

Ozonization of Phenols from *Anacardium occidentale* (cashew)

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ABSTRACT: The phenolic lipid components cardanol and cardol, obtained from heat-processed technical cashew nutshell liquid from *Anacardium occidentale*, and anacardic acid from the natural product, each containing monoene, diene, and triene constituents, were ozonized. The ozonides were reduced chemically and catalytically to give 8-(3-hydroxyphenyl)octanal, 8-(3,5-dihydroxyphenyl)octanal, and 8-(3-hydroxy-2-carboxyphenyl)octanal, respectively, together with formaldehyde, malondialdehyde, butanal, and heptanal in each case. Reduction of the 8-(3-hydroxyphenyl)octanal, which was synthesized from 3-benzyloxybenzaldehyde, gave 3-octylphenol. Oxidation of the aldehyde with potassium permanganate gave 8-(3-hydroxyphenyl)octanoic acid, and reduction with sodium borohydride yielded 8-(3-hydroxyphenyl)octanol. For comparison, the *trans*-diols of cardanol were prepared by treatment of cardanol with peroxyformic acid and cleaved by periodate oxidation to give an alternative route to 8-(3-hydroxyphenyl)octanal but in lower yield. Likewise, the *cis*-diols were obtained with potassium permanganate and cleaved without isolation to give the same product in lower yield compared with ozonization.

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KEY WORDS: Cardanol, cashew nutshell liquid, dihydroxylation, oxidation, ozonization.

Although in recent years there has been great interest in environmental aspects of ozone chemistry, ozonization studies with organic unsaturated compounds have greatly increased. Ozonization reactions have been reviewed (1,2), examined for specific syntheses of isoprenoids (3–5) and fatty materials (6), and generally appraised for industrial use (6).

Ozonization of cardanol methyl ether (Fig. 1) ($R = \text{Me}$) prepared from cardanol ($R = \text{H}$), which is the main phenol (70%) in technical cashew nutshell liquid (CNSL) derived from *Anacardium occidentale* (7), has been used in structural work to establish the double bond positions in the unsaturated constituents **b**, **c**, and **d** (8). Oxidation at the 8-position of the monoene, diene, and triene of semisynthetic cardanol methyl ether is also of interest for the technical use of the product, 8-(3-methoxyphenyl)octanoic acid and of the corresponding aldehyde and alcohol (9–11). However, in pursuing chemical utilization studies of phenolic products, such as the copper extractant, 5-octylsalicylaldoxime, (12), we have examined the ozonization of the mixed unsaturated phenolic constituents of cardanol from technical CNSL, its other chief component cardol (20%), and that of anacardic acid (70%) in the natural product prior to hot decarboxylation. Both cardol and anacardic acid

have mono, diene, and triene alkyl chain constituents **b**, **c**, and **d** (Fig. 1). Another common minor component of both technical and natural CNSL is 2-methylcardol (5%).

Earlier work to determine double bond positions in the methyl ethers of phenolic lipids relied on a general method consisting of vicinal diol formation using performic acid followed by cleavage by Malaprade oxidation, reduction with sodium borohydride, and finally gas–liquid chromatographic comparison of the products with a range of synthetic standards (13). Our ozonization work was carried out in 1984 but remained unpublished. The appearance of recent patents (14,15) on the polymeric uses of ozonization products, first from technical CNSL as adhesive intermediates and second from cardanol as intermediates for polycarbonates, prompts us to publish our earlier results on the ozonization products of the component phenols. In this present account, the use of various solvents in ozonizations, the chemical reduction, and the catalytic hydrogenation of the CNSL ozonides are described. Ozonolysis of cardanol and reduction of the products were compared directly to the products derived from the alternative Swern oxidation followed by the Malaprade cleavage process and also to potassium permanganate oxidation.

The availability at the present time of larger scale and laboratory ozone generators (16,17) has enabled greater experimentation with ozonization, which affords a potential alternative route to other side-chain oxidation methods with cashew phenols.

EXPERIMENTAL PROCEDURES

Materials. Cardanol was obtained either by chromatography (18) or by the Mannich reaction of technical CNSL (19,20) and had a typical composition for **a** (3%), **b** (40%), **c** (17%), and **d** (40%) with an average M.W. of 300. Cardol also was obtained by chromatography of CNSL (18) and contained **b** (10%), **c** (18%), and **d** (72%). Anacardic acid was isolated from natural CNSL either by chromatography or by formation of insoluble salts, filtration, washing, and regeneration by acidification at 0°C (21) and possessed an unsaturated composition similar to cardanol. More recently, the component phenols of technical CNSL have been separated through a biphasic method (22) that is also applicable to anacardic acid in natural CNSL (23).

TLC. TLC was carried out on microscope slides, coated with silica gel G (Merck, Darmstadt, Germany) at a thickness of 0.25 mm and developed using chloroform/ethyl acetate (95:5) as the eluent. Spots were visualized by means of iodine vapor or Rhodamine 6 G (0.1% in ethanol). All reaction mixtures were monitored by TLC. For argentation TLC, silica gel

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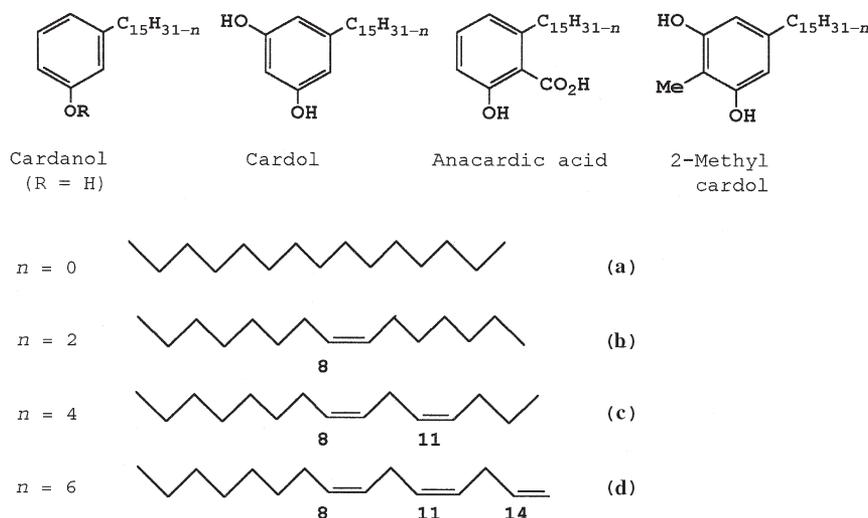


FIG. 1. Formulas of cardanol, cardol, anacardic acid, and 2-methylcardol from cashew.

