Tetrahedron. Vol. 32, pp. 665 to 668. Pergamon Press 1976 Printed in Great Britain

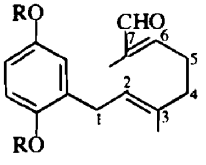
THE STRUCTURE AND SYNTHESIS OF ALLIODORIN

KENNETH L. STEVENS* and LEONARD JURD
Western Regional Research Laboratory, Agricultural Research Service, U.S. Department of Agriculture, Berkeley, CA 94710, U.S.A.

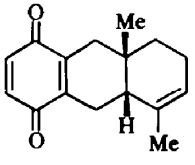
(*Received in USA* 29 *July*, 1975; *Received in UK for publication* 27 *October* 1975)

Abstract—A new phenolic terpene aldehyde, alliodorin (**1a**), has been isolated from *Cordia alliodora* and shown to be a derivative of geranylhydroquinone. Alliodorin diacetate was synthesized by geranylation of hydroquinone followed by acetylation and finally by oxidation with selenium dioxide, thus confirming the assigned structure. Several other compounds from the oxidation reaction were isolated and characterized.

Cordia alliodora, a Panamanian tree belonging to Boraginaceae, possesses considerable resistance to attack by marine boring organisms,[1] termites[2] and terrestial fungi.[3] Extraction of the dry heartwood yielded 0·8% of a crystalline quinol-terpenoid compound now shown to be **1a**,[4] for which the name alliodorin is proposed. This new compound belongs to a class of natural terpenoids, consisting of a terpenoid system joined to resorcinol, quinol or quinone units, many members of which, e.g. grifolin,[5] siccanin,[6] paniceins,[7] have been shown to possess biocidal properties. The isolation of alliodorin is of particular interest, since it is probably the immediate precursor of the cordiachromes, e.g. **2**, recently isolated by Thomson[8] *et al.* from other species of *Cordia*.

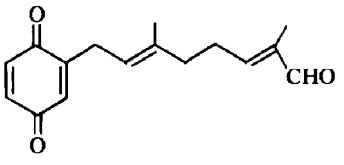


1a: R = H
1b: R = Ac
1c: R = Me

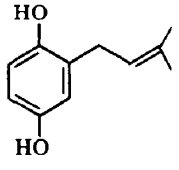


2

Alliodorin (**1a**, m.p. 87°) formed a diacetate (**1b**) upon treatment with acetic anhydride and pyridine, a monooxime (m.p. 108°) a dimethyl ether (**1c**), and is readily oxidized by manganese dioxide to the quinone **3**. The NMR data of these compounds are summarized in Table 1. Irradiation of the doublet at δ 3·21 in alliodorin diacetate (**1b**) caused the triplet at δ 5·25 to collapse to a singlet thus confirming the assignment of vinyl protons. The three aromatic protons of **1a**, **b**, **c** and **1a** oxime all show a typical ABC pattern (1,2,4-substituted aromatic) between δ 6·4–δ 7·0, the spectrum in this region being similar to prenylhydroquinone (**4**).[9]

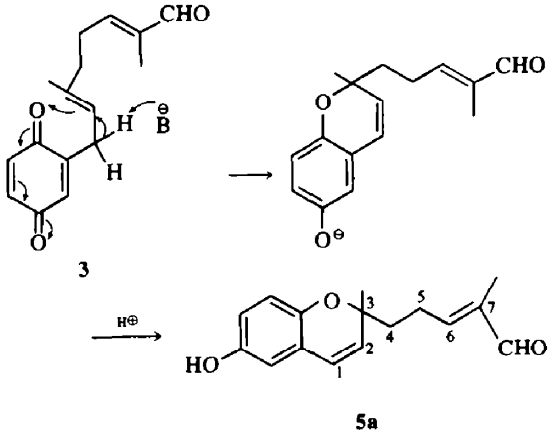


3



4

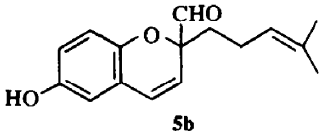
In accord with its assigned structure, the quinone **3** readily cyclized to form a 2,2-di-substituted chromene **5a** in warm pyridine.



