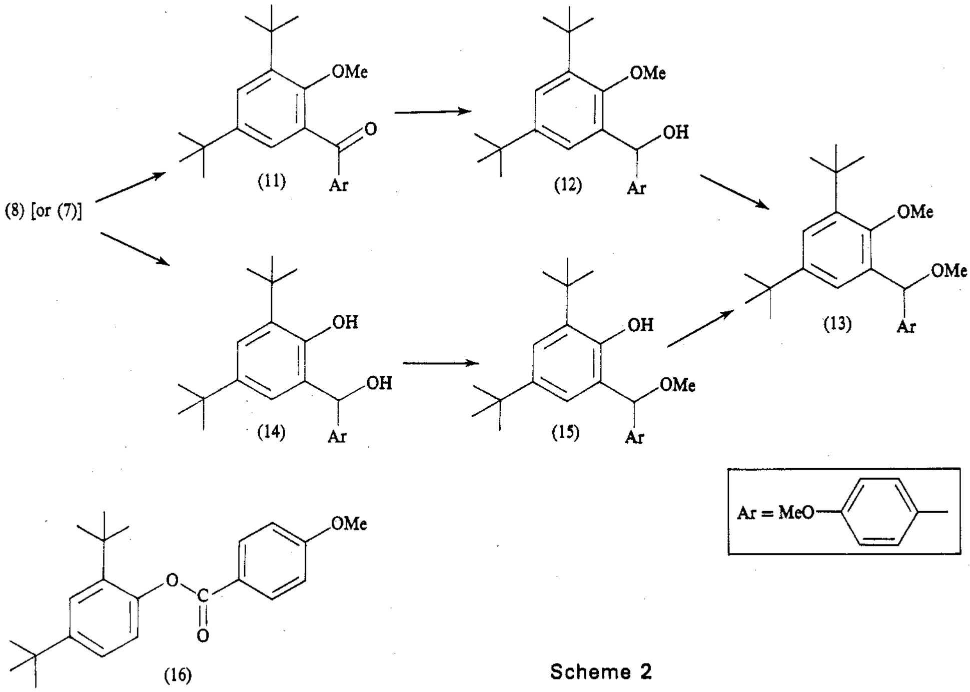
[8] Chang, C. J., *J. Org. Chem.*, 1976, **41**, 1881; *Lloydia*, 1978, **41**, 17.

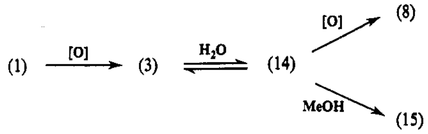
[9] Vogeli, U., and Von Philipsborn, W., *Org. Magn. Reson.*, 1975, **7**, 617.

(Scheme 2) which was reduced to the alcohol (12). With methanol and a trace of acid, (12) was converted into (13); the benzylic ether (13) was also prepared by an alternative route involving initial reduction of (8) to the benzylic alcohol (14) which was converted into the phenolic benzylic ether (15). Methylation of this then gave (13).



Scheme 2

It has previously been reported[10] that 2,6-di-t-butylphenol undergoes a Friedel–Crafts reaction with benzoyl chloride and $AlCl_3$ to form 4-benzoyl-2,6-di-t-butylphenol. However, attempts to synthesize the oxidation product by a similar reaction from 2,4-di-t-butylphenol and *p*-anisoyl chloride were abortive. The ester (16) was formed, even when the reaction was conducted at elevated temperatures.



Scheme 3

The colourless phenol, $C_{23}H_{32}O_3$, isolated from the oxidation mixture after crystallization from methanol, proved to be identical with the benzylic methyl ether (15), prepared through reduction of the yellow oxidation product (8). The formation of (8) and (15) by oxidation of the benzylphenol (1) can be rationalized by assuming that the intermediate *ortho*-quinone methide (3) is initially hydrated as indicated in Scheme 3.

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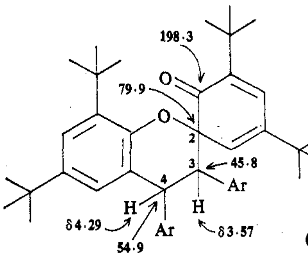
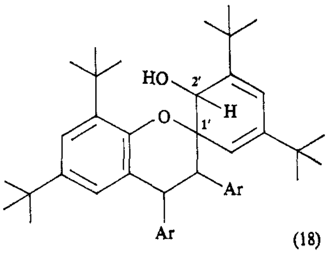
[10] Cook, C. D., and Gilmour, N. D., *J. Org. Chem.*, 1960, **25**, 1429.

Dimer A, the major dimeric product isolated from the oxidation reaction mixture, is thermally unstable, and melts to a deep orange-red liquid which may contain the monomeric *ortho*-quinone methide (3). In accord with earlier[5,6] observations on the oxidation products of other monohydric *o*-alkylphenols the spectral properties of dimer A indicate that it is the expected spiro[2*H*-1-benzopyran-2,1′-cyclohexa-3′,5′-dien]-2′-one derivative (17). Thus, the i.r. spectrum shows the presence of a conjugated carbonyl (ν_{max} 1680 cm^{-1}), and in the ^{1}H n.m.r. spectrum the adjacent H 3 and H 4 protons of the benzopyran ring appear as coupled doublets (*J* 12 Hz) at δ 3·57 and 4·29 respectively. Because of the complexity of the aromatic region in the ^{13}C n.m.r. spectrum of dimer A the signals in this region could not be assigned with confidence. However, signals of a carbonyl carbon (198·3 ppm), a quaternary carbon attached to oxygen (79·9 ppm) and two aliphatic CH groups (45·8 and 54·9 ppm) can clearly be assigned as shown in (17).

