Long-chain Phenols. Part 18.† Conversion of Anacardic Acid into Urushiol ‡

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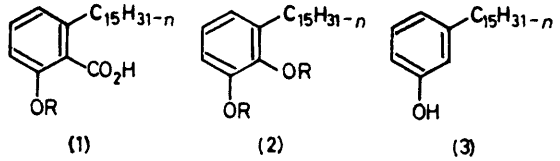
(15 : 0)-Anacardic acid (6-pentadecylsalicylic acid), prepared by reduction of unsaturated anacardic acid from *Anacardium occidentale*, has been converted into anacardic alcohol (6-pentadecylsalicyl alcohol) and thence by oxidation at carbon into anacardaldehyde. Phenolic oxidation of anacardic alcohol led to 8-pentadecyl-1-oxaspiro-[2.5]octa-5,7-dien-4-one, itself readily convertible photochemically, but less so thermally, into anacardaldehyde. Reaction of thionyl chloride with anacardic acid led mainly to the anhydride, which by hydride reduction gave anacardaldehyde less satisfactorily. Dakin oxidation of anacardaldehyde furnished (15 : 0)-urushiol (3-pentadecylcatechol) identical chemically and from argentation t.l.c. with the hydrogenated natural product from *Rhus vernicifera*. (15 : 0)-Cardanol (3-pentadecylphenol) has been detected in hydrogenated urushiol. The composition of the unsaturated constituents of urushiol from *Rhus vernicifera* and *Rhus toxicodendron* and its mode of formation have been discussed. An improved synthesis of (15 : 0)-urushiol has been devised based on an organolithium route. Aromatic methyl ether and ester formation in this series is greatly facilitated by phase-transfer catalysis.

ANARCARDIC acids [1] having side-chains of various lengths and extent of unsaturation are widely distributed in a number of different botanical species, most notably in *Anacardium occidentale*, in which the pentadecyl member (1; R = H, n = 0,2,4,6) is the principal component of natural cashew nut-shell liquid (CNSL). In the industrial extraction process [2] decarboxylation occurs and cardanol (3; n = 0,2,4,6) is formed. *Rhus vernicifera* [3] (poison oak, Japanese lac) and *Rhus toxicodendron* [4] (poison ivy) contain primarily urushiol (2; R = H, n = 0,2,4,6); the monoene and diene are the same, but the triene is structurally different in the side-chain. The similarity in ring substitution in (1) and (2) suggests that biogenetically (1) may undergo transformation into (2), and indeed this has already been suggested.[5]

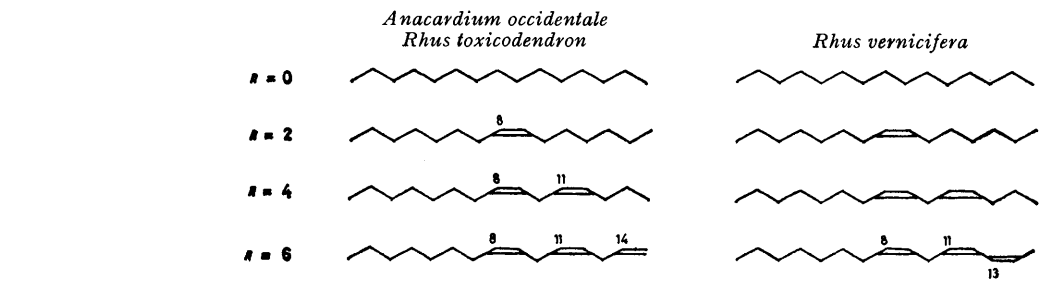


(1) (2) (3)

The object of the present work was first to effect this *in vitro* in the saturated and unsaturated series, and subsequently to examine biological routes. Cardanol (3; n = 0,2,4,6) has been detected in Japanese lac and also represents a possible precursor in the formation of (2). The latter is of interest as an anti-allergy material, and a more convenient synthesis is described than those previously used.[6-9]

RESULTS AND DISCUSSION

Because of the susceptibility of these unsaturated materials to autoxidation, the transformations described were first carried out with the saturated (15 : 0)-series. The reactions used to convert (15 : 0)-anacardic acid to (15 : 0)-urushiol are shown in Scheme 1.



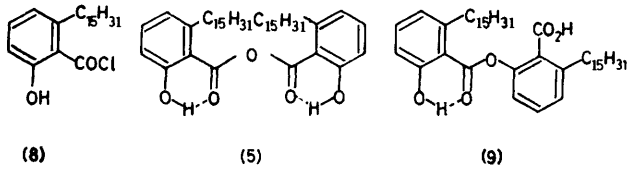
(15 : 0)-Anacardic acid has been prepared from unsaturated anacardic acid (1) (obtained from *Anacardium occidentale* of Mozambique origin) by hydrogenation and by chemical reduction with hydrazine–air,[10] but 'transfer' reduction [11] was only partially effective. Reduction of (15 : 0)-anacardic acid with lithium aluminium hydride gave anacardic alcohol (4; R = R′ = H) (6-pentadecylsalicyl alcohol) in high yield.

Reaction of (15 : 0)-anacardic acid with thionyl chloride in light petroleum containing a small amount of pyridine, although expected to give anacardyl chloride (8), gave a product which from its elemental analysis and spectroscopic and chromatographic properties is the anhydride, which is believed to contain in the crude state

† Part 17, *J. Chem. Soc., Perkin Trans. 1*, 1981, 132.
‡ Presented in part at the 11th IUPAC Symposium on the Chemistry of Natural Products, Varna, Bulgaria, September 1978.

a small amount of an isomeric acidic material, probably (9). The difference in t.l.c. behaviour between the non-polar (5) and the polar (9) is explicable in terms of the hydrogen-bonding shown, which would also explain the relatively low ν(C=O) in the i.r. spectrum. Compound (5) was characterised as the amide and anilide derivatives.

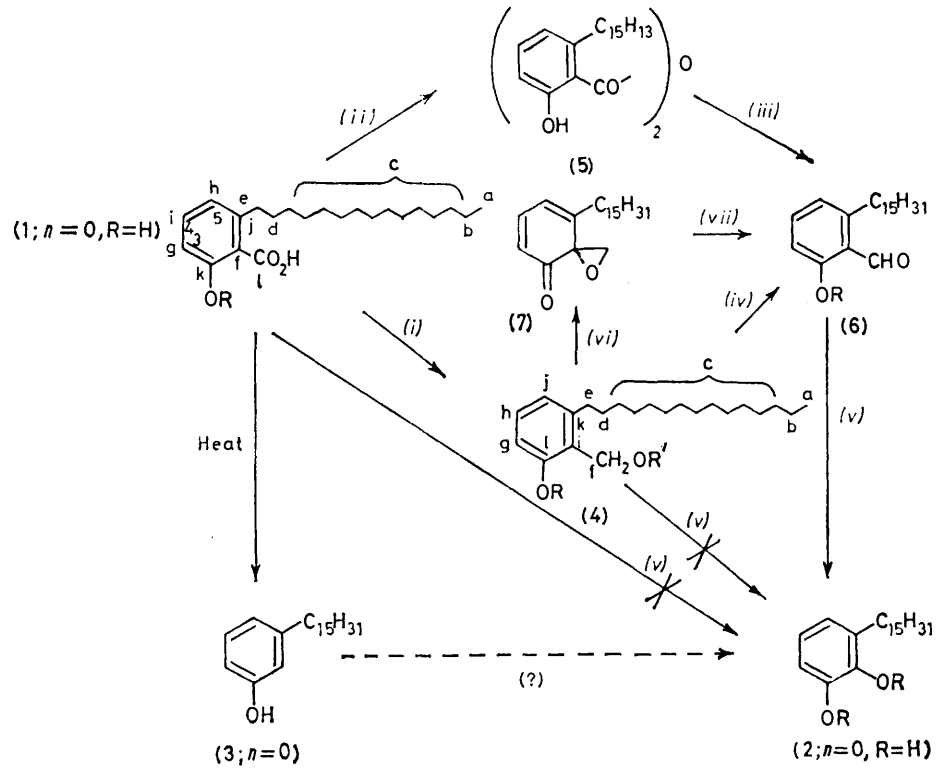
Reduction of (5) with lithium tri-t-butoxy aluminium hydride, a method used for acid chlorides,[12] at low temperatures gave anacardaldehyde (6; R = H) (6-pentadecylsalicylaldehyde), accompanied by some anacardic alcohol and residual material, as found previously with another acid chloride series.[13] A more useful preparation of anacardic aldehyde is by selective oxidation at carbon of anacardic alcohol with pre-formed dipyridine-chromium(VI) oxide [14] or pyridinium chlorochromate [15] ($C_5H_5NHCrO_3Cl$), both in dichloromethane.



(8) (5) (9)

Both these reagents are much superior to the use of chromium trioxide–pyridine without additional solvent, and all other procedures for benzylic-type alcohols such as dinitrogen tetroxide,[16] manganese dioxide,[17] and others were very ineffective. The aldehyde (6; R = H) was characterised as its 2,4-dinitrophenylhydrazone and semicarbazone derivatives, and conversion into the methyl ether (6; R = Me).