3

5a

The NMR spectrum of **5a** showed a pair of doublets (J = 10·0 Hz) at δ 6·31 and δ 5·55 (chromene protons), a vinyl Me group (δ 1·68), a Me singlet at δ 1·38, a vinyl proton triplet (J = 7·0 Hz) at δ 6·57, and a one proton singlet at δ 9·31 (aldehyde). These data rule out the alternative structure (**5b**) which would have two vinyl Me groups at δ 1·68. The terminal location of the aldehyde group was confirmed by a base-catalyzed reverse aldol condensation of alliodorin which yielded 2-methyl-2-pentenal (isolated as its 2,4-DNP), the self condensation product of propionaldehyde, as well as propionaldehyde.



5b

The α,β-unsaturated aldehyde is confirmed by both IR and UV spectra of alliodorin (ν_{max}^{mull} 1675, 2720, 3025, 1645 cm^{-1}), λ_{max}^{EtOH} 227 nm (ϵ 21,300). A prenylhydroquinone chromophore is also substantiated by a λ_{max}^{EtOH} at 295 nm (ϵ 4100), which is identical with that of prenylhydroquinone,[9] λ_{max}^{ether} 295 nm (ϵ 4100).

The 70 eV mass spectrum of alliodorin is shown in Fig. 1.

The most abundant fragment is the benzyl ion (m/e

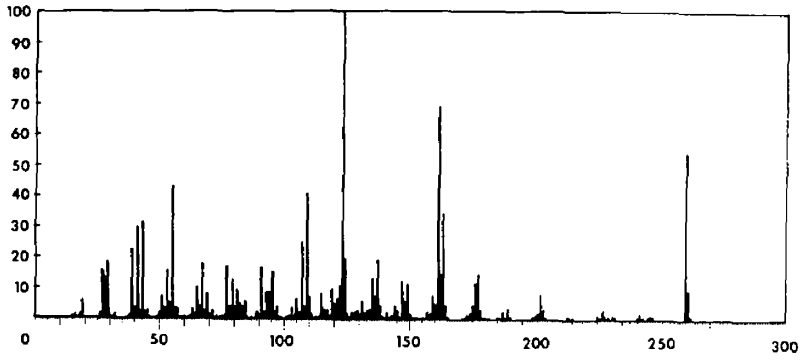
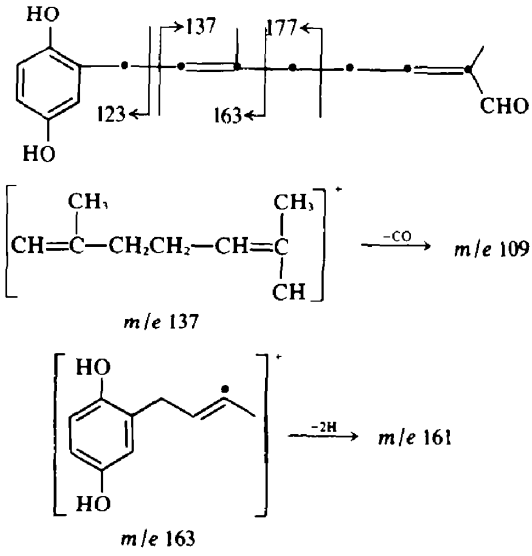


Fig. 1. Mass spectrum of alliodorin (1a) at 70 eV.

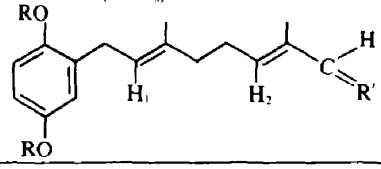


123) followed by a fragment having *m/e* 161 ($C_{10}H_9O_2$). This ion presumably arises from the 163 fragment ($C_{10}H_{11}O_2$) by loss of 2H atoms. Another major fragment *m/e* 109 (C_8H_{13}) results from loss of CO from the *m/e* 137 ion. These data are all consistent with the structure of alliodorin.