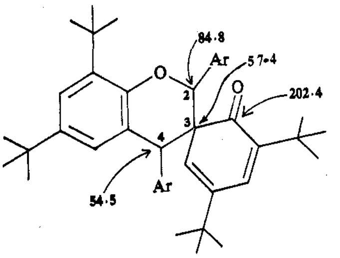


(17)

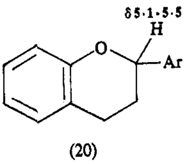


(18)

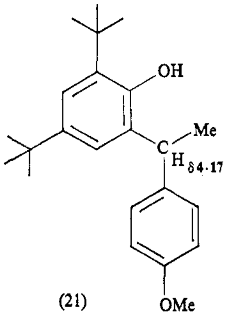
Reduction of dimer A with lithium aluminium hydride yields a crystalline allylic alcohol. In accord with structure (18), the ^{1}H n.m.r. spectrum of the reduction product shows the signal of an OH proton as a 1H doublet at δ 2·73 coupled to a methine proton (H 2′) at 4·68. As expected, reduction of the dimer carbonyl group results in an upfield shift of the cyclohexadiene ring protons from δ 6·55 in (17) to 5·68 and 5·71 in (18).



(19)



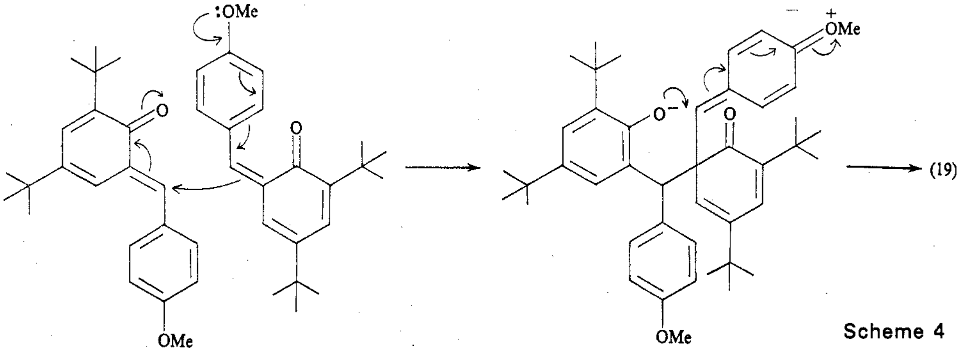
(20)



(21)

Dimer B is isomeric with (17) and on the basis of its spectral properties it is tentatively considered to be the unusual spiro[2*H*-1-benzopyran-3(4*H*),1′-cyclohexa-3′,5′-dien]-2′-one derivative (19). (It is planned to confirm the structure and stereochemistry of this dimer by single-crystal X-ray diffraction experiments.)

The i.r. spectrum has a band at 1635 cm^{-1} which is consistent with a highly conjugated carbonyl group, and the ^{1}H n.m.r. spectrum is similar to that of dimer A except that the two methine protons of the benzopyran ring are not coupled, appearing as singlets at δ 5·12 and 5·26. Either of these two chemical shifts is in line with the shift usually observed (δ 5·1–5·5) for H2 of 2-aryl-2*H*-1-benzopyrans of type (20).[11] Double benzylic methine protons, on the other hand, normally appear upfield at about δ 4·2–4·4, e.g. in the model compound (21) the benzylic proton appears at 4·17. Molecular models of possible stereoisomers of (19) indicate, however, that H4 can be deshielded by the neighbouring carbonyl group and would be expected[12] to undergo a downfield shift. As in the case of dimer A, overlapping olefinic carbon signals in the ^{13}C n.m.r. spectrum of dimer **B** could not be assigned unambiguously. However, signals of a carbonyl carbon at 202·4 ppm, a quaternary carbon at 57·4 ppm, a methine carbon at 54·5 ppm, and a methine carbon bonded to oxygen at 84·8 ppm, are in complete agreement with proposed structure (19). The structure assigned to dimer B suggests that the quinone methide (3), being highly polarizable, may dimerize by either non-ionic or ionic mechanisms, leading to dimers of type (17) and (19) respectively (see Scheme 4).



Scheme 4

Dimer C crystallized together with dimer B from one of the chromatographic fractions. The colourless dimer C crystals were manually separated under a microscope and recrystallized from methanol to give a minute amount of the pure compound. This dimer was shown to be the dihydrobenzofuran derivative (22) by single-crystal X-ray diffraction analysis.

The molecular conformation, atomic thermal motion and the arbitrary numbering scheme used in the X-ray investigation are shown in Fig. 1, produced with the ORTEP program;[13] the relevant crystallographic details are presented in Tables 1–3. The structure of dimer C consists of a dihydrobenzofuran matrix substituted with a pair of methoxyphenyl rings and a di-t-butylphenol unit. The two methoxyphenyl rings are situated on the same side of the molecule (*cis*). The five-membered oxide ring of the dihydrobenzofuran matrix assumes an envelope conformation with C(14), C(21), C(26) and O(27) being planar within ±0·04 Å and C(1) lying out-of-plane by 0·44 Å. All phenyl ring planes in the molecule are highly planar. Dihedral angles between the planes normals of these rings are listed in Table 4. The hydrogen

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[11] Clark-Lewis, J. W., *Aust. J. Chem.*, 1968, **21**, 2059.