Phenolic oxidation of anacardic alcohol (4; R = R′ = H) with sodium periodate [18] in aqueous methanol gave 8-pentadecyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (7) characserised by its u.v., i.r., mass and ^1H n.m.r. spectral properties. It underwent facile photo-chemical transformation in dilute ethanol solution to anacardic aldehyde, probably by way of the intermediate shown, although thermal rearrangement was slow. Evidently the 6-pentadecyl group (*i.e.* 3-pentadecyl, *cf.* Adler *et al.*) sterically hinders the Diels–Alder dimerisation [19] which occurs with the spiroepoxydienone (10) from salicyl alcohol (and 2,4-substituted derivatives; R, R′ various groups) to give (11), although with a bulky group [18] this was prevented and salicylaldehydes were obtained. Alternative cleavage of the epoxy-system to give a methylenedioxy-derivative (12) was not observed [20] and appears to only occur with salicyl alcohols having a phenyl substituent in the CH_2OH group.



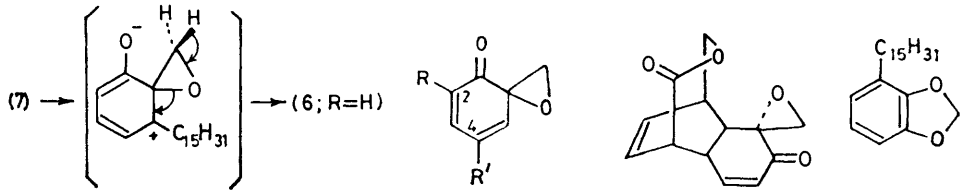
SCHEME 1 (*i*) $LiAlH_4$, THF; (*ii*) $SOCl_2$, pyridine, light petroleum, 30 °C; (*iii*) (*a*) $LiAl(OBu^t)_3H$, −80 °C; (*b*) Pd–$BaSO_4$, H_2, $CS(NH_2)_2$; (*iv*) (*a*) $(C_5H_5N)_2CrO_3$, CH_2Cl_2; (*b*) $C_5H_5N{\cdot}HCl{\cdot}CrO_3$; (*v*) H_2O_2, OH^-; (*vi*) $NaIO_4$; (*vii*) *hv*, MeOH, or heat

Anacardaldehyde underwent Dakin oxidation [21] to afford a rather indifferent yield of 3-pentadecylcatechol, although yields generally in this reaction tend to be low. The dimethyl ether was identical with synthetic (15 : 0)-urushiol dimethyl ether obtained by the organolithium route. The parent phenols were identical by mass

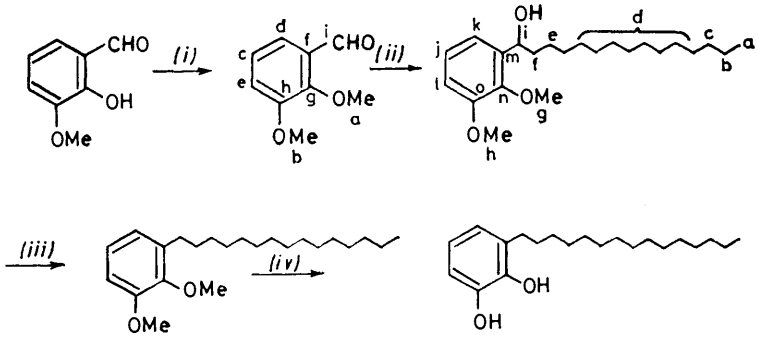
spectrometry and chromatography and with (15 : 0)-urushiol either from argentation t.l.c. of urushiol from Japanese lac or by mild hydrogenation with palladised carbon followed by preparative t.l.c.[22] (15 : 0)-Anacardic acid or anacardic acid alcohol did not undergo Dakin oxidation with alkaline hydrogen peroxide. Similar transformations to those of Scheme 1 with the unsaturated series have not yet been completed.

To characterise certain of the compounds in Scheme 1 some of the reactions were effected with the corresponding methyl ethers. (15 : 0)-Anacardic acid *O*-methyl ether (1; R = Me, n = 0), prepared by prolonged alkaline hydrolysis of methyl anacardate *O*-methyl ether [itself obtained quite pure by the slow methylation of anacardic acid under anhydrous conditions, or in a less pure form containing methyl (15 : 0)-anacardate by a rapid phase-transfer procedure[23]] upon lithium aluminium hydride reduction gave anacardic alcohol *O*-methyl ether (4; R = Me, R′ = H), which was, however, produced more easily by the reduction of methyl anacardate *O*-methyl ether. Anacardic alcohol *O*-methyl ether was readily obtained in excellent yield by the phase-transfer methylation of anacardic alcohol. Anacardic alcohol dimethyl ether (4; R = R′ = Me) was produced in low yield by the methylation of anacardic alcohol with dimethyl sulphate in benzene containing anhydrous potassium carbonate. Methylation of the alcoholic hydroxy-group by the modified phase-transfer method in 50% aqueous potassium hydroxide,[24] commencing with anacardic alcohol as its phenolic methyl ether, was relatively ineffective, but was more successfully achieved by reaction of anacardic alcohol *O*-methyl ether with sodium hydride (weaker bases being of no use) and interaction with dimethyl sulphate in hexamethylphosphoric triamide.

(15 : 0)-Urushiol (2; R = H, n = 0), has been synthesised by several different routes and in those based on n-tetradecylmagnesium bromide with 2,3-dimethoxybenzaldehyde,[6,7] n-octacosane is formed [13] and persists as an impurity difficult to remove by crystallisation, while the reaction of veratrole with pentadecyl-lithium [8] has given erratic results.[9] With a lithium alkyl (Scheme 2) [25] in place of the Grignard reagent the formation of n-octacosane was negligible and the hydrogenolysis and final demethylation with boron tribromide [26] were facile and rapidly effected. Pyridine hydrochloride [13,27] can cause isomerisation in related systems.



Although chemical transformation of anacardaldehyde to urushiol did not proceed smoothly, biological pathways by way of peroxidase or cytochrome P450 may be straightforward. A plausible biogenetic scheme for the formation of anacardaldehyde has been outlined.[1b] A route from anacardic alcohol to the aldehyde would also appear to be feasible. Nevertheless, both anacardic alcohol and anacardaldehyde have not yet been detected in *Anacardium occidentale* or *Rhus* types, and can at most be present only in trace amounts.



SCHEME 2 (*i*) Me_2SO_4, K_2CO_3, benzene; (*ii*) Li, $C_{14}H_{29}Br$, THF; (*iii*) Pd–C/H_2, H^+; (*iv*) BBr_3, CH_2Cl_2

An alternative pathway to urushiol is by hydroxylation of cardanol formed from the natural decarboxylation of anacardic acid. 3,4-Dihydroxyheptadecylbenzene (thitsiol, *iso*-hydrourushiol) [28] may well arise by hydroxylation of 3-heptadecylphenol (C17-cardanol). Chemical hydroxylations such as oxidative ' copperisation ' are known in the mordant azo-dyes based on naphthalene (Pfitzner reaction),[29] in the synthesis of salicyclic acids from basic copper salts,[10,30] and in the formation of catechols from

TABLE 1

Unsaturation (%) of the constituents of *Anacardium* and *Rhus* species

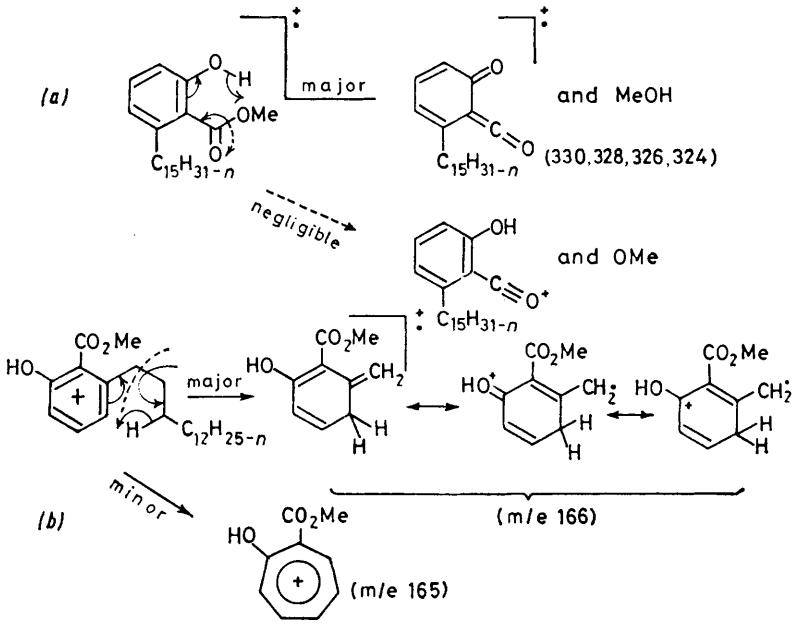
	Saturated (15 : 0)	Monoene (15 : 1)	Diene (15 : 2)	Triene (15 : 3)
Rhus vernicifera (Japanese Lac)				
By mass spectrometry [34] on methyl ethers [a]	5	27	11	48
By mass spectrometry [33,36] on phenols [b]	8.5	19.3	10.1	62
Rhus toxicodendron (Poison Ivy)				
By chromatography [35] (Al_2O_3) on methyl ethers [c]	2	10	64	23
By g.l.c. (2% PEGA) [25,36] on methyl ethers [d]	4.8	31.8	47.5	8.8
Anacardium occidentale (CNSL)				
Anacardic acid by mass spectroscopy	3.7	38.2	16.5	41.7
Cardanol by mass spectrometry	2.0	31.3	15.2	51.5

[a] Uncorrected. [b] Partially corrected for isotope abundance. [c] By gravimetry. [d] Uncorrected for relative response factors.

phenols by way of copper(II) salts in the presence of ammonia.[31] Aspects of hydroxylation which may be relevant to the urushiol system have been discussed.[32] During a chromatographic compositional study of urushiol,[33] a minor peak identical with cardanol (3) was observed by g.l.c. and also confirmed by t.l.c. G.l.c.–mass spectrometry of hydrogenated natural urushiol indicated the presence of saturated cardanol (3; $n = 0$) (*m/e* 304).*

The formation of urushiol, whether by a direct hydroxylation or an oxidative decarbonylation, might well occur after the desaturation process leading to the unsaturated side-chain. The distribution of unsaturation in the constituents of urushiol from *Rhus vernicifera* [33,34] (Japanese lac) is very similar to that in anacardic acid or cardanol from *Anacardium occidentale* as shown in Table 1, despite the structural difference in the triene constituents. In *Rhus toxicodendron*,[25,35] however, it is strikingly different and here a different sequence may apply or an oxidation/reduction mechanism is separately or simultaneously affecting the side-chain.