The stereochemistry of the two ethylenic double bonds was established by comparison of the NMR spectra of alliodorin and its derivatives with those of several model compounds of known configuration, and has been shown to be *trans trans* as previously reported.[4]

Synthesis. Condensation of hydroquinone with geraniol in refluxing 50% aqueous formic acid gave good yields of geranylhydroquinone (oil, 78%).[11] The NMR spectrum of the crude reaction product showed singlets at δ 1·57 (3H) and δ 1·67 (6H) (vinyl Me groups), a doublet at δ 3·25 (2H, J = 7·0 benzylic methylene), and two triplets at δ 5·06 and δ 5·26 (J = 7·0, vinyl) confirming the expected product. Geranylhydroquinone was acetylated with acetic anhydride/pyridine to an oily diacetate (b.p. 170°/70 μ press). The NMR spectrum showed vinyl Me

Table 1. NMR data ($CDCl_3$) of alliodorin and derivatives (100 MHz)



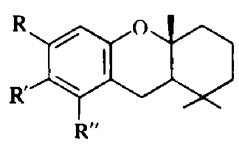
Compound	Aromatic protons	Vinyl Methyls	H_1	H_2	$C^{R'}_{H}$	R	Benzylic protons	Allyl methylene	Quinone protons
R = H R'=O Ia	6.50- 6.73 3H	1.73(s) 6H	5.34(t) 1H J = 7.0	6.50(t) 1H J = 7.0	9.34(s) 1H	5.20(s) 5.55(s) 2H	3.29(d) 2H J = 7.0	2.22(m) 2.49(m) 4H	--
R = Me Ib R'= O	6.6- 6.8 3H	1.72(s) 6H	5.34(t) 1H J = 7.0	6.44(t) 1H J = 7.0	9.34(s) 1H	3.74(s) 3H 3.76(s) 3H	3.30(d) 2H J = 7.0	2.05- 2.60(m) 4H	--
R = Ac Ic R'=O	6.80- 7.00 3H	1.68(s) 3H 1.72(s)	5.25(t) 1H J = 7.0	6.40(t) 1H J = 7.0	9.35(s) 1H	2.25(s) 6H	3.21(d) 2H J = 7.0	2.0- 2.6(m) 4H	
R = H R'= NOH	6.40- 6.70 3H	1.70(s) 3H 1.76(s) 3H	5.38(t) 1H J = 7.0	5.69(t) 1H J = 7.0	9.68(s) 1H	3.09(s) 1H 7.44(s) 1H	3.26(d) 2H J = 7.0	2.0- 2.5(m) 4H	
Quinone R'= O H H		1.69(s) 3H 1.76(s) 3H	5.25(t) 1H J = 7.0	6.47(t) 1H J = 7.0	9.40(s) 1H		3.16(d) 2H J = 7.0	2.26(t) 2H J = 7.0 2.48(t) 2H, J = 7.0	6.78 2H 6.55 1H

groups at δ 1·58 (3H) and δ 1·65 (6H), two acetate Me singlets at δ 2·21 and δ 2·24, a benzylic methylene doublet (J = 7·0 Hz) at δ 3·20 (2H) and 2 vinyl triplets (J = 7·0 Hz) at δ 5·06 (1H) and δ 5·20 (1H), confirming the expected structure.

Oxidation of geranylhydroquinone diacetate with selenium dioxide gave a mixture of products from which was isolated (chromatography on Sephadex (LH-20) and silica gel) a fraction (3%) identical in all respects to natural alliodorin diacetate (Table 1). Bhalerao and Rapoport[14] have studied the oxidation of a number of olefins with selenium dioxide and found that gemdimethyl olefins give exclusively *trans*-alcohols or -aldehydes. Hence, the oxidation of geranylhydroquinone diacetate would be expected to proceed with the formation of the *trans* aldehyde.