[12] Jackman, L. M., and Sternhell, S., 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' p. 91 (Pergamon Press: New York 1969).

[13] Johnson, C. K., ORTEP, Oak Ridge National Laboratory, Tennessee, Rep., ORNL, 1965, 3794.

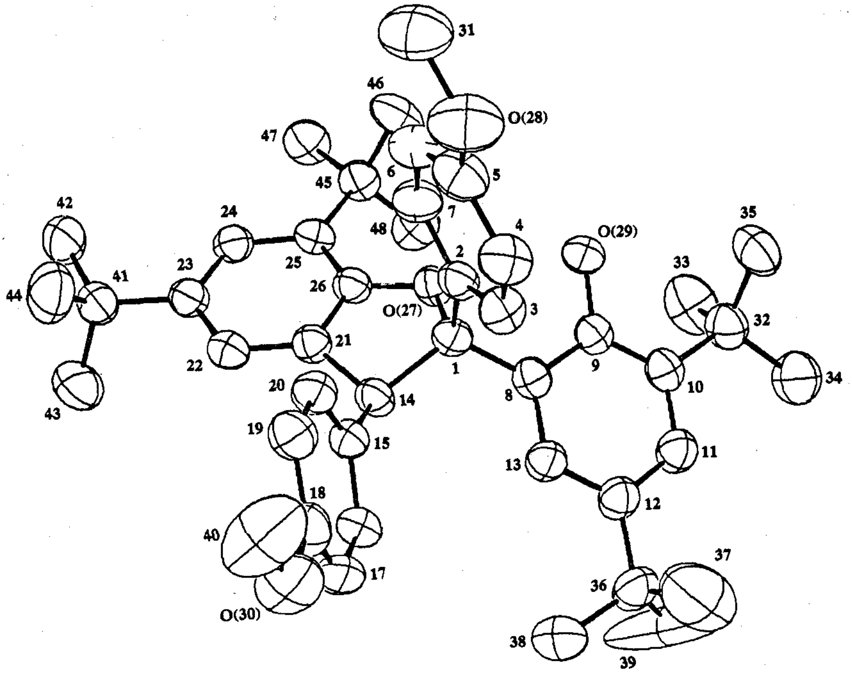


Fig. 1. Structure of dimer C. The thermal ellipsoids are shown at the 50% probability level; hydrogen atoms are excluded for clarity. Carbon atoms are designated by numerals only.

Table 1. Fractional coordinates for non-hydrogen atoms (e.s.d. values are in parentheses)

Atom	10^4x	10^4y	10^4z	Atom	10^4x	10^4y	10^4z
O(27)	1551·6(8)	3060(2)	−1818(1)	C(21)	0977(1)	1948(3)	−2920(2)
O(28)	−0706(1)	3904(2)	−0433(2)	C(22)	0683(1)	1784(3)	−3747(2)
O(29)	2100·9(9)	3688(2)	−0292(1)	C(23)	0724(1)	2720(3)	−4328(2)
O(30)	−0789(1)	−2287(2)	−1924(2)	C(24)	1085(1)	3778(3)	−4055(2)
C(1)	1273(1)	2046(2)	−1420(2)	C(25)	1399(1)	3981(3)	−3226(2)
C(2)	0769(1)	2635(3)	−1137(2)	C(26)	1311(1)	3036(3)	−2671(2)
C(3)	0542(1)	2002(3)	−0539(2)	C(31)	−1029(2)	4998(4)	−0824(3)
C(4)	0059(1)	2444(3)	−0314(2)	C(32)	3019(1)	2821(3)	1089(2)
C(5)	−0229(1)	3541(3)	−0694(2)	C(33)	3393(2)	3446(4)	0569(3)
C(6)	−0015(1)	4202(3)	−1285(2)	C(34)	3428(2)	2087(4)	1810(3)
C(7)	0480(1)	3739(3)	−1502(2)	C(35)	2718(2)	3877(4)	1486(2)
C(8)	1744(1)	1545(3)	−0686(2)	C(36)	2226(1)	−1682(3)	0394(2)
C(9)	2133(1)	2384(3)	−0148(2)	C(37)	1967(4)	−1881(5)	1153(4)
C(10)	2561(1)	1937(3)	0533(2)	C(38)	1855(3)	−2519(4)	−0289(3)
C(11)	2573(1)	0610(3)	0693(2)	C(39)	2836(3)	−2122(5)	0612(8)
C(12)	2189(1)	−0254(3)	0184(2)	C(40)	−1333(2)	−1810(5)	−1864(3)
C(13)	1785(1)	0232(3)	−0499(2)	C(41)	0388(1)	2548(3)	−5247(2)
C(14)	1055(1)	1059(3)	−2173(2)	C(42)	0450(2)	3705(4)	−5808(2)
C(15)	0535(1)	0206(3)	−2157(2)	C(43)	0614(2)	1346(4)	−5601(2)
C(16)	0624(1)	−1099(3)	−2032(2)	C(44)	−0270(2)	2380(4)	−5307(3)
C(17)	0175(1)	−1922(3)	−1962(2)	C(45)	1802(1)	5135(3)	−2942(2)
C(18)	−0371(1)	−1430(3)	−2014(2)	C(46)	1552(2)	5997(3)	−2371(2)
C(19)	−0479(1)	−0128(3)	−2175(2)	C(47)	1857(2)	5974(3)	−3687(2)
C(20)	−0024(1)	0672(3)	−2244(2)	C(48)	2413(1)	4666(3)	−2515(2)