G-coated slides were developed in silver nitrate (0.1 M) and dried in subdued light before use.

GLC. GLC was performed on a Pye Unicam 105/2 (Cambridge, United Kingdom) chromatograph equipped with an FID. Analyses were conducted on glass columns, 5' by 3/16" i.d., containing acid-washed celite coated with 5% OV-17 and nitrogen as carrier gas at 40 mL/min with an oven temperature at 220°C.

Spectroscopy. IR spectra were recorded with samples as liquid films on NaCl plates or in KBr discs on PerkinElmer 700 (Beaconsfield, Buckinghamshire, United Kingdom) and Unicam SP 200 (Pye Unicam, Cambridge, United Kingdom) spectrophotometers. ^1H NMR spectra were determined by using a Varian T60 instrument (Varian Scientific Equipment, Palo Alto, CA) with tetramethylsilane as internal standard using CCl_4 as solvent in all experiments. MS was carried out with a modified AEI MS 902 instrument (Associated Electrical Industries, Manchester, United Kingdom) at 70 eV in the temperature range 160–180°C and insertion of solute (20% in diethyl ether) by a standard capillary mounted in the quartz tip of the probe.

Ozonization. Ozonizations were conducted in a fume hood with a Wallace and Tiernan Products (Tonbridge, Kent, United Kingdom) ozonator model no. BA 023, by passage of compressed air at 25 L/h and applied voltage 100 V where ozonized air is produced containing 0.6 g ozone/25 mL/h (0.024 g/mL/h). The magnetically stirred reaction flask was cooled to -78°C with a CO_2 /acetone bath, and a constant flow of ozonized air ensured by passage through a large flask prior to entering the reaction vessel. Connections between glass components were made with polyvinylchloride tubing. Completion of ozonation was indicated when the exit gases from the reaction flask liberated iodine from a final trap flask containing 10% aqueous potassium iodide.

Hydrogenation. Hydrogenations were carried out in a glass hydrogenation apparatus capable of being evacuated and filled with either nitrogen or hydrogen as desired at atmospheric pressure for use either at constant pressure or constant volume. Throughout, 5% palladium-charcoal was used as the hydrogenation catalyst with ethyl acetate as solvent. Reaction mixtures from ozonizations were transferred to the hydrogenation flask for catalytic reduction.

Ozonization of cardanol and catalytic hydrogenation of the ozonide to 8-(3-hydroxyphenyl)octanal, 4. A number of ozonizations, summarized in Table 1, were initially carried out in ethyl acetate (25 mL/g cardanol) at -78°C to establish appropriate conditions, which led to the procedure given in detail for the experiment with cardanol (2.0 g).

Cardanol (**a**, **b**, **c**, and **d**) (2.0 g, 6.66 mmol) in ethyl acetate (50 mL) was treated with ozonized air for 3 h at -78°C , the mixture was left overnight at low temperature, and ozonization was resumed for 9 h. The reaction mixture was hydrogenated in the presence of the catalyst Pd-C (0.48 g), which resulted in an uptake of hydrogen (236 mL). Filtration and recovery by evaporation of the filtrate *in vacuo* to remove volatile aldehydes gave 2.30 g of crude pale brown oil containing traces of solvent. For characterization, the product was evaporated further *in vacuo* to constant weight to remove heptanal; IR, ν_{max} (film/ cm^{-1}), 2720 (C–O), 1700 (C=O) cm^{-1} ; ^1H NMR, δ_{H} (60 MHz, CCl_4 , ppm), 1.45 (*m*, 10H, 5 CH_2), 2.20 (*m*, 2H, CH_2CO), 2.60 (*t*, 2H, CH_2Ar), 6.60–7.05 (*m*, 4H, HAr), 8.25 (*s*, 1H, OH, D_2O exch.), 9.20 (*s*, 1H, CHO); *m/z* (M^+ , 220), ($\text{C}_{14}\text{H}_{20}\text{O}_2$ requires 220), 108 ($\text{C}_7\text{H}_8\text{O}$, base peak), 107 ($\text{C}_7\text{H}_7\text{O}$), 74, 59, 45, 31, 29 (CHO). A small chemical shift at δ 9.0 was attributed to traces of saturated cardanol, which was unozonized.

Ozonization in different solvents and chemical reduction of the ozonide to 4. Ozonizations were conducted in meth-

TABLE 1
Ozonization of Cardanol in Ethyl Acetate and Catalytic Hydrogenation of the Ozonide to 8-(3-hydroxyphenyl)Octanal, 4

| Cardanol (g) | Time ^a (h) | Pd-C (g) | H ₂ (mL) | Product (g) | Theory (g) | Yield (%) ^b |
|--------------|-----------------------|----------|---------------------|-------------|------------|------------------------|
| 1.0 | 2.5 | 0.17 | 108 | 0.94 | 1.109 | 84.7 |
| 10.0 | 4.5 | 0.50 | 1027 | 10.27 | 11.09 | 92.6 |
| 2.0 | 12 | 0.48 | 236 | 2.30 | 2.218 | 103.6 ^c |

^aReaction time is for ozonization. Hydrogenations in all cases proceeded rapidly.

^bYields, after hydrogenation of the ozonide, were calculated on the basis that cardanol contained the saturated (3%, M.W. 304, unchanged in the ozonization), monene (40%, M.W. 302), diene (17%, M.W. 300), and triene (40%, M.W. 298) constituents and that product 4 contained an equimol proportion of heptanal (M.W. 114) and saturated cardanol.

^cTLC indicated >100% theoretical yield owing to traces of retained solvent.