Mass Spectra of Constituents of Methyl Anacardate.—The mass spectra (Scheme 3) of the constituents of methyl anacardate possessed two common features, one characteristic of salicylates [37] and the other of phenols bearing an alkyl chain *meta* to the hydroxy-group.[13,38] Both (*a*) and (*b*) involved hydrogen transfer and in the latter case β-cleavage resulted in a resonance-stabilised fragment to a greater extent than direct β-cleavage with no transfer. In the former the preferred pathway presumably has a lower activation energy.



SCHEME 3

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra were recorded on a Unicam SP 200 (liquids as films and solids as KBr discs). ^1H N.m.r. spectra were determined on a Varian T60 instrument (with $SiMe_4$ as internal standard), and ^{13}C n.m.r. spectra were determined on a Varian CFT20 with $SiMe_4$ as internal standard. In ' off resonance ', splitting is desig-

* Cardanol has been found in *Anacardium semecarpus*, the major phenol of which is (2; $n = 2$) (D. S. Naidu, *J. Indian Inst. Sci.*, 1925, **8A**, 129).

nated by st (singlet), dt (doublet), tt (triplet), qt (quartet). The shifts are reported followed by (lettered C atom, splitting). Numbering and lettering for ^1H and ^{13}C n.m.r. spectra, respectively, are given in the formulae of Schemes 1 and 2. Mass spectra were determined on a Perkin-Elmer Hitachi RMS 4 instrument (Brunel University), an MS 9 (PCMU), and by the courtesy of Mr. D. Carter, School of Pharmacy, University of London, on an MS 902. Microanalyses were determined by B.M.A.C. Ltd., Teddington, Middlesex, and by Mr. G. Crouch, School of Pharmacy, Brunswick Square, London WC1.

Gas-liquid chromatography (g.l.c.) was carried out on a Pye 104 instrument equipped with a flame-ionisation detector and Vitatron recorder. The glass columns were 5 ft × 3/16 in (internal diameter) with 3% SE 30 on diatomite C. The carrier gas was nitrogen with flow 45 cm^3 min^{-1} (8 lb in^{-2}), temperature 220 °C.

Column chromatography was carried out on Spence Grade H alumina and on silica gel (MFC).

Thin layer chromatography (t.l.c.) was carried out with Kieselgel G (Merck). Analytical plates (10 × 8 cm × 0.25 mm) and preparative plates (20 × 20 cm × 1 mm) were run in solvent A, light petroleum (40—60 °C)–diethyl ether (70 : 30); solvent B, ethyl acetate–chloroform, (5 : 95); solvent C, chloroform–light petroleum (40—60 °C), (30 : 70); solvent D, light petroleum (40—60 °C)–diethyl ether–formic acid (49 : 49 : 2); solvent E, chloroform–ethyl acetate–formic acid, (95 : 5 : 2). Due to the hydrophobic nature of the compounds in this work, acidic and neutral components of reaction mixtures could not be separated in the usual way, and preparative t.l.c. was used for nearly all mixtures. Spots or bands were visualised with 0.1% ethanolic rhodamine 6G or dichlorofluorescein and viewed with u.v. illumination. The rhodamine was removed by washing light petroleum solutions of products with water. Argentation t.l.c. was carried out on self-prepared plates by the use of 15% $AgNO_3$ (on the weight of silica gel) introduced at the aqueous slurrying stage of the layer. Development away from bright light was desirable. Plates (analytical and preparative) were visualised with 0.1% ethanolic dichlorofluorescein. Bands were eluted with ether–methanol (9 : 1) overnight, in the dark at ambient temperature followed by filtration, evaporation of the filtrate, extraction with light petroleum, washing with water to remove silver nitrate, drying, and recovery.

Cashew nuts (Mozambique) were as previously used. Natural urushiol or Japanese lac (*Rhus vernicifera*) was provided by Dr. M. Sato, National Industrial Research Institute, Sendai, Japan, through the help of the Japanese Trade Centre, London.

Reactions with alkyl-lithiums were carried out under nitrogen in an evacuable apparatus described previously.[13]

(15 : 0)-*Anacardic Acid* (6-*Pentadecylsalicylic Acid*).—From natural Mozambique cashew nut-shell liquid (CNSL) [13] (86.4 g) anacardic acid was extracted in the following way. Lead hydroxide was prepared from lead nitrate (151 g) in water (600 cm^3) added to sodium hydroxide (39.6 g) in water (200 cm^3) and after 1 h the supernatant liquid was decanted from the heavy precipitate which was washed until free of alkali with water and finally with industrial methylated spirit (1 000 cm^3). Mozambique CNSL (86.4 g) in methylated spirits (400 cm^3) was added, the mixture stirred and the lead anacardate collected by filtration, washed, and the wet solid in the presence of diethyl ether stirred and vigorously shaken with cold dilute nitric acid to gradually liberate anacardic acid as an oil (containing the four constituents) which was washed with brine until neutral, dried and recovered to give the acid (59.5 g, 69%; this type of CNSL contains *ca.* 70% anacardic acid); τ (CCl_4) −0.92 (2 H, br s, OH · · · CO_2H, D_2O exchangeable), 2.6—2.8 (1 H, m, Ar-H), 3.1—3.3 (2 H, m, Ar-H), 4.6—4.7 (m, HC=CH), 4.9—5.1 (m, CH_2=C), 6.9—7.1 (2 H, t, CH_2Ar), 7.1—7.2 (m, CH_2–CH=CH–), 7.8—8.1 (m, CH_2–CH=CH), 8.2—8.9 (m, $[CH_2]$), and 9.0—9.3 (3 H, t, Me).

(i) *Catalytic hydrogenation.* The acid (30 g) in ethyl acetate (200 cm^3) containing 10% Pd–C (3.0 g) was hydrogenated in a Parr hydrogenator (at 15 lb in^{-2}) at ambient temperature. After absorption of hydrogen (3 532 cm^3 = 200 lb in^{-2} pressure drop) had ceased (argentation t.l.c. monitoring, solvent E), the mixture was filtered and the (15 : 0)-anacardic acid recovered as a colourless solid, m.p. 87—88 °C (lit.,[6] 91.5 °C) (24.9 g, 83%); R_F 0.166 (solvent B). In ethanol solution, more Pd–C (50%) was required to effect complete saturation. The rate of hydrogenation appeared to be markedly affected by any residual lead and either treatment of the acid with a cation-exchange resin or further addition of catalyst was required. Methyl anacardate (preparation subsequently) was hydrogenated at a faster rate than the acid, probably due to the adsorption of the latter on the catalyst surface.

(ii) *Chemical reduction.** Into unsaturated anacardic acid (4.25 g; 0.125 mol) in ethanol (50 cm^3) at 50 °C with agitation (magnetic stirrer) of the mixture, air was passed and 100% hydrazine hydrate (2.0 g) added. After 44 h argentation t.l.c. (solvent D) indicated unsaturation was negligible. The cooled mixture was extracted with carbon tetrachloride (4 × 50 cm^3) and the total extract washed with dilute hydrochloric acid, then with water, dried, filtered, and concentrated to give an oil which solidified, m.p. 80—83 °C (3.40 g, 79%).

(iii) '*Transfer*' *reduction.* A solution of unsaturated anacardic acid (5.0 g) in cyclohexene (36 cm^3) containing 10% Pd–C (0.50 g) was refluxed under nitrogen during 100 h (70—80 °C). Argentation t.l.c. indicated that some reduction had occurred but it was very incomplete; τ ($CDCl_3$), 1.4 (2 H, br s, CO_2H · · · OH, D_2O exchangeable), 2.5 (1 H, m, Ar-H), 3.2 (2 H, m, Ar-H), 6.9 (2 H, t, CH_2Ar), 8.68 (26 H, m, $[CH_2]_{13}$), and 9.09 (3 H, t, Me); $\nu_{max.}$ (KBr) 3 600 (OH), 1 665 (C=O), and 700 cm^{-1} (CH); δ_C ($CDCl_3$) 14.2(a), 22.8 (b), 28.89, 29.8 (c), 32.1 (d), 36.5 (e), 111.2 (f, st), 115.7 (g, dt), 122.5 (h, dt), 134.7 (i, dt), 147.4 (j, st), 163.5 (k, st), and 174.4 (l, st). The assignments were based on 'off-resonance' measurements and Sadtler Nos. 480, 1 621, 2 866, and 4 618 for methyl salicylate, ethylbenzene, 3-ethylphenol, and 2-toluic acid, respectively.