Table 2. Interatomic distances (Å) for non-hydrogen atoms (the mean e.s.d. is 0·005 Å)

Atoms	Distance	Atoms	Distance	Atoms	Distance
C(1)–C(2)	1·517	C(12)–C(13)	1·377	C(24)–C(26)	1·398
C(1)–C(8)	1·516	C(12)–C(36)	1·527	C(24)–C(45)	1·533
C(1)–C(14)	1·595	C(14)–C(15)	1·524	C(26)–O(27)	1·378
C(1)–O(27)	1·484	C(14)–C(21)	1·517	C(31)–O(28)	1·433
C(2)–C(3)	1·402	C(15)–C(16)	1·384	C(32)–(C33)	1·527
C(2)–C(7)	1·394	C(15)–C(20)	1·381	C(32)–C(34)	1·534
C(3)–C(4)	1·368	C(16)–C(17)	1·393	C(32)–C(35)	1·544
C(4)–C(5)	1·396	C(17)–C(18)	1·371	C(36)–C(37)	1·543
C(5)–C(6)	1·391	C(18)–C(19)	1·394	C(36)–C(38)	1·516
C(5)–O(28)	1·359	C(18)–O(30)	1·367	C(36)–C(39)	1·469
C(6)–C(7)	1·395	C(19)–C(20)	1·389	C(40)–O(30)	1·406
C(8)–C(9)	1·407	C(21)–C(22)	1·377	C(41)–C(42)	1·551
C(8)–C(13)	1·402	C(21)–C(26)	1·384	C(41)–C(43)	1·535
C(9)–C(10)	1·388	C(22)–C(23)	1·389	C(41)–C(44)	1·543
C(9)–O(29)	1·380	C(23)–C(24)	1·398	C(45)–C(46)	1·527
C(10)–C(11)	1·407	C(23)–C(41)	1·535	C(45)–C(47)	1·541
C(10)–C(32)	1·537	C(24)–C(25)	1·397	C(45)–C(48)	1·518
C(11)–C(12)	1·397				

Table 3. Interatomic angles (degrees) (the mean e.s.d. is 0·3°)

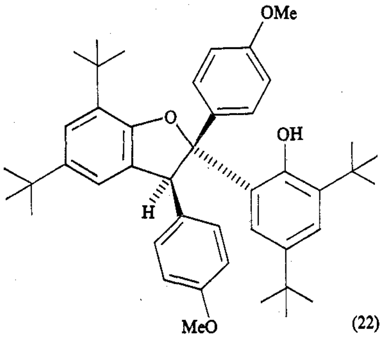
Atoms	Angle	Atoms	Angle	Atoms	Angle
C(2)–C(1)–C(8)	111·6	C(8)–C(13)–C(12)	122·3	C(1)–O(27)–C(26)	109·0
C(2)–C(1)–C(14)	112·2	C(1)–C(14)–C(15)	117·7	C(5)–O(28)–C(31)	118·0
C(2)–C(1)–O(27)	108·7	C(1)–C(14)–C(21)	100·9	C(18)–O(30)–C(40)	118·4
C(8)–C(1)–C(14)	115·3	C(15)–C(14)–C(21)	116·1	C(10)–C(32)–C(33)	109·9
C(8)–C(1)–O(27)	106·4	C(14)–C(15)–C(16)	119·0	C(10)–C(32)–C(34)	111·9
C(14)–C(1)–O(27)	101·9	C(14)–C(15)–C(20)	123·2	C(10)–C(32)–C(35)	110·5
C(1)–C(2)–C(3)	119·8	C(16)–C(15)–C(20)	117·8	C(33)–C(32)–C(34)	108·1
C(1)–C(2)–C(7)	122·5	C(15)–C(16)–C(17)	121·9	C(33)–C(32)–C(35)	109·2
C(3)–C(2)–C(7)	117·4	C(16)–C(17)–C(18)	119·3	(C34)–C(32)–C(35)	107·1
C(2)–C(3)–C(4)	121·8	C(17)–C(18)–C(19)	119·9	C(12)–C(36)–C(37)	107·8
C(3)–C(4)–C(5)	120·0	C(17)–C(18)–O(30)	116·3	C(12)–C(36)–C(38)	113·8
C(4)–C(5)–C(6)	119·9	C(19)–C(18)–O(30)	123·8	C(12)–C(36)–C(39)	110·8
C(4)–C(5)–O(28)	115·8	C(18)–C(19)–C(20)	119·6	C(37)–C(36)–C(38)	104·8
C(6)–C(5)–O(28)	124·3	C(15)–C(20)–C(19)	121·4	C(37)–C(36)–C(39)	109·1
C(5)–C(6)–C(7)	119·2	C(14)–C(21)–C(22)	131·1	C(38)–C(36)–C(39)	110·3
C(2)–C(7)–C(6)	121·7	C(14)–C(21)–C(26)	108·5	C(23)–C(41)–C(42)	113·4
C(1)–C(8)–C(9)	121·3	C(22)–C(21)–C(26)	120·2	C(23)–C(41)–C(43)	109·2
C(1)–C(8)–C(13)	120·5	C(21)–C(22)–C(23)	119·4	C(23)–C(41)–C(44)	109·6
C(9)–C(8)–C(13)	118·1	C(22)–C(23)–C(24)	118·4	C(42)–C(41)–C(43)	108·3
C(8)–C(9)–C(10)	121·8	C(22)–C(23)–C(41)	119·5	C(42)–C(41)–C(44)	107·3
C(8)–C(9)–O(29)	120·3	C(24)–C(23)–C(41)	122·1	C(43)–C(41)–C(44)	109·0
C(10)–C(9)–O(29)	117·9	C(23)–C(24)–C(25)	124·4	C(25)–C(45)–C(46)	110·0
C(9)–C(10)–C(11)	117·3	C(24)–C(25)–C(26)	114·0	C(25)–C(45)–C(47)	111·9
C(9)–C(10)–C(32)	122·7	C(24)–C(25)–C(45)	123·5	C(25)–C(45)–C(48)	109·5
C(11)–C(10)–C(32)	120·0	C(26)–C(25)–C(45)	122·5	C(46)–C(45)–C(47)	106·4
C(10)–C(11)–C(12)	122·8	C(21)–C(26)–C(25)	123·5	C(46)–C(45)–C(48)	112·1
C(11)–C(12)–C(13)	117·6	C(21)–C(26)–O(27)	112·0	C(47)–C(45)–C(48)	106·9
C(11)–C(12)–C(36)	120·2	C(25)–C(26)–O(27)	124·5		
C(13)–C(12)–C(36)	122·2				