In addition to alliodorin diacetate, a compound analyzing for $C_{18}H_{26}O_3$ was isolated as an oil from the oxidation reaction.

The NMR spectrum showed three Me singlets at δ 0·88, 0·97 and 1·19, one acetate Me group at δ 2·22, a 6H multiplet at δ 1·30–1·80, a 1H multiplet at δ 1·80–2·05 (methine), a 2H multiplet at 2·5–2·7 (benzylic), and a 3H multiplet at δ 6·60–6·80 (aromatic). From a comparison of these data with the spectra of the chromans **8a**, **b**, **c** and **d** reported by Mechoulam[13] and Manners,[14] the compound may be considered to be the chroman **8e**.



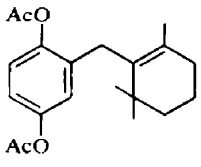
8

trans **a**: R = C_5H_{11}, R′ = H, R″ = OH

CIS **b**: R = C_5H_{11}, R′ = H, R″ = OH

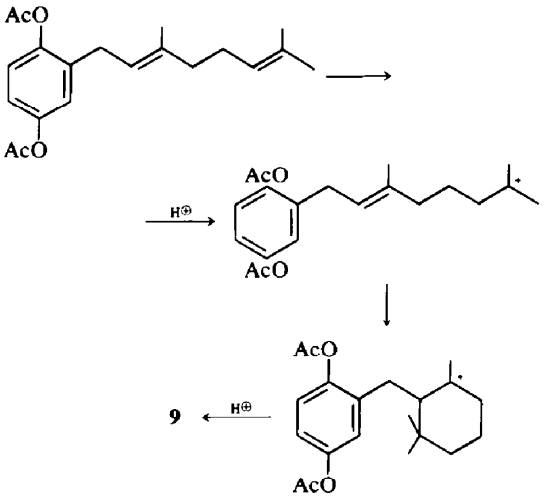
trans **c**: R = Me, R′ = H, R″ = OH
trans **d**: R = OH, R′ = H, R″ = Me
trans **e**: R = H, R′ = OAc, R″ = H

Chroman **8e** probably arises *via* an acid catalyzed cyclization during the oxidation with selenium dioxide. A similar mechanism was suggested by Manners in the formation of **8c** and **8d**. Another product (m.p. 112°), isolated in a small amount from the reaction mixture has a molecular weight (70 eV MS) of 330 corresponding to elemental composition $C_{20}H_{26}O_4$. The NMR spectrum in $CDCl_3$ was as follows: δ 0·92 (s, 6H, gem dimethyl group), δ 1·50 (s, 3H, vinyl methyl), δ 1·40–1·80 (m, 4H, methylene groups), δ 2·08 (t, 2H, J = 7·0 Hz, vinyl methylene), δ 2·29 (s, 3H, acetate), δ 2·36 (s, 3H, acetate), δ 3·27 (s, 2H, benzylic methylene), and δ 6·8–7·0 (3H, aromatic). These data are consistent with the cyclohexane derivative **9**. The formation of **9** during the synthesis of

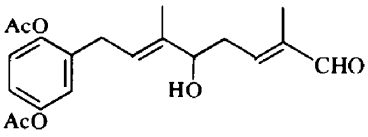


9

alliodorin may involve sequential protonation, cyclization, and deprotonation of geranlyhydroquinone diacetate:



Once alliodorin is formed in the reaction mixture, oxidation continues to give an allylic alcohol (oil). The NMR data unequivocally establish the structure as **10**:



10

δ 1·68 (s, 3H, vinyl Me), δ 1·72 (s, 3H, vinyl Me), δ 2·25 (s, 3H, acetate), δ 2·27 (s, 3H, acetate), δ 2·58 (t, 2H, J = 7·0 Hz, vinyl methylene), δ 3·24 (d, 2H, J = 7·0 Hz, benzylic methylene), δ 4·17 (t, 1H, J = 6·5 Hz, carbinol proton), δ 5·50 (t, 1H, J = 7·0 Hz, non-conjugated vinyl proton), δ 6·47 (t, 1H, J = 7·0 Hz, conjugated vinyl proton), δ 6·85–7·00 (m, 4H, aromatic and hydroxyl protons) and δ 9·35 (s, 1H, aldehyde proton).