Acetylation with acetic anhydride (containing 1% sulphuric acid) gave the *O*-acetyl derivative which crystallised from light petroleum as needles, m.p. 63—64 °C (Found: C, 73.5; H, 9.8. $C_{24}H_{38}O_4$ requires C, 73.84; H, 9.74%); τ (CCl_4) −1.3 (1 H, s, CO_2H, D_2O exchangeable), 2.43—3.2 (3 H, m, Ar-H), 7.07—7.33 (2 H, t, CH_2Ar), 7.74 (3 H, s, COMe), 8.77 (26 H, m, $[CH_2]_{13}$), and 9.03—9.27 (3 H, t, Me).

Methyl (15 : 0)-*Anacardate* (*Methyl* 6-*Pentadecylsalicylate*).—No details of this preparation or spectral characterisation have previously been given although carried out first in 1964 (J. H. P. Tyman, unpublished work). Esterification was effected by diazomethane or more slowly by methanol–

* The reduction of double bonds was observed by the author in the preparation of hydrazides of unsaturated fatty acids (B.P. 795,674/1955) but was not reported further at that time.

boron trifluoride since the usual esterification procedures failed.[39]

(*i*) (15 : 0)-Anacardic acid (5.5 g) in ether (50 cm^3) was cooled in ice and an ice-cold ethereal solution (265 cm^3) containing diazomethane (0.71 g) added slowly until nitrogen evolution ceased and the solution was faintly yellow. The mixture was concentrated at ambient temperature and the residue crystallised from light petroleum to give colourless needles, m.p. 41—42 °C (lit.,[40] 41—42 °C; 46 °C [41]) (5.44 g, 95%), R_F 0.34 [chloroform–light petroleum (20 : 80)].

(*ii*) (15 : 0)-Anacardic acid (1.002 g) in methanol (20 cm^3) containing boron trifluoride was refluxed for a prolonged time with addition of more methanol (20 cm^3) until the original acid (t.l.c., solvent B) had substantially reacted. Concentration, dilution with water, recovery by ethereal extraction, and separation of unchanged acid by its insolubility in light petroleum (40—60 °C) followed by crystallisation gave methyl (15 : 0)-anacardate, identical with the product from (*i*). Unsaturated anacardic acid (5 g) was also methylated with ethereal diazomethane and hydrogenated in ethanol (80 cm^3) containing 10% Pd–C (0.5 g) to give the same product, m.p. 40—42 °C. A report * of the formation of the methyl ether methyl ester by treatment of unsaturated anacardic acid with diazomethane followed by hydrogenation, with no analytical or spectroscopic characterisation, must be discounted from the results of several authors.[40-42] In our experience, methylation of the phenolic hydroxy-group was not effected by the use of diazomethane with methanol or even tetrafluoroboric acid. The boron trifluoride–methanol procedure was much less effective because of polymerisation side-reactions in the case of the unsaturated acid; τ (CCl_4) −0.8 (1 H, br s, OH), 2.8 (1 H, m, Ar-H), 3.3 (2 H, m, Ar-H), 6.1 (3 H, s, OMe), 7.2 (2 H, t, CH_2Ar), 8.7 (26 H, m, $[CH_2]_{13}$), and 9.2 (3 H, t, Me).

Dimethyl (15 : 0)-*Anacardate* (*Methyl* 6-*Pentadecylsalicylate Methyl Ether*).—Dimethyl anardate was prepared by interaction of (15 : 0)-anacardic acid with dimethyl sulphate under anhydrous conditions (an improved method), or by phase-transfer catalysis in aqueous solution. The latter method was considerably quicker.

(*i*) A solution of (15 : 0)-anacardic acid (0.91 g) in benzene (10 cm^3) containing anhydrous potassium carbonate (1.714 g) and dimethyl sulphate (1.2 cm) was refluxed for several days until etherification and esterification were substantially complete (t.l.c., solvent C). The mixture was filtered, the filtrate washed with warm water repeatedly to remove residual dimethyl sulphate, and the organic layer dried and concentrated to give an oil. Crystallisation from light petroleum gave, at 0 °C, dimethyl anacardate, m.p. 39—40 °C (lit.,[6] 37—37.5 °C), R_F 0.21 [chloroform–light petroleum (20 : 80)].

(*ii*) (15 : 0)-Anacardic acid (0.488 g) in dichloromethane (10 cm^3) and water (10 cm^3) was treated with 3M sodium hydroxide solution (1.8 cm^3), 40% Triton B (0.05 cm^3), and dimethyl sulphate (1.2 cm^3) and the mixture ' vibromixed '. The creamy emulsion was agitated in this way for 1 h and left overnight, by which time two clear layers had formed. Since the reaction was incomplete (t.l.c., solvent C) 40% Triton B (0.45 cm^3), 3M sodium hydroxide solution (0.9 cm^3) and dimethyl sulphate (1.2 cm^3) were added. The mixture was vibromixed and after 2 h methylation was considerably more complete (t.l.c.) although both methyl and dimethyl anacardate were present (t.l.c. and ^{1}H n.m.r. indicated 20% methyl anacardate). Work-up as before followed by recovery and crystallisation gave dimethyl anacardate. Preparative t.l.c. was the most convenient procedure for obtaining both methyl anacardate and dimethyl anacardate. Complete removal of dimethyl sulphate was necessary prior to ^{1}H n.m.r. examination owing to its almost identical OMe signal with those in the two former materials; τ (CCl_4) 2.77—3.1 (1 H, m Ar-H), 3.30—3.60 (2 H, m, Ar-H), 6.20 (6 H, 2 s, 2 OMe), 7.60 (2 H, t, CH_2Ar), 8.17 (26 H, m, $[CH_2]_{13}$), and 9.17 (3 H, t, Me). Dimethyl anacardate and methyl anacardate showed a remarkable difference in polarity in t.l.c.[22] experiments due to the internal hydrogen bonding of the latter, resulting in a higher R_F for the phenolic ester compared with the dimethyl compound. By contrast the hydrogen bonding in anacardic alcohol must be extremely weak since the phenolic methyl ether has a higher R_F than the phenolic alcohol.

Model Experiments in the Salicyl Series.—Salicylic acid suspended in light petroleum containing pyridine reacted with thionyl chloride to yield salicylyl chloride, m.p. 14—17 °C (lit.,[43] 19.5 °C). Reduction at −75 °C (1 h) of salicylyl chloride (2 g) with a diglyme solution (10.5 cm^3) of the precipitate from dry t-butyl alcohol (2 g) and lithium aluminium hydride (0.5 g) gave on work-up salicylaldehyde (1.17 g) (75%); the 2,4-dinitrophenylhydrazone had m.p. 246—247 °C (lit.,[44] 248 °C); R_F 0.6 (solvent B). Salicylaldehyde (6.455 g) in methanol reduced with sodium borohydride (5 g) in alkaline solution followed by acidification and work-up gave salicyl alcohol (4.5 g, 69%) as needles, m.p. 86—87 °C (from water) (lit.,[44] 87 °C); R_F 0.19 (solvent B). Methylation of salicyl alcohol with dimethyl sulphate in the usual anhydrous way gave the dimethyl ether as an oil, $\nu_{max.}$ 3 350 cm^{-1} (CH) and 1 650 cm^{-1} (CO). Salicyl alcohol phenolic methyl ether was prepared from 2-methoxybenzoic acid by reduction in tetrahydrofuran with lithium hydride, R_F 0.47 (solvent B). Oxidation of salicyl alcohol (0.124 g) with dipyridine–chromium(VI) oxide (1.548 g) in dichloromethane (22 cm^3) gave salicylaldehyde (0.119 g, 98%), R_F 0.64 (solvent B). Oxidation of salicyl alcohol (0.12 g) with pyridinium chlorochromate gave salicylaldehyde (0.07 g), R_F 0.62 (solvent B).

Anacardic Alcohol (6-*Pentadecyl Alcohol*).—Dry anacardic acid (5 g, 0.143 mol), in dry tetrahydrofuran (85 cm^3) was added (1.5 h) to stirred lithium aluminium hydride (2.5 g) in tetrahydrofuran (25 cm^3) and the mixture refluxed (2.25 h); after the addition of ethyl acetate, it was acidified, and extracted with ether. The alkali-washed combined ethereal extracts were concentrated and anacardic alcohol † crystallised from light petroleum as pale yellow prisms (4 g, 83%), m.p. 61.5—62 °C (lit.,[41] 65—66 °C; by reduction of methyl anacardate), R_F 0.29 (solvent B) (Found: C, 78.9; H, 11.65. Calc. for $C_{22}H_{38}O_2$: C, 79.04; H, 11.36%); τ (CCl_4), 3.1 (1 H, m, Ar-H), 3.4 (2 H, m, Ar-H), 4.7 (2 H, s, 2 OH, D_2O exchangeable), 5.3 (2 H, s, ArCH_2O), 7.5 (2 H, t, CH_2Ar, 8.69 (26 H, m, $[CH_2]_{13}$), and 9.09 (3 H, t, Me); $\nu_{max.}$ (KBr) 3 600 (OH), 2 800 and 2 875 (CH_2), and 1 585 and 1 455 cm^{-1} (C=C); δ_C ($CDCl_3$) 14.1 (a), 22.7 (b), 29.7, 31.7, 31.9 (c), 32.2 (d), 33.2 (e), 59.7 (f, tt), 114.3 (g, dt), 121.6 (h, dt), 122.9 (i, st), 128.8 (j, at), 141.4 (h, st), and 156.3 (l, st).