atom of the hydroxy group on the di-t-butylphenol unit assumes the closest possible position to the oxygen atom of the furan ring; the observed distance O(27)–O(29) distance is 2·61 Å. The observed orientation of the hydroxy group is desirable since it provides a more efficient and stable molecular packing in the crystal structure by enhancing the formation of intramolecular hydrogen bonding between O(27) and O(29) and also a six-membered chelate ring [O(29), HO(29), O(27), C(1), C(8) and C(9)]. This effect probably causes the angle C(14)–C(1)–C(8) to be greater (115·3°) and the angle O(27)–C(1)–C(8) slightly lower (106·4°) than tetrahedral. Other observed interatomic bond lengths and angles in the molecule are generally acceptable. The thermal vibrational motion of the atoms are within the normal range except for the slightly higher values of the t-butyl groups which presumably are due to methyl torsion. There is no evidence of hydrogen bonding between molecules in the crystal structure.

Table 4. Dihedral angles (degrees) between plane normals

Plane	Definition	Planes	Angle	Planes	Angle
1	C(2)–C(7)	1–2	82·1	2–3	53·4
2	C(8)–C(13)	1–3	37·5	2–4	31·9
3	C(15)–C(20)	1–4	87·7	3–4	74·8
4	C(21)–C(26)				

In agreement with structure (22), the ^1H n.m.r. spectrum of dimer C has a 1H singlet at δ 5·51, which may be assigned to H3 of the dihydrobenzofuran nucleus, whereas the hydroxyl proton appears as a 3H multiplet with two aromatic protons in the aromatic region of the spectrum. In the ^{13}C n.m.r. spectrum, C3 appears as a doublet at 57·8 ppm, whereas oxygen-linked quaternary carbon C2 appears as a singlet at 98·0 ppm.



(22)

Experimental*

General

All melting points are uncorrected. ^1H n.m.r. spectra, unless stated otherwise, were determined in $CDCl_3$ with $SiMe_4$ as internal standard on a Varian EM-390 instrument. U.v. spectra were determined in ethanol and i.r. spectra in mineral oil.

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* Reference to a company and/or product named by the U.S. Department of Agriculture is only for purpose of information and does not imply approval or recommendation of the product to the exclusion of others which may also be suitable.

Oxidation of 2,4-Bis(1,1-dimethylethyl)-6-(4-methoxyphenylmethyl)phenol (1)

Silver oxide (100 g) was added to a solution of (1) (50 g) in acetone (200 ml). A vigorous exothermic reaction occurred and the solvent boiled. After 40 min, the warm, filtered, deep red reaction solution was evaporated to an oil which was dissolved in Skellysolve F. The solution was concentrated to about 250 ml and cooled, whereupon dimer A (17) crystallized (4·1 g). The filtrate from dimer A was evaporated and the residue digested with methanol, leaving more dimer A as an undissolved residue (2·6 g). The methanol filtrate from dimer A was evaporated to an oil which was chromatographed on a silicic acid column and eluted with Skellysolve F containing a trace of ethyl acetate. Evaporation of the highest R_F band gave a residue which crystallized from methanol to give the benzophenone derivative (7) (12·7 g). Later chromatographic fractions were similarly crystallized from methanol to give small yields of dimers B (19), C (22), D and E, and the benzylic methyl ether derivative (15).