TABLE 2
Ozonization of Cardanol (0.50 g) in Different Solvents and Reduction of the Ozonide with Glacial Acetic Acid and Zinc Dust (1.0 g) to 8-(3-hydroxyphenyl)Octanal, 4

| Solvent (mL) | Time ^a (h) | Acetic acid (mL) | Product (g) | Yield (%) ^b |
|------------------------|-----------------------|------------------|-------------------|------------------------|
| MeOH, 12.5 | 4 | 32 (aq. 50%) | 0.20 | 36 |
| Lp, 10 | 2.2 | 20 | 0.53 | 95.6 |
| Et ₂ O, 100 | 1.0 | 15 | 0.70 ^c | 96.0 |
| CCl ₄ , 100 | 1.5 | 20 | 0.41 | 74.0 |

^aReaction time is for ozonization.

^bYields calculated as in Table 1, except for ozonization in Et₂O when hept-aldehyde was removed *in vacuo*.

^cCardanol (1.0 g) used in this experiment. Lp, light petroleum ether.

anol, light petroleum ether (40–60°C), diethyl ether at –78°C, and in carbon tetrachloride at –20°C as listed in Table 2. In each case, with the exception of methanol, the solvent was presaturated with ozone, and ozonization was then completed by passage of ozonized air in the usual way. The products were reduced with zinc and acetic acid. Light petroleum ether was first purified by treatment with ozone, then sulfuric acid, and recovered by distillation. For diethyl ether, the experiment is described in full below, leading after potassium permanganate oxidation of the aldehyde to the acid, 5.

Ozonization of cardanol, chemical reduction of the ozonide to 4, and oxidation to 8-(3-hydroxyphenyl)octanoic acid, 5. Cardanol (1.00 g, 3.33 mmol) in diethyl ether (100 mL) at –78°C (presaturated at –70°C with ozone) was further saturated with ozone to complete the ozonization (TLC monitoring). Glacial acetic acid (20 mL) and powdered zinc (1.0 g) were then added, and the mixture was stirred and allowed to reach ambient temperature overnight. Workup by filtration and then washing of the filtrate with 2% sodium bicarbonate solution (50 mL), drying (sodium sulfate), and evaporation *in vacuo* to constant weight afforded a crude pale yellow oil (0.70 g, 96%) identical spectroscopically with the aldehyde prepared by hydrogenation. To a mixture of the aldehyde (0.70 g, 3.18 mmol) in water (10 mL) containing sodium carbonate (1.0 g), cooled in an ice/water bath, a solution of potassium permanganate (1.0 g) in water (20 mL) was added. The reaction mixture was then allowed to reach ambient temperature, manganese oxides were removed by filtering, and the acidified filtrate was extracted with diethyl ether (2 × 50 mL). The combined extracts were dried and evaporated to give a crude pale brown oil; IR, ν_{\max} (film/cm⁻¹), 3300 (O–H), 2950, 2850 (C–H), 1700 (C=O), 1570 (C=C), 1450 (C–H), 1405 (C–O), 1240 (OH bend), 1100 (OH deformation) cm⁻¹; ¹H NMR, δ_{H} (60 MHz, CCl₄, ppm) 1.35–1.40 (*m*, 10H, CH₂), 2.15 (*t*, 2H, CH₂CO₂H), 2.30 (*t*, 2H, CH₂Ar), 6.85–7.70 (*m*, 4H, HAR), 8.20–9.25 (*s*, 2H, OH, HO₂C, D₂O exch.); *m/z* (M⁺, 236), C₁₄H₂₀O₃ requires 236.

Reduction of the aldehyde from ozonolysis to 6, 8-(3-hydroxyphenyl)octanol. The aldehyde (0.20 g, 0.91 mmol) obtained from zinc/acetic acid reduction of the ozonide in methanol (3 mL) was added to sodium borohydride (0.10 g) in water (20 mL), and after 4 h the mixture was carefully acidified with dilute hydrochloric acid (10 mL) and extracted with

diethyl ether (2 × 10 mL). The extract was then dried (Na₂SO₄) and evaporated *in vacuo* to give a crude pale yellow oil (0.15 g, 74%); IR, ν_{\max} (film/cm⁻¹) 3300 (*s*, O–H), 1440 (C–O) cm⁻¹; ¹H NMR, δ_{H} (60 MHz, CCl₄, ppm) 1.35–1.40 (*m*, 12H, 6CH₂), 2.60 (*t*, 2H, CH₂Ar), 3.75–3.80 (*t*, 2H, CH₂OH), 6.80–7.30 (*m*, 4H, HAR), 9.15 (*bs*, 2H, 2OH, D₂O exch.); *m/z* (M⁺, 222), C₁₄H₂₂O₂ requires 222).

Wolff–Kishner reduction of the aldehyde, 7, 8-(3-hydroxyphenyl)octanal to 3-octylphenol, 7. The aldehyde (4.0 g, 16.9 mmol) in diethylene glycol (135 mL) containing 98% hydrazine hydrate (27 mL) was heated at 110°C for 4 h, at which time TLC monitoring showed that no aldehyde remained and hydrazone formation was complete. Potassium hydroxide (37 g) was added and the mixture refluxed for 6 h, cooled, diluted with water (200 mL), neutralized, and extracted with light petroleum ether (3 × 100 mL). The combined extracts were washed with water (200 mL), dried (Na₂SO₄), and evaporated to give a crude brown oil (2.12 g, 57%); ¹H NMR, δ_{H} (60 MHz, CCl₄, ppm) 0.95 (*t*, 3H, Me), 1.35 (*m*, 12H, 6CH₂), 2.55 (*t*, 2H, CH₂Ar), 5.55 (*bs*, 1H, HO, exch. D₂O), 6.85–7.35 (*m*, 4H, HAR); *m/z* (M⁺ 206, C₁₄H₂₂O requires 206), 108, 57, 48, 29; chromatographically and spectroscopically identical to synthetic 3-*n*-octylphenol.

Synthesis of 3-octylphenol, 7. 3-Benzyloxybenzaldehyde was reacted in THF containing lithium with 1-bromoheptane to give 1-(3-benzyloxyphenyl)octan-1-ol, which was hydrogenolyzed to 3-octylphenol by adaptation of an earlier method (24).