The assignments were made on the basis of off-resonance measurements. They show similarity to Sadtler Nos. 855, 1 621, 1 864, and 2 866 for salicyl alcohol, ethylbenzene, benzyl alcohol, and 3-ethylphenol, respectively.

* P. T. Izzo and C. R. Dawson, *J. Org. Chem.*, 1949, **14**, 1039.

† This compound was first prepared during studies in 1964 on the minor phenolic component, 2-methylcardol, of CNSL (J. H. P. Tyman, *Chem. Commun.*, 1967, 982).

Anacardic Anhydride (6-*n*-*Pentadecylsalicylic Anyhydride*). —(15 : 0)-Anacardic acid (3.48 g, 0.01 mol) in light petroleum (15 cm^3) containing pyridine (0.02 g, 0.22 mmol) was reacted with thionyl chloride (0.62 cm^3, 8.5 mmol) at 30 °C. The mixture became more homogeneous and after 48 h was filtered. Concentration left an oil which possessed an acid chloride-type odour. An aliquot was suspended in light petroleum and the clear solution was removed and evaporated to dryness to yield an oil which solidified to give *anacardic anhydride*, m.p. 43—44 °C. After removal of all solvent under vacuum a sample was analysed (Found: C, 77.3; H, 10.35; Cl, 0. $C_{22}H_{35}O_2Cl$ requires C, 72.03; H, 9.55; Cl, 9.68%. $C_{44}H_{70}O_5$ requires C, 77.87; H, 10.32%); R_F 0.85 and 0.15 (solvent B). The mass spectrum did not show molecular ions at *m/e* 366, 368, although acid chlorides (benzoyl chloride as a reference) give small peaks. T.l.c. showed a (minor) polar and a (major) non-polar spot. The minor component is most probably the isomeric phenolic ester acid and not anacardic acid, since t.l.c. did not indicate this. The anhydride structural assignment was strengthened by the observation in the benzoyl reference series in which the R_F values were chloride > anhydride > acid; $\nu_{max.}$ (KBr) 3 460 and 3 300 (OH), 2 930 and 2 855 (CH_2), 1 743 and 1 720 (C=O), 1 610 and 1 470 (C=C), 1 315, 1 230, and 1 060 cm^{-1}.

The anhydride (0.10 g) in dry tetrahydrofuran (2 cm^3) was vigorously shaken with concentrated ammonia (10 cm^3) to yield gradually a greyish white precipitate, which was filtered off. Crystallisation and recrystallisation gave shiny plates of *anacardamide*, m.p. 91—92 °C (lit.,[41] 80 °C) (Found: N, 3.9. Calc. for $C_{22}H_{37}O_2N$: N, 4.03%); τ (CCl_4), 0.07—1.67 (br s, OH and NH_2, D_2O exchangeable), 2.67—3.67 (3 H, m, Ar-H), 7.3 (2 H, t, CH_2Ar), 8.75 (26 H, m, $[CH_2]_{13}$), and 9.1 (3 H, t, Me); $\nu_{max.}$ (KBr) 3 420 (OH), 3 320 and 3 180 (NH), 1 660 and 1 615 cm^{-1} (CO), and 1 470 cm^{-1} (C=C).

Interaction of the anhydride (0.20 g) with aniline (2 cm^3) in benzene (5 cm^3) on the steam-bath until reaction (t.l.c.) was complete, dilution with water, ethereal extraction, acidic extraction, and concentration of the ether gave a solid which (t.l.c., solvent B) contained at least four components. By reference to the R_F value of salicylanilide, the second band from the bottom appeared to be the product and preparative t.l.c., followed by recovery and crystallisation gave greyish buff prisms. Three further crystallisations (light petroleum, 40—60 °C) yielded shiny prisms of *anacardic anilide*, m.p. 81—82 °C (lit.,[41] 78 °C) (0.14 g, 60.0%) (Found: C, 79.3; H, 9.85; N, 3.15. Calc. for $C_{28}H_{41}O_2N$: C, 79.43; H, 9.69; N, 3.31%); τ (CCl_4) 1.80—2.20 (2 H, br s, OH, NH, D_2O exchangeable), 2.60—3.84 (8 H, m, Ar-H), 6.60 (2 H, t, CH_2Ar), 8.75 (26 H, m, $[CH_2]_{13}$), and 9.1 (3 H, t, Me); $\nu_{max.}$ (KBr) 3 205 (OH), 2 935 and 2 855 (CH_2), 2 690 and 2 600 (NH), 1 634 (CO), 1 605, 1 556 (C=C), 1 494, 1 354, 1 254, and 756 cm^{-1}; *cf.* salicylanilide, 3 310 cm^{-1} (OH), 2 690, 2 575 (NH), 1 623, 1 565 (C=C), 1 437, 1 337, 1 238, and 757 cm^{-1}.

Anacardaldehyde (6-*Pentadecylsalicylaldehyde*).—(i) *From anacardic alcohol.* (*a*) Oxidation by the Oppenauer method in acetone solution with aluminium t-butoxide produced some anacardaldehyde (J. H. P. Tyman, unpublished work, 1964) but the procedure was inferior to the use of chromium trioxide–pyridine in solvent. Chromium(VI) oxide (2.0 g) was added under nitrogen with stirring to anhydrous pyridine (160 cm^3) at 15—20 °C and the complex washed repeatedly with light petroleum, filtered, dried, and stored in a vacuum desiccator. Anacardic alcohol (0.33 g, 1 mmol) was added to dipyridine–chromium(VI) oxide (1.548 g) in dichloromethane (22.0 cm^3). The oxidation was complete (t.l.c.) in 15 min and the organic material from the filtered and concentrated mixture was purified by preparative t.l.c. (solvent B) to give *anacardaldehyde* (6-*n*-*pentadecylsalicylaldehyde*) as prisms from light petroleum, m.p. 45—46 °C (0.28 g, 84%), R_F 0.81 (solvent B) (Found: C, 79.5; H, 11.05. $C_{22}H_{36}O_2$ requires, C, 79.51; H, 10.84%); τ (CCl_4), −2.2 (1 H, s, OH, D_2O exchangeable), −0.7 (1 H, s, ArC*H*O), 2.8 (3 H, m, Ar-H), 7.1 (2 H, t, CH_2Ar), 8.7 (26 H, m, $[CH_2]_{13}$), and 9.02 (3 H, t, Me) (Found: M^+, 332. $C_{22}H_{36}O_2$ requires *M*, 332); $\nu_{max.}$ (KBr) 3 140 (OH), 2 875 (CH_2), 1 650 (C=O), and 1 585 cm^{-1} (C=C); $\lambda_{max.}$ 217, 285, and 340 nm.

(*b*) Pyridinium chlorochromate was prepared by the addition of chromium trioxide (100 g) to 6M hydrochloric acid (184 cm^3) followed by treatment (over 10 min) of the mixture at 0 °C with pyridine (79 g). The solid was collected, washed (light petroleum), and dried to give 173 g (79%) of the product.

Anacardic alcohol (2 g, 6 mmol) in dichloromethane (112 cm^3) was mixed with pyridinium chlorochromate complex (5.50 g), stirred (90 min) at ambient temperature, filtered, and the organic layer washed with water, dried, and concentrated to give an oil which was purified by preparative t.l.c. to give anacardaldehyde, identical with preparation (*a*), m.p. 44—46 °C (yield 67%).

Anacardaldehyde (0.05 g) formed a 2,4-*dinitrophenylhydrazone* (0.077 g) as orange-red needles, m.p. 139—140 °C (Found: C, 57.9; H, 7.95; N, 10.65. $C_{28}H_{40}O_5N_4$ requires C, 56.30; H, 7.81; N, 10.94%).

(ii) *From anacardic anhydride.* The precipitate from the addition of dry t-butyl alcohol (0.655 g, 8.9 mmol) to ethereal lithium aluminium hydride (0.106 g, from 5.62 cm^3 of 5M solution) was allowed to settle, the ether decanted, and the solid dissolved in diglyme (2.2 cm^3). The solution was added (1 h) to anacardic anhydride (1 g, 2.7 mmol) in diglyme (1.1 cm^3) maintained at −75 °C (solid CO_2–acetone). The mixture was allowed to rise to ambient temperature (1 h), diluted with ice, acidified, ethereally extracted, and the crude product (0.98 g), as an oil containing some starting material purified by preparative t.l.c. to give anacardaldehyde (0.78 g, 86%); R_F 0.82 (solvent B). The product was identical spectroscopically with the product from (i) but contained traces of the alcohol and acid anhydride.

Preliminary experiments showed that the Rosenmund reduction of the product from anacardic acid treated with thionyl chloride in dry xylene containing Pd–$BaSO_4$ and thiourea followed by refluxing (140—150 °C) during the passage of hydrogen produced anacardaldehyde (the procedure will be described in a subsequent publication).

Methylation of anacardaldehyde with dimethyl sulphate in benzene containing anhydrous potassium carbonate gave the methyl ether. Reduction of anacardaldehyde in methanol with sodium borohydride gave anacardic alcohol.