EXPERIMENTAL

NMR spectra were determined on a Varian HA-100 spectrometer at 100 MHz with TMS as an internal standard. Mass spectra were obtained on an EAI low resolution, quadrupole mass spectrometer and a CEC-110 high resolution instrument. IR spectra were recorded on a Perkin-Elmer Model 237 spectrometer.

Isolation of alliodorin (**1a**). The heartwood of *Cordia alliodora* was pulverized in a hammermill (1/3″ screen) and extracted successively with skelly "F", ether, acetone, and MeOH. The ether extract was chromatographed on Sephadex (LH-20) using $CHCl_3$/MeOH (9:1) as the eluting solvent. Alliodorin crystallized from ether/skelly "F", m.p. 87°, IR (nujol): 3350, 2720, 1675, 1698, 1602 cm^{-1}. MS *m/e* (rel. abundance): 260 (55), 163 (34), 101 (70), 137 (19), 123 (100), 109 (41), 107 (26), 55 (44), 43 (32), 41 (30), 39 (23). (Found: C, 73·8; H, 7·73; Calc for $C_{16}H_{20}O_3$: C, 73·8; H, 7·74). Oxime m.p. 108° (ether/skelly "F"). (Found: C, 70·0; H, 7·67; Calc for $C_{16}H_{21}O_3N$: C, 69·8; H, 7·69%).

Dimethyl ether (**1c**)

Method (*a*). To 100 mg (0·38 mmole) of alliodorin was added acetone (20 ml) dimethylsulfate (100 mg) and a large excess of K_2CO_3. The mixture was stirred at room temp. for 45 min, evaporated to dryness on the steam bath, diluted with water, allowed to stand 1 hr, and extracted with ether. The ethereal extract was washed with water, dried, and evaporated to give dimethylalliodorin as an oil. See text for NMR details.

Method (*b*). To 50 g of the crude acetone extract of *C. alliodora* was added acetone (500 ml) K_2CO_3 (100 g) and dimethylsulfate (50 g). Work-up in the usual manner gave a dark oil, which on distillation (70 μ, 195°) gave 6·3 g (12·6%) of light colored oil which by NMR was alliodorin dimethyl ether.

Base degradation of alliodorin. Alliodorin (100 mg) was placed in a 250 ml round bottom flask filled with a N_2 inlet and gas outlet, which was connected so that exiting gas passed through a soln of 2,4-dinitrophenylhydrazine reagent. 10% NaOH aq (30 ml) was added to the alliodorin and the mixture heated while being swept with N_2. The ppt which formed in the 2,4-D reagent was collected, recrystallized ($EtOH/H_2O$) to give m.p. 153°. Comparison (mmp, NMR, IR) with authentic 2 - methyl - 2 - pentenal - 2,4 - DNPH confirmed its identity.

Quinone (**3**). Alliodorin (100 mg) in benzene was stirred with an excess of activated MnO_2 for 1 hr at room temp. After filtration and removal of the solvent the yellow oil gave NMR ($CDCl_3$): δ 1·69 (s, 3H); δ 1·76 (s, 3H); δ 2·26 (m, 2H); δ 2·48 (m, 2H); δ 3·16 (d, 2H, J = 7·0 Hz); δ 5·25 (t, 1H, J = 7·0 Hz); δ 6·47 (t, 1H, J = 7·0 Hz); δ 6·54 (s, 1H); δ 6·78 (s, 2H); δ 9·40 (s, 1H).