1-(3-Benzyloxyphenyl)octan-1-ol. A mixture of 3-benzyloxybenzaldehyde (8.48 g, 40 mmol) and 1-bromoheptane (8.95 g, 50.0 mmol) was added through a pressure-equalized funnel under nitrogen to lithium chips (0.9 g, 130 mmol) in THF (25 mL) cooled to 0°C. The lithium turned a golden color, and reaction was allowed to continue overnight at 0°C, after which the mixture was carefully diluted with saturated ammonium chloride solution (100 mL), extracted with ether (3 × 100 mL), and the combined extracts were washed with water until neutral, dried, and concentrated to give a crude pale pink oil (7.65 g, 61%), which was purified by preparative TLC on silica gel G (CHCl₃/EtOAc, 95:5) and visualized by treating with Rhodamine 6G, to separate minor impurities and gave the pure secondary alcohol; *R_f* (CHCl₃/EtOAc, 95:5) 0.42; (found: C, 80.63; H, 9.07%. C₂₁H₂₈O₂ requires C, 80.65; H, 9.11%); ¹H NMR, δ_{H} (60 MHz, CCl₄, ppm) 0.95 (*t*, 3H, Me), 1.30 (*m*, 12H, CH₂), 3.45 (*bs*, 1H, OH, exch. D₂O), 4.30–4.55 [*t*, 1H, CH(OH)], 4.95 (*m*, 2H, OCH₂Ph), 6.60–7.05 (*m*, 4H, 4HAr), 7.15 (*s*, 5H, Ph).

3-Octylphenol (7). A mixture of 1-(3-benzyloxyphenyl)octan-1-ol (2.15 g, 6.89 mmol) in ethanol (25 mL) containing 5% Pd-C (0.60 g) and concentrated sulfuric acid (2 drops) was hydrogenolyzed at atmospheric pressure and temperature by agitating with hydrogen. To complete the reaction, the addition of catalyst (0.50 g) was sometimes desirable. The reaction progress was monitored by TLC and was complete with absorption of hydrogen (441 mL) after which the mixture was filtered under nitrogen. The filtrate was concentrated to give a crude pink oil (1.65 g, 77%), which was purified by preparative TLC; *R_f* 0.40 (CHCl₃/EtOAc, 19:1); (found: C, 81.77; H, 10.29%, C₁₄H₂₂O

requires C, 81.55%; H, 10.68%; δ_{H} as for 3-octylphenol prepared from ozonization and reductive treatment.

Ozonization of anacardic acid to 6-(8-formylheptyl)-2-hydroxybenzoic acid, 8. Anacardic acid (Fig. 1a–d) (1.0 g, 2.91 mmol) in ethyl acetate (25 mL) was ozonized at -78°C for 5.5 h, at which time TLC monitoring indicated that no acid remained. The mixture was hydrogenated in the presence of Pd-C (0.12 g), and reduction was considered to be complete upon absorption of hydrogen (110 mL). Filtration of the mixture and rotary evaporation of the filtrate *in vacuo* gave a crude brown oil (0.80 g, 73%); IR, ν_{max} (film/ cm^{-1}), 3300 (O–H), 2980 (C–H), 2850 (CH, arom.), 1710 (C=O), 1650–1670 (C=O, H-bonded), 1610 (CH, arom.), 1460, 1240, 1140, 920, 830 cm^{-1} ; ^1H NMR, δ_{H} (60 MHz, CCl_4 , ppm), 0.90 (*t*, Me), 1.30 (*m*, 10H, CH_2), 2.20 (*t*, 2H, CH_2CHO), 2.80 (*t*, 2H, CH_2Ar), 6.80 (*m*, 3H, HAr), 8.50 (*bs*, 2H, OH, HO_2C , D_2O exch.), 9.80 (*s*, 1H, CHO). The small peak at δ 0.90 was due to some heptanal; *m/z* (M^+ 264, $\text{C}_{15}\text{H}_{20}\text{O}_4$ requires 264), 108 ($\text{C}_7\text{H}_8\text{O}$, base peak by loss of CO_2).

Ozonization of cardol to 5-(8-formylheptyl)-1,3-benzene-diol, 9. Cardol (Fig. 1a–d) (0.36 g, 1.14 mmol) in ethyl acetate (75 mL) was treated at -78°C with ozonized air, and the reaction, which was monitored (TLC), was complete after 4.5 h. The mixture was then hydrogenated with the addition of Pd-C (0.25 g). After the uptake of hydrogen (53 mL), the mixture was filtered and the filtrate evaporated *in vacuo* to give a crude brown oil; IR, ν_{max} (film/ cm^{-1}) 3300 (*s*, C–H), 1695 (*s*, C=O) cm^{-1} ; *m/z* (M^+ 236, $\text{C}_{14}\text{H}_{20}\text{O}_3$ requires 236). Before examination of the ^1H NMR spectrum, the product had semi-polymerized although faint chemical shifts were present for CHO, HAr, and CH_2 groups.

Hydroxylation of cardanol and of cardanol acetate with performic acid and cleavage of the product with periodic acid to give 8-(3-hydroxyphenyl)octanal, 4. (i) *Cardanol.* Initially, the stabilities of the aromatic ring in (15:0)-cardanol toward performic acid and of cardanol (Fig. 1) to periodic acid were examined. More than 80% of slightly discolored material was recovered in each case.