8-*Pentadecyl*-1-*oxaspiro*[2.5]*octa*-5,7-*dien*-4-*one*.—To anacardic alcohol (0.1656 g) in methanol (5.0 cm^3), a solution of sodium periodate (0.1461 g) in water (1.25 cm^3) was added. A sticky material slowly separated and the mixture was placed in a warm water-bath at 30 °C. After 16 h a yellowish solid had formed and t.l.c. (solvent B) indicated a major new component together with a little remaining anacardic alcohol. The mixture was diluted with water, ethereally extracted, and the extract washed with water,

dried, and concentrated to give a solid, m.p. 65—79 °C, which was crystallised (light petroleum) to afford pale yellow prisms of the *spiroepoxydienone* (0.08 g), m.p. 78—79 °C, R_F 0.46 ($CHCl_3$) (Found: C, 78.9; H, 10.9%; *M*, 332.2715. $C_{22}H_{36}O_2$ requires C, 79.52; H, 10.84%; *M*, 332.2715); τ ($CDCl_3$) 2.73—3.07 (1 H, m, H-5), 3.67—4.07 (2 H, m, H-3 and H-4), 6.87 (2 H, d, spiro-CH_2O), 8.46 (2 H, m, CH_2–C=C), 8.73 (26 H, m, $[CH_2]_{13}$), and 9.13 (3 H, t, Me); $\nu_{max.}$ (KBr) 2 930 and 2 860 (CH_2), 1 650 (C=O), 1 630 and 1 465 cm^{-1} (C=C); $\lambda_{max.}$ (MeOH) 327 nm, changed within a few minutes to the spectrum of the aldehyde; *m/e* 332 (M^+, strong; $C_{22}H_{36}O_2$ requires *M*, 332). Upon heating (at 120—140 °C) formation of some anacardaldehyde occurred with residual dienone still present. Reduction with sodium borohydride gave anacardic alcohol. Irradiation, in a glassware modified medium-pressure Hanovia P.C.R. (125 W), of the spiroepoxydienone (9 mg) in ethanol (2 cm^3) during 1.5 h gave complete conversion to anacardaldehyde, m.p. 44—48 °C (R_F 0.68, chloroform). Alternatively a fluorescent lamp of the type used to view t.l.c. plates was equally effective with an unshielded methanolic solution of the dienone.

Anacardic Alcohol O-*Methyl Ether* (6-*Pentadecylsalicyl Alcohol* O-*Methyl Ether*).—Anacardic alcohol *O*-methyl ether was prepared by methylation of anacardic alcohol by the anhydrous method, by phase-transfer catalysis, and by lithium aluminium hydride reduction of anacardic acid *O*-methyl ether or of dimethyl anacardate.

(i) *By methylation procedures.* (*a*) Anacardic alcohol (0.163 g) in benzene (3 cm^3) containing anhydrous potassium carbonate (0.802 g) and dimethyl sulphate (0.3 cm^3) was refluxed on a steam-bath. After 6 h t.l.c. (solvent B) showed the presence of unchanged alcohol, the monomethyl ether, and less polar materials. The crude product isolated by dilution with water, ethereal extraction, and water washing, was dried and purified by preparative t.l.c. [solvent chloroform–light petroleum (40—60 °C)] followed by crystallisation of the recovered material from light petroleum (40—60 °C) at 0 °C to give colourless prisms, m.p. 55—56 °C.

(*b*) Anacardic alcohol (0.4624 g) in dichloromethane (10 cm^3) and water (10 cm^3) was treated with 40% Triton B (0.5 cm^3) and dimethyl sulphate (0.6 cm^3) and the mixture vibromixed. After 2 h the creamy thick suspension had changed to two clear layers and t.l.c. (solvent B) showed almost complete formation of the required phenolic methyl ether in high yield after work-up in the usual way.

(ii) *By lithium aluminium hydride reduction.* (*a*) (15 : 0)-Anacardic acid *O*-methyl ether was prepared by the hydrolysis of dimethyl anacardate (m.p. 41—42 °C) with alcoholic potassium hydroxide solution followed by acidification and recrystallisation (or preparative t.l.c.); it was obtained as prisms, m.p. 78 °C (lit.,[6] 82 °C); τ (CCl_4) −1.23 (1 H, br s, CO_2H, D_2O exchangeable), 2.62—2.92 (H-4, ' t ', Ar-H, J_o 8 Hz), 3.20—3.37 (H-5 and H-3, 2 d, Ar-H, J_o 8, J_m 3 Hz), 6.15 (3 H, s, OMe), 7.23—7.47 (2 H, t, CH_2Ar), 8.77 (26 H, m, $[CH_2]_{13}$), and 9.03 (3 H, t, Me).

The acid (0.3 g; 8.3 mmol) in dry tetrahydrofuran (5 cm^3) was added dropwise (1.5 h) to lithium aluminium hydride (0.15 g, 3.9 mmol) and the mixture refluxed (2.25 h), worked up in the usual way, and recrystallised from light petroleum (40—60 °C) at 0 °C to give colourless prisms, m.p. 57—58 °C, of *anacardic alcohol* O-*methyl ether*.

(*b*) Dimethyl anacardate (1.0 g) in dry tetrahydrofuran (10 cm^3) was treated with lithium aluminium hydride (0.5 g), stirred (3 h) at ambient temperature and then at 60 °C (5 h). T.l.c. monitoring indicated complete reaction and the mixture was worked up as before, followed by preparative t.l.c. purification (solvent, chloroform), to yield after crystallisation (light petroleum, 0 °C) anacardic alcohol *O*-methyl ether as prisms, m.p. 57—58 °C, identical chromatographically and in m.p. with the previous three preparations (Found: C, 78.8; H, 11.62. $C_{23}H_{40}O_2$ requires C, 79.30; H, 11.49%); τ (CCl_4), 3.0 (3 H, m, Ar-H), 4.0 (1 H, s, OH, D_2O exchangeable), 5.4 (2 H, s, ArCH_2O), 6.18 (3 H, s, OMe), 7.5 (2 H, t, CH_2Ar), 8.7 (26 H, m, $[CH_2]_{13}$), and 9.08 (3 H, t, Me); $\nu_{max.}$ (KBr) 3 400 (OH), 2 875 and 2 800 (CH_2), 1 585 and 1 455 (C=C), and 1 145 cm^{-1} (C–O–C). Washing with dilute ammonia was found ineffective as a procedure [23] for removing unchanged dimethyl sulphate and hot water washing was considerably more useful.

Anacardic Alcohol Dimethyl Ether.—In all cases the yields were small except by the last two procedures below which gave rather better efficiency. To aid in the identification of bands for preparative t.l.c. it was found useful to use benzyl alcohol and its methyl ether together with anacardic alcohol *O*-methyl ether as reference materials. Interaction of anacardic alcohol (0.1 g, 0.3 mmol) in benzene (2 cm^3) containing dimethyl sulphate (0.374 g, 2.96 mmol) and potassium carbonate (0.413 g, 2.99 mmol) by refluxing (6 h) and work-up in the usual way followed by preparative t.l.c. (solvent B) gave *anacardic alcohol dimethyl ether* as an oil in low yield.

Attempts to pre-form the dilithio-salt of anacardic alcohol with lithium methoxide followed by its interaction with dimethyl sulphate in tetrahydrofuran solution were not very effective, but the sodium salt of anacardic alcohol *O*-methyl ether interacted reasonably satisfactorily with dimethyl sulphate in hexamethylphosphoric triamide.

Anacardic alcohol *O*-methyl ether (0.1235 g) in dry tetrahydrofuran (2.5 cm^3) was treated with sodium hydride (0.0174 g) and after 2 h the solvent was removed under vacuum, replaced by hexamethylphosphoric triamide (1 cm^3), and dimethyl sulphate (0.15 cm^3) added. The mixture was warmed (16 h) and, after t.l.c. monitoring, worked up in the usual way to give an oil containing the starting material and the dimethyl ether. Mass spectrometry revealed a molecular ion (M^+) at *m/e* 362; $C_{24}H_{42}O_2$ requires *M*, 362.

Anacardic alcohol *O*-methyl ether (0.15 g) in light petroleum (6 cm^3) was vibromixed with 50% aqueous potassium hydroxide [from potassium hydroxide (1.5 g) and water (1.5 cm^3)], 40% tetrabutylammonium hydroxide (1 cm^3), and dimethyl sulphate (0.8 cm^3). T.l.c. monitoring indicated (after 16 h) the presence of some dimethyl ether but the reaction was not complete. The reaction mixture was worked up in the usual way to give an oil purified by preparative t.l.c. (solvent, chloroform) to give, after recovery, *anacardic alcohol dimethyl ether* as an oil showing a single band on t.l.c. (Found: M^+, 362.3185. $C_{24}H_{42}O_2$ requires *M*, 362.3184); τ (CCl_4) 2.94—3.57 (3 H, m, Ar-H), 5.67 (2 H, s, ArCH_2O), 6.27 (3 H, s, ArOMe), 6.80 (3 H, s, MeO), 7.40 (2 H, t, ArCH_2), 8.73 (26 H, m, $[CH_2]_{13}$), and 9.13 (3 H, t, Me). Benzyl methyl ether (prepared by phase-transfer catalysis) had τ (CCl_4) 2.87 (5 H, m, Ar-H), 5.73 (2 H, s, ArCH_2O), and 6.80 (3 H, s, MeO).

3-*n*-*Pentadecylcatechol.*—As a model experiment, salicylaldehyde (5.7 g) was converted by aqueous alkaline hydrogen peroxide to catechol, m.p. 102—104 °C (lit.,[43b] 105 °C) (3.1 g, 60%), R_F 0.24 (solvent B). In a similar way, o-vanillin yielded 3-methoxycatechol (R_F 0.20, solvent B).