[3,5-Bis(1,1-dimethylethyl)-2-hydroxyphenyl](4-methoxyphenyl)methanone (7)

The benzophenone oxidation product (7) [or (8)] crystallized from methanol as glistening, brightly yellow *plates*, m.p. 116–117°, which give an intense green colour with alcoholic ferric chloride (Found: C, 77·6; H, 8·3; $M^{+\bullet}$, 340·2043. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%; $M^{+\bullet}$, 340·2038). λ_{max} 354 (log ε 4·63), 293 (4·97) nm. ν_{max} 1615 cm^{-1}. *m/e* 340 (42·5%), 326 (13·8), 325 (62·6), 232 (11·6), 217 (100), 190 (7·6), 175 (13·8), 161 (8·7), 155 (8·1), 135 (17·8). ^{1}H n.m.r. δ 1·23, $C(CH_3)_3$; 1·34, $C(CH_3)_3$; 3·87, OCH_3; 6·95, d, *J* 9 Hz, 2ArH; 7·44, d, *J* 2·5 Hz, ArH; 7·55, d, *J* 2·5 Hz, ArH; 7·69, d, *J* 9 Hz, 2ArH; 12·60, OH.

A mixture of the benzophenone (7) (0·5 g), dimethyl sulfate (3·0 ml), potassium carbonate (5 g) and acetone (20 ml) was refluxed for 3 h, concentrated, and diluted with water. The oily product crystallized from aqueous methanol to give *[3,5-bis(1,1-dimethylethyl)-2-methoxyphenyl](4-methoxyphenyl)methanone* (11) as colourless, thick needles, m.p. 77–78° (0·48 g) (Found: C, 77·5; H, 8·5. $C_{23}H_{30}O_3$ requires C, 77·9; H, 8·5%). ν_{max} 1660 cm^{-1}. ^{1}H n.m.r. δ 1·26, $C(CH_3)_3$; 1·37, $C(CH_3)_3$; 3·48, OCH_3; 3·82, OCH_3; 6·88, d, *J* 9 Hz, 2ArH; 7·15, d, *J* 3 Hz, ArH; 7·44, d, *J* 3 Hz, ArH; 7·83, d, *J* 9 Hz, 2ArH.

[3,5-Bis(1,1-dimethylethyl)-2-methoxyphenyl](4-methoxyphenyl)methanol (12)

The benzophenone (11) (0·3 g) was reduced with sodium borohydride (0·3 g) in methanol (5 ml). After 30 min, the product was precipitated with water and recrystallized from Skellysolve F to give (12) as thick, colourless *needles*, m.p. 93–94° (0·26 g) (Found: C, 77·4; H, 9·0. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·0%). ^{1}H n.m.r. δ 1·23, $C(CH_3)_3$; 1·39, $C(CH_3)_3$; 2·52, d, *J* 4 Hz, OH; 3·66, OCH_3; 3·78, OCH_3; 6·15, d, *J* 4 Hz, CH; 6·83, d, *J* 9 Hz, 2ArH; 7·15–7·35, m, 4ArH.

[3,5-Bis(1,1-dimethylethyl)-2-hydroxyphenyl](4-methoxyphenyl)methanol (14)

The oxidation product (7) (1·0 g) was suspended in methanol (25 ml), and treated with sodium borohydride (0·3 g). After 5 min, water was added and the product was extracted with ether. The residue obtained on evaporation of the ether was crystallized from Skellysolve F and from methanol to give (14) as colourless *needles*, m.p. 115–116° (0·85 g) (Found: C, 77·0; H, 8·9. $C_{22}H_{30}O_3$ requires C, 77·1; H, 8·8%). ν_{max} 3350, 3450 cm^{-1}. ^{1}H n.m.r. δ 1·19, $C(CH_3)_3$; 1·38, $C(CH_3)$; 2·67, d, *J* 3 Hz, OH; 3·75, OCH_3; 5·90, d, *J* 3 Hz, CH; 6·68, d, *J* 2·5 Hz, ArH; 6·86, d, *J* 9 Hz, 2ArH; 7·25, d, *J* 2·5 Hz, ArH; 7·27, d, *J* 9 Hz, 2ArH; 8·05, OH.

2,4-Bis(1,1-dimethylethyl)-6-[methoxy(4-methoxyphenyl)methyl]phenol (15)

A solution of the benzylic alcohol (14) (0·1 g) in methanol (1 ml) was warmed, treated with a drop of concentrated HCl, and allowed to cool. The crystalline product was recrystallized from methanol to give (15) as glistening, colourless *needles*, which melted at 113° to an orange liquid (Found: C, 77·3; H, 9·1. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·1%). ν_{max} 3350 cm^{-1}. ^{1}H n.m.r. δ 1·19, $C(CH_3)_3$; 1·38, $C(CH_3)_3$; 3·40, OCH_3; 3·76, OCH_3; 5·23, CH; 6·67, d, *J* 2·5 Hz, ArH; 6·83, d, *J* 9 Hz, 2ArH; 7·20, d, *J* 2·5 Hz, ArH; 7·27, d, *J* 9 Hz, 2ArH; 8·20, OH.