Cardanol (Fig. 1) (2.69 g, 8.97 mmol) added to 98% formic acid (17.25 mL) was cooled to 0°C , the suspension was slowly treated with 30% H_2O_2 (1.1 g, 32.0 mmol), and the suspension was left for 1 wk. After diluting with water, the reaction mixture was extracted with diethyl ether; the combined extracts were washed with NaCl solution (100 mL), dried, and evaporated to give a crude pale brown oil (2.85 g, 76.3%) comprising a mixture of vicinal monoformates (from the 8,9-diol, the 8,9,11,12-tetraol, and the 8,9,11,12,14,15-hexaol) having an R_f value below that of cardanol and an IR spectrum with an absorption peak at 1720 cm^{-1} (formate). The product was hydrolyzed with 1 M NaOH solution (30 mL) by warming for 3 h (with TLC monitoring). The cooled mixture was acidified with dilute hydrochloric acid, extracted with diethyl ether ($2 \times 100\text{ mL}$), and the combined extracts were dried (Na_2SO_4) and evaporated to give a crude brown viscous liquid (1.39 g, 56.1%) consisting of the *trans*-polyols having a low R_f value with strong IR absorption at 3300 cm^{-1} (OH) and absence of C=O absorption; in the ^1H NMR, δ_{H} (60 MHz, CCl_4 , ppm) 0.9

(*t*, Me), 1.30 (*m*, CH_2), 2.35–2.55 (*t*, 2H, CH_2), 3.35–3.45 (*m*, CH(OH)), 5.0–5.60 (*bs*, OH, D_2O exch.), 6.4–6.8 (*m*, 4H, HAr). The experiment was repeated with cardanol (10 g) to give yields of 73 and 53% for the hydroxylation/formoxylation and hydrolysis stages, respectively. The chemical shift at δ 0.90 was due to traces of (15:0)-cardanol.

The polyol product (0.80 g, 2.20 mmol) in ethanol (60 mL) was added to potassium periodate (1.50 g) in 1 M sulfuric acid (75 mL), and the mixture was stirred at 40°C for 20 min, after which dilution with water, extraction with diethyl ether, drying (Na_2SO_4), and recovery by evaporation *in vacuo* afforded the crude product as a pale oil (0.61 g, 80.4%, as a mixture of **4** with heptanal), having strong IR absorption at 1690 cm^{-1} . After rotary evaporation *in vacuo* to constant weight to remove heptanal, the product was spectrally similar to that obtained from ozonolysis.

(ii) *Cardanol acetate.* Although stability experiments indicated that relatively little attack on the aromatic ring and the OH group had occurred, it was of interest to examine the use of cardanol acetate. This was prepared from mixed cardanol (3.98 g, 13.27 mmol) in pyridine (14 mL) containing acetic anhydride (7 mL) by warming for 2 h followed by dilution with iced water, extraction with light petroleum ether, acidic washing, drying (Na_2SO_4), and evaporation to afford a pale brown oil (4.30 g, 95%).

Cardanol acetate (3.07 g, 8.87 mmol) with 98% formic acid (17.25 mL) was cooled in an ice bath, stirred, and treated slowly with 30% H_2O_2 (1.10 g, 32.0 mmol). After TLC monitoring and reaction overnight, the mixture was extracted with light petroleum ether ($3 \times 100\text{ mL}$), and the combined extracts were washed with NaCl solution, dried (Na_2SO_4), and evaporated to give a crude pale brown oil (2.15 g, 52%; yield calculated on basis of the percent composition of the unsaturated constituents of cardanol and formation of the monoformate of each *trans*-polyol as the phenolic acetate) with IR absorption maxima at 1700 and 1750 cm^{-1} (mono OCHO and OCOMe) and diminished alkene absorption (2970 cm^{-1}). The formylated acetylated product (1.59 g) was hydrolyzed with 1 M sodium hydroxide (17 mL) and warmed at 40°C until TLC monitoring indicated hydrolysis to the *trans*-polyols was complete. Workup as before afforded a viscous brown oil (1.16 g, 92.0%); IR, ν_{max} (film/ cm^{-1}) 3300 cm^{-1} (OH); ^1H NMR, δ_{H} (60 MHz, CCl_4 , ppm) 0.90 (*t*, Me), 1.35 (*m*, 12H, CH_2), 2.35–2.60 (*t*, 2H, CH_2Ar), 3.40 [*m*, 4H, CH(OH)], 3.4–5.0 (*bs*, 4H, OH, D_2O exch.), 6.60–7.2 (*m*, 4H, HAr). [The peak at δ 0.90 is due to traces of (15:0)-cardanol.] The polyol product (0.28 g, 0.77 mmol), in ethanol (20 mL), was added to potassium periodate (0.50 g) in 1 M sulfuric acid (25 mL), and the mixture was warmed to 40°C and stirred for 20 min. After monitoring by TLC, the cooled mixture was diluted with water, neutralized with 1 M NaOH solution, and extracted with light petroleum ether. The combined extracts were dried (Na_2SO_4) and rotary evaporated *in vacuo* to give a crude pale oil (0.22 g, 92.4%) consisting of **4** (plus heptanal); IR, ν_{max} (film/ cm^{-1}), 1700 cm^{-1} (C=O); ^1H NMR, δ_{H} (60 MHz, CCl_4 , ppm), 1.30 (*s*, 12H CH_2), 2.20 (*t*, 2H, CH_2CO), 2.80 (*t*, 2H, CH_2Ar), 6.45–6.80 (*m*, 4H, HAr), 9.1 (*s*, 1H, CHO), 9.60 (*s*, 1H, OH, D_2O exch.). After removal of heptanal by evapora-

tion to constant weight *in vacuo*, the spectroscopic properties resembled those of products from ozonolysis and reduction. The product polymerized upon storage.

Oxidation of cardanol with potassium permanganate to 4. Oxidation of cardanol in aqueous alkaline suspension with potassium permanganate gave a mixture of the diol, tetraol, and hexaol in relatively low yield, which was spectroscopically the same as that from performic acid treatment followed by hydrolysis.

To cardanol (2.15 g, 7.20 mmol) suspended in iced water (80 mL) containing KOH (2.0 g), powdered potassium permanganate (4.0 g, 25.3 mmol) was gradually added and the mixture allowed to stir over 2 h during which time the color changed from dark green to dark brown. Excess permanganate was removed by sulfur dioxide treatment to give a pale yellow mixture, which was neutralized with hydrochloric acid and filtered to remove some precipitated material. The filtrate was extracted with diethyl ether, and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to constant weight to give a crude pale brown oil (0.87 g, 54.6%), the yield being calculated on the composition of cardanol. The IR spectrum was identical to that of product **4** from ozonization and hydrogenation. Upon storage, the product polymerized. From spectral examination, the precipitated material also contained some product. With the same proportions of reactants but a shorter reaction time, the product contained unchanged alkene.