Anacardaldehyde (0.05 g) was dissolved in 3M sodium hydroxide solution and during the addition of 6% hydrogen peroxide solution (0.5 cm^3) the temperature was kept between 40 and 50 °C. After the addition was complete the dark mixture was cooled, acidified, ethereally extracted, extracted with aqueous sodium hydroxide, and the organic material recovered from the alkaline solution purified by preparative t.l.c.; R_F 0.43 (solvent B). The combined results of five experiments (from 508.2 mg) yielded 97 mg (20.3%) of a brownish solid consisting of crude 3-n-pentadecylcatechol. It proved difficult to remove the associated brown impurity. The product was chromatographically identical (t.l.c. and g.l.c., see retention times) with synthetic 3-n-pentadecylcatechol; τ (CCl_4) 3.2 (3 H, m, Ar-H), 3.0—5.0 (2 H, br s, 2 OH, D_2O exchangeable), 7.6 (2 H, t, CH_2Ar), 8.6 (26 H, m, $[CH_2]_{13}$), and 9.0 (3 H, t, Me); $\nu_{max.}$ 3 450 (OH), 2 950 and 2 850 (CH_2), and 1 585 cm^{-1} (C=C) (Found: M^+, 320.2705. $C_{21}H_{36}O_2$ requires M, 320.2715). A C_{17} homologue (Found: M^+, 348.4016. $C_{23}H_{40}O_2$ requires M, 348.3028) arising from C_{17} anacardic acid was present.

Methylation of the semi-pure 6-n-pentadecylcatechol (50 mg) by refluxing (26 h) in benzene (2 cm^3) containing dimethyl sulphate (0.0984 g) and potassium carbonate (0.1078 g), washing of the crude product with 1M sodium hydroxide solution, and crystallisation from light petroleum gave white needles, m.p. 32—34 °C (lit.,[7] 36.5—37 °C); these were identical with the product of methylation of synthetic urushiol, m.p. 33—34 °C, obtained by the anhydrous method in benzene solution containing dimethyl sulphate and potassium carbonate or by the phase-transfer method in which (15 : 0)-urushiol (0.53 g) in dichloromethane (8 cm^3) and water (6 cm^3) was treated with 3M sodium hydroxide (1.83 cm^3) and 40% Triton B (0.25 cm^3), and vibromixed under nitrogen during the addition of dimethyl sulphate (1.2 cm^3). After 2 h, methylation was complete, as shown by t.l.c. and ^1H n.m.r. examination and the product was isolated in the usual way; R_F 0.89 (solvent B). The retention times (g.l.c.) were identical.

Attempted Dakin Reaction on Anarcardic Acid.—The reaction of anacardic acid (1) with hydrogen peroxide in alkaline solution at ambient temperature (60 h), in warm ethanolic alkaline solution (4 h), or in aqueous alkaline ethylene glycol (24 h) all failed to produce urushiol. The first experiment was carried out as follows.

Anacardic acid (0.943 g) in 3M sodium hydroxide solution (1.8 cm^3) diluted with water (1 cm^3), was treated with 6% hydrogen peroxide (2.55 cm^1) during 10 min. The solution was warmed and then left (60 h) under nitrogen. After acidification, ethereal extraction, and recovery, t.l.c. examinations howed no new band. More drastic conditions led to the formation of a small amount of cardanol by decarboxylation.

2,3-*Dimethoxybenzaldehyde.*—A mixture of *o*-vanillin (25 g, 0.164 mol) in benzene (200 cm^3) containing anhydrous potassium carbonate (45.4 g, 0.33 mol) and dimethyl sulphate was refluxed (26 h), the cooled material diluted with water, and the organic layer extracted exhaustively with 1M sodium hydroxide solution. The product recovered from the organic layer was crystallised from ethanol to give pale yellow needles, m.p. 52.5—54 °C (lit.,[45] 54 °C) (24.2 g, 89%), R_F 0.62 (solvent B); the 2,4-dinitrophenylhydrazone had m.p. 224—225 °C; τ (CCl_4) −0.5 (1 H, s, CHO), 2.90 (3 H, m,Ar-H), and 6.15 (6 H, s, 2 OMe); δ_C ($CDCl_3$), 55.4 (a, qt), 61.5 (b, qt), 117.9 (c, dt), 118.4 (d, dt), 123.6 (e, dt), 129.4 (f, st?), 152.3 (g, st), 152.7 (h, st), and 189.2 (i, dt). The assignments were made on the basis of off-resonance measurements. They show similarity to Sadtler Nos. 1 737 and 2 069 for 2-methoxybenzaldehyde and 2,5-dimethoxybenzaldehyde, respectively; $\nu_{max.}$ (KBr) 2 850 (C–H), 1 650 (ArC=O), and 1 585 cm^{-1} (C=C).

1-(2,3-*dimethoxyphenyl*)*pentadecan*-1-*ol.*—Tetrahydrofuran (10 cm^3) and lithium cubes (*ca.* 1—2 mm) (0.347 g, 0.05 mol) were introduced into the nitrogen filled apparatus and cooled to 0 °C. 2-3-Dimethoxybenzaldehyde (3.32 g, 0.02 mol) and freshly distilled 1-bromotetradecane (5.54 g, 0.02 mol) were mixed and added slowly (2 h) to the stirred lithium which was maintained at 0 °C. After complete reaction, the filtered mixture was concentrated. The residue was decomposed with ice-cold dilute hydrochloric acid, the mixture was ethereally extracted and washed with sodium hydrogencarbonate and the dried, recovered organic material distilled *in vacuo* to give four fractions; the main one, b.p. 200 °C/0.03 mmHg after recrystallisation (methanol, light petroleum) gave white prisms, m.p. 36—37 °C (lit.,[7] 35—36 °C) (4.56 g, 63%) of 1-(2,3-dimethoxyphenyl)-pentadecan-1-ol, R_F 0.64 (solvent B) (Found: C, 76.2; H, 11.15. Calc. for $C_{23}H_{40}O_3$: C, 75.82; H, 10.99%); τ (CCl_4), 3.15 (2 H, m, Ar-H), 5.25 (1 H, r, C*H*Ar), 6.18 (6 H, s, 2 OMe), 8.16 (1 H, s, OH, D_2O exchangeable), 8.76 (26 H, m, $[CH_2]_{13}$), and 9.14 (3 H, t, Me); δ_C ($CDCl_3$) 14.1 (a), 22.8 (b), 26.2 (c), 29.50, 29.8 (d), 32.0 (e), 38.5 (f), 55.7 (g, qt), 60.8 (h, st), 69.7 (i, dt), 111.3 (j, dt), 118.8 (k, dt), 124.1 (l, dt), 138.6 (m, st), 146.3 (n, st), and 152.4 (o, st). The assignments were based on off-resonance measurements. They show similarity to Sadtler Nos. 1 864 and 3 188 for benzyl alcohol and *o*-methoxybenzyl alcohol, respectively.

1,2-*Dimethoxy*-3-*n*-*pentadecylbenzene.*—1-(2,3-Dimethoxyphenyl)pentadecan-1-ol (2.5 g) in ethanol (50 cm^3) containing concentrated sulphuric acid (drops) and 10% Pd–C (0.25 g) was hydrogenolysed at 25 lb in^{-2} and ambient temperature. The filtered mixture was worked up in the usual way and the recovered organic material (2.1 g) purified by preparative t.l.c. (solvent B) to remove a trace of the starting material. The recovered product was recrystallised from light petroleum to give 1,2-dimethoxy-3-n-pentadecylbenzene (3-n-pentadecylveratrole) as white prisms, m.p. 34—35 °C (lit.,[7] 36.5—37 °C) (2.0 g, 84%), R_F 0.89 (solvent B) (Found: C, 79.45; H, 11.55. Calc. for $C_{23}H_{40}O_2$: C, 79.31; H, 11.49%); τ (CCl_4), 3.3 (3 H, m, Ar-H), 6.2 (6 H, s, 2 OMe), 7.4 (2 H, t, CH_2Ar), 8.7 (26 H, m, $[CH_2]_{13}$), and 9.13 (3 H, t, Me); $\nu_{max.}$ (KBr) 2 870 and 2 940 (CH_2), 1 580 and 1 600 (C=C), and 1 135 cm^{-1} (C–O).

3-*n*-*Pentadecylcatechol* [(15 : 0)-*Urushiol*].—To a solution of boron tribromide (0.4 cm^3, 0.27 g, 1 mmol) in dry dichloromethane (0.6 cm^3) was added 3-n-pentadecylveratrole (0.19 g, 0.54 mmol) in dichloromethane (5 cm^3) at −80 °C (solid CO_2–acetone). After 10 h, hydrochloric acid (5 cm^3) was added and the ethereally extracted and recovered product gave, after recrystallisation from light petroleum, 3-n-pentadecylcatechol as off-white prisms, m.p. 58—59 °C (lit.,[7] 58—59 °C; lit.,[46] 59—60 °C) (0.13 g, 76%), R_F 0.42 (solvent B) (Found: C, 78.25; H, 11.0. Calc. for $C_{21}H_{36}O_2$: C, 78.75; H, 11.25%); when less than the above proportion of boron tribromide was used, g.l.c. evidence was found for the presence of a monomethyl ether, probably 1-hydroxy-2-methoxypentadecylbenzene, and different from the 2-hydroxy-1-methoxypentadecylbenzene found in the methylation of urushiol; τ (CCl_4) 3.4 (3 H, m, Ar-H), 5.1 (2 H, s, ArOH, D_2O exchangeable), 7.4 (2 H, t, CH_2Ar), 8.85 (26 H, m, $[CH_2]_{13}$), and 9.2 (3 H, t, Me) (Found: M^+,

320.2715. $C_{21}H_{36}O_2$ requires M, 320.2715); $\nu_{max.}$ (KBr) 3 460 (OH), 2 945 and 2 860 (CH_2), and 1 600 and 1 578 cm^{-1} (C=C). By argentation t.l.c. (15% $AgNO_3$) [solvent, chloroform–ethyl acetate (80 : 20)] the synthetic product agreed in R_F value with the spot of highest R_F in a natural urushiol sample. The product of hydrogenation of urushiol (Pd–C) was also identical with the synthetic material.