1,5-Bis(1,1-dimethylethyl)-2-methoxy-3-[methoxy(4-methoxyphenyl)methyl]benzene (13)

A mixture of (15) (0·2 g), dimethyl sulfate (2 ml), potassium carbonate (5 g) and acetone (10 ml) was refluxed for 2 h, concentrated, and diluted with water. The solid product crystallized from methanol to give (13) as colourless *needles*, m.p. 120° (0·15 g) (Found: C, 77·8; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·2%). ^{1}H n.m.r. δ 1·22, $C(CH_3)_3$; 1·37, $C(CH_3)_3$; 3·30, OCH_3; 3·65, OCH_3; 3·75, OCH_3; 5·61, CH; 6·81, d, *J* 9 Hz, 2ArH; 7·21–7·32, m, 4ArH.

2,4-Bis(1,1-dimethylethyl)phenyl 4-Methoxybenzoate (16)

Anhydrous aluminium chloride (10 g), 2,4-di-t-butylphenol (10·3 g), and 4-methoxybenzoyl chloride (8·6 g) were mixed, warmed to 60°, and allowed to stand for 20 min. Water was then added and the product was collected. Recrystallized successively from aqueous methanol and from Skellysolve F, (16) was obtained as colourless, brittle *needles*, m.p. 108–109° (13·0 g). The same product was obtained by reaction of 2,4-di-t-butylphenol with 4-methoxybenzoyl chloride in pyridine (Found: C, 77·6; H, 8·4. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%). ν_{max} 1730 cm^{-1}. ^{1}H n.m.r. δ 1·29, $C(CH_3)_3$; 1·38, $C(CH_3)_3$; 3·85, OCH_3; 6·97, d, *J* 9 Hz, 3ArH; 7·26, dd, *J* 9, 2·5 Hz, ArH; 7·31, d, *J* 2·5 Hz, ArH; 8·15, d, *J* 9 Hz, 2ArH.

*3′,5′,6,8-Tetrakis(1,1-dimethylethyl)-3,4-bis(4-methoxyphenyl)-3,4-dihydrospiro[2*H*-1-benzopyran-2,1′-cyclohexa-3′,5′-dien]-2′-one (Dimer A) (17)*

Recrystallized from acetone/methanol, (17) separated as slightly yellow *plates*, which melted at 227° to a deep orange-red liquid (Found: C, 81·4; H, 8·7; M$^{+\bullet}$, 648·4207. $C_{44}H_{56}O_4$ requires C, 81·4; H, 8·7%; M$^{+\bullet}$, 648·4178). ν_{max} 1680, 1615 cm^{-1}. *m/e* 648 (75·1%), 421 (18·5), 324 (42·6), 310 (23·7), 293 (43·7), 267 (18·5), 227 (15·9), 201 (17·3), 147 (11·9), 121 (27·4). ^{1}H n.m.r. δ 0·98, $C(CH_3)_3$; 1·07, $C(CH_3)_3$; 1·10, $C(CH_3)_3$; 1·31, $C(CH_3)_3$; 3·57, d, *J* 12 Hz, CH; 3·61, OCH_3; 3·65, OCH_3; 4·29, d, *J* 12 Hz, CH; 6·25, d, *J* 2 Hz, CH; 6·32–6·65, m, 6CH; 6·82, d, *J* 8 Hz, 2ArH; 6·84, d, *J* 8 Hz, 2ArH; 7·13, d, *J* 2 Hz, CH.

A solution of dimer A (0·2 g) in tetrahydrofuran (25 ml) was refluxed with lithium aluminium hydride (0·07 g) for 1 h. Saturated aqueous ammonium chloride was added to the cooled mixture until a granular precipitate formed. This was filtered off. Evaporation of the filtrate gave a residue which crystallized from acetone/methanol to yield *3′,5′,6,8-tetrakis(1,1-dimethylethyl)-3,4-bis(4-methoxyphenyl)-3,4-dihydrospiro[2*H*-1-benzopyran-2,1′-cyclohexa-3′,5′-dien]-2′-ol* (18) as colourless needles, m.p. 174–175° (0·15 g) (Found: C, 80·9; H, 9·0. $C_{44}H_{58}O_4$ requires C, 81·2; H, 9·0%). ^{1}H n.m.r. [(D_6)acetone] δ 1·03, 2$C(CH_3)_3$; 1·12, $C(CH_3)_3$; 1·38, $C(CH_3)_3$; 2·73, d, *J* 7 Hz, OH; 3·62, 2OCH_3; 3·78, d, *J* 11 Hz, H3; 4·35, d, *J* 11 Hz, H4; 4·68, d, *J* 7 Hz, H2′, 5·68, H6′; 5·71, H4′; 6·56, d, *J* 9 Hz, 2ArH; 6·59, d, *J* 2·5 Hz, ArH; 6·65, d, *J* 9 Hz, 2ArH; 6·85, d, *J* 9 Hz, 2ArH; 7·21, d, *J* 9 Hz, 2ArH; 7·26, d, *J* 2·5 Hz, ArH.