RESULTS AND DISCUSSION

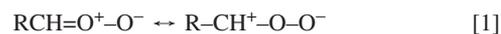
Ozonizations. Because reaction of *o*-cresol in aqueous solution with ozone has been described (25), it was desirable to establish the stability of the aromatic ring in (15:0)-cardanol even in a dry organic solvent. In an experiment carried out at -78°C in chloroform, no attack was observed, and more than 90% of the material recovered was identical to the starting material according to TLC and spectroscopic evidence. Anhydrous solvents were used in all experiments to avoid the formation of H_2O_2 (26). TLC monitoring proved to be a useful method for following the progress of all reactions.

Owing to the slow reaction at -78°C , prolonged reaction times were required, and presaturation of the solvent with ozone was adopted, a procedure advocated (26) to avoid side reactions. In the workup by evaporation *in vacuo* at ambient temperature, the volatile aldehydes formaldehyde, butanal (b.p. 75°C), and malondialdehyde, which exists as an enolic, intramolecularly hydrogen-bonded compound, were removed with the solvent ethyl acetate (b.p. 76°C), leaving heptanal (b.p. 153°C) and the product **4**, which also contained traces of saturated cardanol unreactive to ozone. Table 1 depicts the conditions and yields with ethyl acetate as solvent and those for catalytic hydrogenation in which 1 mol of hydrogen was rapidly consumed per mole of ozonide, in agreement with the formation of two aldehydes from each trioxane. Spectroscopy (NMR) and TLC provided evidence that the first two products contained a small percentage of unreacted alkene.

Table 2 summarizes the results of ozonizations in different solvents followed by chemical reduction of the ozonides. Lit-

tle variation was found in the reaction course in either ethyl acetate or diethyl ether, although with light petroleum ether the ozonide separated from solution. Generally, light petroleum and diethyl ethers were the preferred solvents partly owing to the ease of their removal from the product with avoidance of long work-up times and possible side reactions of the aldehydic product with the solvent. Ozone addition occurred without autoxidation at methylenic groups. In carbon tetrachloride, reaction was necessary at -20°C , and ozone absorption was noticeably faster and side reactions were evident, producing a darker product. The ozonization yields when methanol was used were low, possibly due to unusual side reactions. Ozonide reduction with zinc in acetic acid gave excellent yields (96%) after rotary evaporation of crude products to constant weight *in vacuo* to remove heptanal, and with reactions in diethyl ether and light petroleum ether yields were only less than quantitative due to the inert saturated cardanol present in the starting material. Yields were calculated in a similar way to those reactions given in Table 1. Some of the influence of solvent dependency described (27) in the ozonization of fatty substrates appears to have been minimized in the present work by operating at low temperature. Although a variety of methods have been described (28) for the reduction of the trioxane, we found it convenient to use either catalytic hydrogenation with hydrogen at atmospheric pressure in ethyl acetate containing 5% palladium-carbon or chemical reduction in acetic acid containing zinc, both of which methods gave comparable yields. Spectroscopic monitoring of ozonide formation by ^1H NMR examination indicated a broad band at δ 5.10 characteristic of the trioxane ring hydrogens (29).

The reaction pathway shown in Figure 2 is typified by the reaction of cardanol monoene **b** with the initial formation of addition molozonide (the secondary ozonide) **1b**, its transformation to the zwitterion transition complex **2b**, and interaction of this to afford the trioxane **3b**, the primary ozonide, by way of the Criegee mechanism. This remains the accepted mechanism, although recent stereochemical modifications (30) have been discussed. In the zwitterion transition state **2b**, a close association of the dioxy (Eq. 1) and aldehyde (Eq. 2) components must occur leading to the formation of **3b** by the interaction of the carbocation contribution in both Equations 1 and 2 of the zwitterion **2b**:



The reduction stage is depicted at the end of Figure 2, showing the formation of heptanal and 8-(3-hydroxyphenyl)octanal, **4**.

Similar sequences can be formulated for cardanol diene **c** and triene **d** to give the molozonides **1c** and **1d**, zwitterion complexes, **2c** and **2d**, and, finally primary ozonides **3c** and **3d**. Reduction of these in each case afforded **4**, together with butanal and malondialdehyde from the original 8:11-diene **c** and formaldehyde and malondialdehyde from the 8:11:14-triene **d**. The aldehydes formaldehyde, butanal, malondialdehyde, and heptanal were identified as their 2,4-dinitrophenylhydrazones alongside authentic samples by both GLC and TLC (Goh, S.C., and J.H.P. Tyman, unpublished data).