Chroman (**8e**). The previously prepared **3** (500 mg) was dissolved in 10 ml pyridine and heated on the steam bath for 6 hr then evaporated to dryness. Chromatography on Sephadex, LH-20, gave the desired chroman as an oil (see text for NMR details). Mol. wt. by MS required for $C_{16}H_{18}O_3$ 258·1256; obs. 258·1260.

Geranylhydroquinone diacetate. Hydroquinone (1 mole), geraniol (1 mole) and 500 ml of 50% aqueous formic acid was refluxed for 24 hr then cooled. After addition of water the oil was separated, dried, and dissolved in benzene. Ac_2O (2 mole) and 10 ml pyridine were added and the soln allowed to stand at room temp. for 2 hr. Water was added and the benzene extract washed with water then dried over $MgSO_4$. After filtration and removal of the solvent, the product was distilled at 70 μ pressure (170°) NMR ($CDCl_3$): δ 1·68 (s, 6H), δ 2·23 (s, 3H), δ2·24 (s, 3H), δ 3·23 (d, 2H, J = 7·0 Hz), δ 5·10 (t, 1H, J = 7·0 Hz), δ 5·21 (t, 1H, J = 7·0 Hz), δ 6·85–7·00 (m, 3H).

Oxidation of geranylhydroquinone diacetate with selenium dioxide. Geranylhydroquinone diacetate (16·5 g, 0·05 mole), 250 ml abs alcohol, and freshly sublimed selenium dioxide (16·5 g, 0·05 mole) were refluxed for 12 hr, cooled, and diluted with 500 ml water. The misture was stirred for 15 min then extracted with ether. The etheral extract was washed with water, 10% $NaHCO_3$ aq, water, then dried over $MgSO_4$. After filtration the solvent was removed leaving a mixture which was refluxed with a large amount of skelly "F". The insoluble portion (13·73 g) was chromatographed on 700 g of silica gel using chloroform as solvent. The following compounds were eluted: **8e**, **9**, **1b** (3%) and **10**, (see text for NMR details).

REFERENCES

[1]C. R. Southwell and J. D. Bultman, *Biotropica* **3**, 81 (1971); cf. C. H. Edmondson, *Caribbean Forester* **10**, 37 (1948).
[2]T. C. Scheffer and C. G. Duncan, *Tropical Woods* **92**, 1 (1947).
[3]J. P. Perry, Jr. and Jorge Martinez Lima, *J. Forestry* **62**, 398 (1964).
[4]K. L. Stevens, L. Jurd, and G. Manners, *Tetrahedron Letters* 2955 (1973).
[5]M. Isobe and T. Goto, *Tetrahedron* **24**, 945 (1968).
[6]K. T. Suzuki and S. Nozoe, *Chem. Commun.* 527 (1971); *Tetrahedron Letters* 2457 (1969). K. Hirai, S. Nozoe, K. Tsuda, K. Ishibashi and M. Shirasaka, *Ibid.* 2177 (1967).
[7]G. Cimino, S. De Stefano, and L. Minale, *Tetrahedron* **29**, 2565 (1969).
[8]M. Moir and R. H. Thomson, *J. Chem. Soc.* Perkin I, 1352 (1973).
[9]L. Jurd, K. Stevens, and G. Manners, *Tetrahedron Letters* 2275 (1971).
[10]A. F. Thomas and M. Ozainne, *Chem. Commun.* 46 (1969).
[11]G. Manners, L. Jurd and K. Stevens, *Tetrahedron* **28**, 2949 (1972).
[12]U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.* **93**, 4835 (1971).
[13]R. Mechoulam and B. Yagen, *Tetrahedron Letters* 5349 (1969).
[15]G. Manners, L. Jurd, and K. Stevens, *Tetrahedron* **29**, 2949 (1972).