*3′,5′,6,8-Tetrakis(1,1-dimethylethyl)-2,4-bis(4-methoxyphenyl)spiro[2*H*-1-benzopyran-3(4*H*),1′-cyclohexa-3′,5′-dien]-2′-one (Dimer B) (19)*

Dimer B crystallized from methanol as slightly yellow rhombohedric *crystals*, m.p. 189–190° (Found: C, 81·5; H, 8·8; M$^{+\bullet}$, 648·4194. $C_{44}H_{56}O_4$ requires C, 81·4; H, 8·7%; M$^{+\bullet}$, 648·4178). ν_{max} 1635, 1605 cm^{-1}. *m/e* 648 (0·9%), 511 (2·2), 469 (3·0), 355 (2·5), 324 (17·9), 323 (13·9), 293 (15·6), 267 (8·8), 227 (5·6), 167 (9·7), 121 (19·1), 119 (20·5). ^{1}H n.m.r. δ 0·87, $C(CH_3)_3$; 1·38, $C(CH_3)_3$; 3·67, OCH_3; 3·69, OCH_3; 5·12, CH; 5·26, CH; 6·28, br s, 2CH; 6·55, d, *J* 8 Hz, 2ArH; 6·64, d, *J* 8 Hz, 2ArH; 6·73, d, *J* 2 Hz, CH; 6·84, d, *J* 8 Hz, 2ArH; 7·16, d, *J* 8 Hz, 2ArH; 7·21, d, *J* 2 Hz, CH.

6-[5,7-Bis(1,1-dimethylethyl)-2,3-bis(4-methoxyphenyl)-2,3-dihydrobenzofuran-2-yl]-2,4-bis(1,1-dimethylethyl)phenol (Dimer C) (22)

Dimer C separated from methanol as glistening, colourless *prisms*, m.p. 168–169° (Found: C, 81·3; H, 8·8; mol. wt, 648. $C_{44}H_{56}O_4$ requires C, 8·4; H, 8·7%; mol. wt, 648). ν_{max} 3475, 1635, 1605 cm^{-1}. *m/e* 648 (10%), 646 (13·5), 631 (3·8), 591 (2·7), 540 (3·9), 442 (3·56), 324 (2·8), 309

(2·0), 270 (2·48), 255 (6·0), 135 (3·0), 121 (2·3). ^{1}H n.m.r. δ 1·17, $C(CH_3)_3$; 1·29, $C(CH_3)_3$; 1·34, $C(CH_3)_3$; 1·47, $C(CH_3)_3$; 3·63, OCH_3; 3·68, OCH_3; 5·51, H3 (benzofuran); 6·27–6·85, m, 8ArH; 7·10–7·30, m, OH and 2ArH; 7·47–7·72, m, 2ArH.

Crystallography

Crystal data for (*22*).—$C_{44}H_{56}O_4$, dimer C, M 648·9, monoclinic, space group $P2_1/n$* [$C_{2h}{}^5$, No. 14 (variant)], a 23·643(8), b 10·430(4), c 16·518(5) Å, β 104·75(1)°, U 3939(2) Å^3, $D_c(Z = 4)$ 1·09 g cm^{-3}, $F(000)$ 1408; Cu Kα radiation (Ni filtered), λ 1·5418 Å, μ 5·33 cm^{-1}. Specimen size: 0·25 by 0·41 by 0·21 mm.

Structure determination.—Intensity data were measured with a G.E. four-circle automatic diffractometer at room temperature by means of the $\theta/2\theta$ scanning technique—the scan rate was 1° min^{-1} and the backgrounds were measured at 0·5° on each side of the scan limits; $2\theta_{max}$ 110°; 5091 reflections were measured, 4944 of these were unique, 214 measured as zero and 271 other reflections had $I < \sigma(I)$. Intensity data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods with MULTAN.[14] Positional and thermal parameters were refined by a full-matrix least-squares program which minimizes the function $\Sigma w(\Delta F)^2$ where $\Delta F = |F_o| - |F_c|$; the weighting factor $w = 1/\sigma^2(F)$ when $I > \sigma(I)$; otherwise $w = 0$. Scattering factors for all non-hydrogen atoms were from Cromer and Waber[15] and those for hydrogen atoms were from Stewart, Davidson and Simpson.[16] Positions of hydrogen atoms were located from a difference-Fourier synthesis. During the final stages of refinement secondary extinction correction was made as suggested by Zachariasen[17] to minimize the discrepancy between $|F_o|$ and $|F_c|$ of the most intense reflections. Scattering factors for oxygen were corrected for anomalous dispersion.[18] Thermal parameters: C and O anisotropic; H isotropic—due to the restriction of the number of refined parameters in the least-squares program used, the positional and thermal parameters of hydrogen atoms were held constant in the final cycle of least-squares refinement. Residuals: $R_1 = 0·068$ for 4459 [$I > \sigma(I)$] reflections and 0·076 for all (4944) reflections. $R_2 = [\Sigma w(\Delta F)^2/\Sigma w F_o{}^2]^{1/2} = 0·092$, and the standard deviation of an observation of unit weight was 2·77. Final positional parameters for the non-hydrogen atoms are given in Table 1. The interatomic distances and angles are listed in Tables 2 and 3, respectively. Computations: all calculations were carried out on the Lawrence (Berkeley) Laboratory CDC-7600 computer with the XRAY76 program library furnished by Drs A. Zalkin and L. Templeton. Material deposited:† thermal parameters for the non-hydrogen atoms, fractional coordinates and isotropic thermal parameters for the hydrogen atoms, a table of bond lengths involving hydrogen atoms, and a table of observed structure factors, standard deviations and the difference $F_o - F_c$.

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* Equivalent positions: (x, y, z), $(\bar{x}, \bar{y}, \bar{z})$, $(1/2-x,\ 1/2+y,\ 1/2-z)$, $(1/2+x,\ 1/2-y,\ 1/2+z)$.

† Copies are available on application to the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002.

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