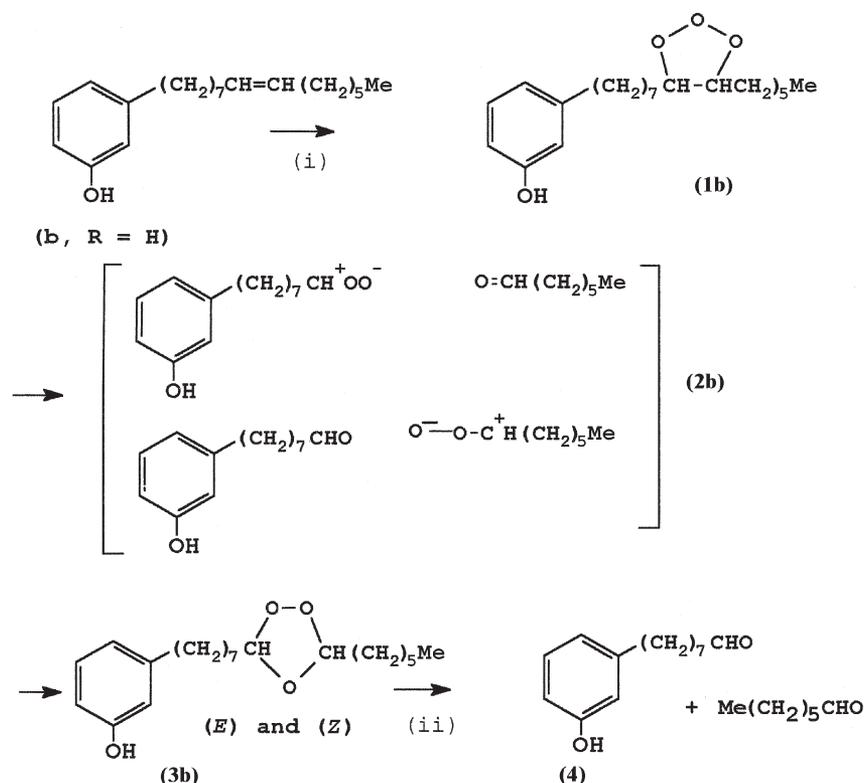


FIG. 2. Ozonization of cardanol monoene **b**. Reagents: (i) O_3 , EtOAc, $-78^\circ C$; (ii) Pd-C, H_2 or Zn/AcOH.

The aldehyde product, 8-(3-hydroxyphenyl)octanal, **4**, was converted to the corresponding acid, 8-(3-hydroxyphenyl)octanoic acid, **5**, by oxidation with potassium permanganate in aqueous sodium carbonate solution. Reduction of **4** in methanolic solution with sodium borohydride gave the corresponding alcohol 8-(3-hydroxyphenyl)octanol, **6**. Conversion of **4** to the hydrazone with hydrazine hydrate and Wolff-Kishner reduction gave 3-octylphenol, **7**, as shown in Figure 3.

The structure of product was independently confirmed by its synthesis from 3-benzyloxybenzaldehyde and 1-bromoheptane in THF containing lithium to afford 1-(3-benzyloxyphenyl)octan-1-ol, which was catalytically hydrogenolyzed in ethanol containing 5% palladium-carbon to 3-octylphenol, **7**, to give the spectroscopically identical product as the Wolff-Kishner reduction of **4** (see Experimental Procedures section).

In a way similar to cardanol (Fig. 1), anacardic acid, the main component phenol of natural CNSL, was ozonized in ethyl acetate solution at $-78^\circ C$ and the ozonide catalytically reduced to 6-(formylheptyl)-2-hydroxybenzoic acid, **8**, as depicted in Figure 4A, which shows only the reaction of the monoene constituent **b**, also known as ginkgolic acid (10), from *Ginkgo biloba*. The ozonization of this acid has been described in a structural study (31).

Cardol (Fig. 1) from CNSL, upon ozonization in ethyl acetate at $-78^\circ C$ followed by catalytic reduction, afforded some 5-(8-formylheptyl)-1,3-benzenediol, **9**, which proved to be a highly reactive monomer, readily polymerizable during isolation, although from TLC monitoring of the reaction mixture rather than from the limited spectroscopic evidence on the final product which had largely polymerized, it is believed to have

been obtained initially. The reaction of the monoene constituent, **b**, is shown in Figure 4B. Similarly, the diene **c** and triene **d** gave **9**. Although the relatively unactivated aromatic rings in cardanol

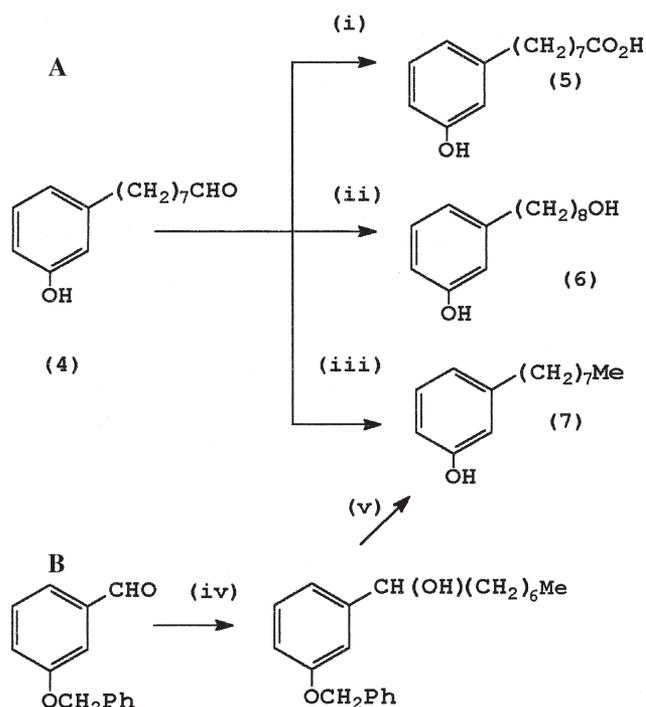


FIG. 3. (A) Reactions of **4** [8-(3-hydroxyphenyl)octanal], and (B) synthesis of **7** (3-octylphenol). Reagents: (A) (i) $KMnO_4$, Na_2CO_3 . (ii) $NaBH_4$, MeOH. (iii) NH_2NH_2 , digol; KOH, reflux. (B) (iv) Li, THF, $C_7H_{15}Br$; aq. NH_4Cl . (v) Pd-C, H_2 , EtOH.