Hydrogenation of natural Urushiol (Japanese Lac).—Natural urushiol (5.2455 g) in ethyl acetate (48 cm^3) containing 10% Pd–C (0.5215 g) was hydrogenated at 15 lb in^{-2} until hydrogen absorption ceased (3 days). The mixture was filtered and the filtrate concentrated to give a brown semi-solid, 0.5002 g of which was separated by preparative t.l.c. (solvent B). Six bands were observed and the upper one (purplish in colour) was isolated in the usual way. The recovered urushiol, a sticky brown crystalline solid, was purified by several crystallisations from light petroleum (charcoal) to give (15 : 0)-urushiol, m.p. 56—57 °C.

Cardanol in Urushiol.—T.l.c. (solvent B) of natural urushiol gave an upper spot agreeing in R_F with a reference sample of cardanol. G.l.c.–m.s. of a sample of hydrogenated (Pd–C) urushiol gave, for the first small peak, *m/e* 304; retention time and complete mass spectrum, identical with that of (15 : 0)-cardanol.

Gas-liquid Chromatography.—On 3% SE30 with a nitrogen flow rate of 45 cm^3 min^{-1} at 220 °C the following retention times (min), retention relative to (15 : 0)-cardanol = 1, and retention relative to (15 : 0)-anacardic alcohol dimethyl ether = 1, were observed; (15 : 0)-anacardic alcohol dimethyl ether (7.6, 0.35, 1.00), (15 : 0)-urushiol dimethyl ether (15.6, 0.72, 2.05), (15 : 0)-anacardaldehyde (20.6, 0.95, 2.71), (15 : 0)-urushiol (31.8, 1.47, 4.18), methyl (15 : 0)-anacardate (27.1, 1.25, 3.56), and anacardic alcohol phenolic methyl ether (43.6, 2.01, 5.75). This series compared with the salicyl in which the following were found on SE30 at 100 °C [retention time (min), retention relative to salicyl alcohol dimethyl ether = 1]; salicyl alcohol dimethyl ether (1.4, 1.00), salicyl aldehyde (1.6, 1.14) salicylaldehyde *O*-methyl ether (4.4, 3.14), methyl salicylate (3.4, 2.43), and salicyl alcohol phenolic methyl ether (5.4, 3.86).

^1H *N.M.R. Absorption of Aromatic Protons* * *in Compounds* (1)—(6) *and their Derivatives.*—Protons in the aromatic region for compounds (1)—(6) have been generally given as multiplets. Table 2, and details on the assignment in certain cases, serves to characterise these protons more fully.

TABLE 2

Compound	Calculated τ values [47] H-5 *	H-4 *	H-3 *
(1; R = H, *n* = 0)	2.72	2.56	3.01
(2; R = H, *n* = 0)	7.01	3.01	3.30
(2; R = Me, *n* = 0)	3.19	3.24	3.24
(4; R = H)	2.83	2.76	3.12
(4; R = Me)	3.04	2.73	3.09
(5)	2.67	2.46	2.97
(6; R = H)	2.68	2.55	2.97
(4) Phenolic methyl ether	3.04	2.73	3.09
Dimethyl (15 : 0)-anacardate	2.99	2.58	3.06
(15 : 0)-Anacardic acid *O*-methyl ether	2.93	2.53	2.98
Methyl (15 : 0)-anacardate	2.80	2.61	3.09
(15 : 0)-Anacardic acid *O*-acetate	2.72	2.42	2.72

* Numbering according to the formulae in Scheme 1 [formula (2) is numbered the same for consistency, and not according to nomenclature].

The observed spectra for these components contained the following chemical shifts and coupling constants.

Anacardic acid (1; R = H, *n* = 0); H-4 at τ 2.6 [doublet of doublets (' triplet ') (J_o 7 Hz)]; H-5 at τ 3.1; H-3 at τ 3.28 (J_o 7, J_m 2 Hz).

Urushiol (2; R = H, *n* = 0); H-5, H-4, and H-3 appeared as a broad unresolved multiplet.

Compound (2; R = Me, *n* = 0) dimethyl ether; insufficient resolution (J_o 6, J_m 1 Hz).

Compound (4; R = H); H-4 at τ 3.12 [doublet of doublets (J_o 7 Hz)]; H-5 and H-3, τ *ca.* 3.44 (J_o 7, J_m 1 Hz) (not resolved).

Compound (5); H-4 τ *ca.* 2.77 (not resolved), H-5 at τ *ca.* 7.2; H-3 at τ *ca.* 3.34 (not resolved).

Compound (6; R = H); H-5 at τ *ca.* 2.67 (' triplet ', not resolved); H-4 and H-3, τ *ca.* 3.33 (' triplet ', not resolved).

Compound (4) phenolic methyl ether; H-4 at τ *ca.* 2.89 (J_o 8 Hz); H-5 and H-3 at τ *ca.* 3.33 (J_o 8, J_m 3 Hz).

Dimethyl anacardate; H-4 at τ 2.83 (J_o 8 Hz); H-5 and H-3 at τ 3.33 (J_o 8, J_m 4 Hz) (not resolved).

Methyl anacardate; H-4 at τ *ca.* 2.80 (J_o 8 8z); H-5 and H-3 at τ *ca.* 3.35 (J_o 8 Hz) (not resolved).

Anacardic acid *O*-methyl ether; H-4 at τ *ca.* 2.83 (J_o 8 Hz), H-5 at τ 3.30 (J_o 7, J_m 4 Hz) (not resolved).

Anacardic acid *O*-acetate: H-4 at τ *ca.* 2.55 (J_o 7 Hz); H-5 and H-3 at τ *ca.* 2.9 (J_o 8 Hz).

Separation of Unsaturated Anacardic Acid (1, R = H) *and Unsaturated Methyl Anacardate* (1, R = Me).—Argentation t.l.c. of anacardic acid as described [48] in ether–light petroleum (30 : 70) containing 1% formic acid followed by methylation of each constituent with diazomethane was used to obtain the methyl esters. Alternatively, unsaturated anacardic was methylated and separated [chloroform–ethyl acetate (9:1)] by preparative t.l.c.

Mass Spectra of Constituents of Methyl Anacardate [*Methyl Ester of* (1)].—Although (15 : 0)-anacardic acid itself gave a mass spectrum showing a molecular ion, accompanying decarboxylation made it more convenient to use methyl anacardate. Spectra were determined at 70 eV by direct insertion at *ca.* 170 °C. Accurate masses of the molecular ions were determined for the monoene, diene, and triene.

Methyl (15 : 0)-anacardate: *m/e* 362, 330, 301, 287, 273, 259, 245, 231, 217, 213, 199, 190, 185, 176, 166 (base peak), 165, 162, 161, 148, 147, 146, 134, 120, 106, 104, 90, 82, 80, 76, 68, 56, 54, 43, and 41.

Methyl (15 : 1)-anacardate (monoene): *m/e* 360, 328, 310, 299, 286, 272, 258, 244, 240, 230, 226, 217, 212, 203, 202, 201, 200, 199, 196, 188, 187, 186, 179, 177, 176, 175, 175, 174, 173, 172, 166 (base peak), 165, 163, 162, 161, 149, 148, 146, 136, 135, 134, 133, 122, 121, 120, 110, 109, 108, 106, 98, 97, 96, 92, 81, 69, 57, 55, 43, 41, and 32 (Found, M^+, 360.2665. $C_{23}H_{36}O_3$ requires M, 360.2664).

Methyl (15 : 2)-anacardate (diene): *m/e* 358, 326, 231, 214, 201, 200, 187, 178, 173, 166, 165, 161, 147 (base peak), 134, 121, 109, 107, 105, 95, 93, 91, 81, 79, 77, 69, 67, 55, and 41 (Found, M^+, 358.2552. $C_{23}H_{34}O_3$ requires M, 358.2508).

Methyl (15 : 3)-anacardate (triene): *m/e* 356, 324, 295, 284, 276, 256, 244, 236, 232, 227, 218 (base peak), 205, 201, 200, 187, 178, 175, 173, 166, 165, 162, 161, 160, 159, 149,

* Numbering according to the formulae in Scheme 1 [formula (2) is numbered the same for consistency, and not according to nomenclature].

148, 147, 146, 145, 135, 134, 133, 121, 120, 119, 109, 108, 107, 105, 96, 95, 94, 91, 81, 80, 79, 78, 77, 69, 67, 66, 65, 55, and 41.

We thank Mr. S. P. S. Ahdan for some technical assistance with certain experiments and for repeating others.

[8/1310 *Received*, 14*th July*, 1978]

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