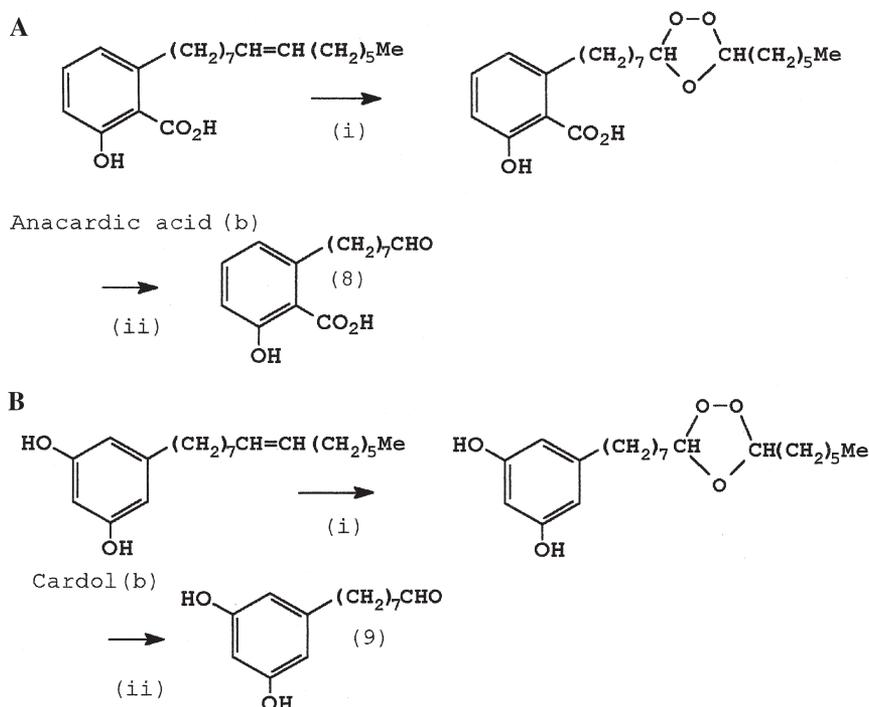


FIG. 4. Ozonization of (A) anacardic acid and (B) cardol. Reagents: (i) O_3 , EtOAc, $-78^\circ C$; (ii) Pd-C, H_2 .

and anacardic acid survived reaction with ozone at $-78^\circ C$, in the aromatic ring of cardol there is a higher level of activation due to the presence of two hydroxyl groups, and a small degree of side reaction at that site could not be excluded. In a synthesis (32) of the plant growth regulator, lasiodiplodin, the ozonization of the diacetate of cardol **a,b,c,d** afforded the corresponding dihydroxy analog of **6** after sodium borohydride reduction and hydrolysis, but the aldehyde **9** was never isolated.

The structure of the polymer appears likely to involve self-condensation of **9** as well as a resorcinol/aldehyde condensation, perhaps commencing during workup. This indeed suggests its use in polymerization applications as an alternative to conventional CNSL/formaldehyde processes.

The *m*-substitution in products from cardanol and anacardic acid was demonstrable from their MS spectra by the value of the ratio m/z of the ions 108/107 (24), that at 108 being the base peak ascribable to formation of a resonance-stabilized ion by β -fission of the side chain with hydrogen atom transfer and that at 107 to a tropylium ion. In the case of the product **9** from cardol, the expected ratio 124/123 was less discernible, but the molecular ion observed affords some evidence that this very reactive compound had been produced.

Dihydroxylations with performic acid and with potassium permanganate and cleavage of products. Of several different procedures for cleavage of the side chain in the component phenols of CNSL, it was of interest to compare ozonization/reduction with hydroxylation methods that give either *cis* or *trans* stereoisomeric polyols. These latter two processes are followed by oxidative cleavage at the main center of interest, namely, the 8,9-position in the polyol mixture of the diol, tetraol, and hexaol collectively to give **4**. It was first established in separate experiments that the aromatic ring in car-

danol was stable to the reagents, peroxyformic acid and periodic acid.

The *trans* polyols of cardanol **b,c,d** ($R = H$) were formed by Swern reaction with peroxyformic acid. This sequence is depicted in Figure 5, which shows only the reaction of the monene constituent **b** to give the *trans*-8,9-diol (**10a**, $R = H$) by way of the monoformate of **10a** ($R = H$). The *trans* hydroxylation is accompanied by formation of the mono formate ester of each vicinal diol, which was hydrolyzed to give the parent diol, tetraol, and hexaol, cleavage of each of which with periodic acid by the Malaprade reaction then afforded the common oxidation product 8-(3-hydroxyphenyl)octanal, **4**. As with ozonization, only the volatile aldehydes formaldehyde, butanal, and malondialdehyde were removed in the workup. The product **4**, when freed of heptanal by rotary evaporation *in vacuo* to constant weight, was spectroscopically identical to the product from ozonization/catalytic reduction. However, the overall yield of the aldehyde did not approach that from ozonization.

A similar reaction (shown in Fig. 5 only for the monoene) was carried out with cardanol acetate **1a,b,c**, and **d** ($R = Ac$) to give the monoformate of **10a** ($R = Ac$) and thence the polyol by hydrolysis (**10a**, $R = H$). The average overall yield of polyols was 40.7%, and to the product **4** was 35.1%.

Reaction of cardanol **a,b,c,d** with potassium permanganate in aqueous alkaline conditions gave the *cis*-tetraol and *cis*-hexaol along with the *cis*-diol **10b**, depicted in Figure 5, which shows only the reaction of the monene **b**. The polyols were not isolated but reacted unselectively to give the common aldehyde **4**. The yield to product **4** was 55%. Selective formation of the *cis*-diol **10b** by means of an immobilized osmium reagent (33) is of potential interest by comparison with the use of permanganate, which is unselective and can lead to overoxidation.

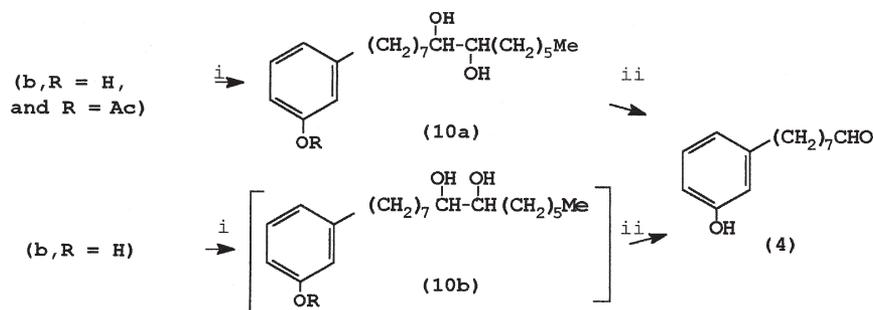


FIG. 5. *Cis* and *trans* dihydroxylation of cardanol, and oxidation to 7. Reagents: (a) (R = H, Ac), (i) HCO_2H , H_2O_2 ; HO^- . (ii) KIO_4 , H_2SO_4 . (b) (i) KMnO_4 , KOH ; SO_2 .

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