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The Chemistry of Non-Isoprenoid Phenolic Lipids

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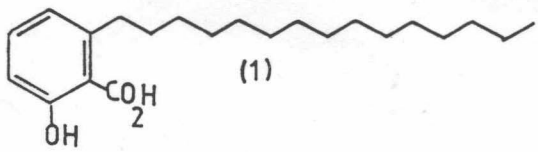
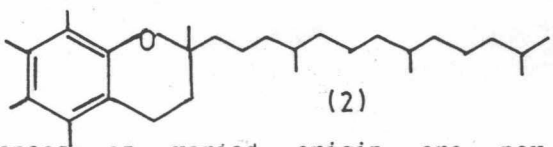
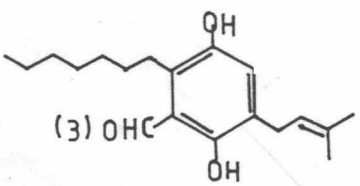
1 INTRODUCTION

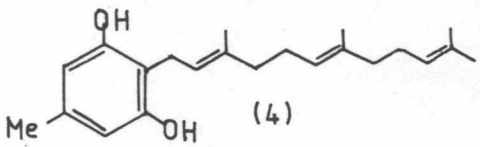
The phenolic lipids generally consist of two types, either of isoprenoid or polyketide origin (ref. 1). This review is concerned with the latter group typified by anacardic acid (1). α-Tocopherol (2) is a representative member of the former group.





Substances of varied origin are now recognised such as flavoglaucin (3) and grifolin (4) (ref. 2),





although these are outside the scope of the present review.

2 NOMENCLATURE

A comprehensive system which takes account of the chain length, double bond position and its stereochemistry is desirable but has not been widely accepted. Trivial and systematic names are both used. Cardanol, one of the more well known of the non-isoprenoid phenolic lipids, is a mixture comprising saturated monoene, diene and triene constituents. The most abundant chain

length in this mixture is C_{15} accompanied by a small proportion of C_{17}. In the technical literature cardanol has been named as having a pentadecadienyl side chain partly because the average unsaturation is dienoid and the heterogeneity of cardanol was not recognised in early chemical studies. A convenient system for the four constituents of cardanol follows fatty acid nomenclature so that the saturated, monoene, diene and triene are (15:0)-, (15:1)-, (15:2)-, and (15:3)-cardanol respectively. A systematic (IUPAC) name for (15:2)-cardanol, which has the cis configuration at the 8- and 11- double bonds, is 3-[(ZZ)-pentadec-8,11-dienyl]phenol or, more specifically but unofficially, 3-[8(Z),11(Z)-pentadecadienyl]phenol. A useful esoteric expedient would be to use the terminology (15:2)-8(Z), 11(Z)-cardanol or (15:2) $^{8(Z),11(Z)}$-cardanol*. Semisystematic names abound as, for example with the cashew phenol, cardol. (15:0)-Cardol is 5-pentadecylresorcinol and in the IUPAC system 1,3-dihydroxy-5-pentadecylbenzene. With the phenolic acids, (15:0)-anacardic acid is 2-hydroxy-6-pentadecylbenzoic acid rather than 6-pentadecylsalicylic acid, although named as a phenol, 2-carboxy-3-pentadecylphenol employs a lower set of numbers. In the present review IUPAC names will be used wherever possible.

3 TYPES OF NON-ISOPRENOID PHENOLIC LIPIDS

3.1 Introduction

It is some years since the chemistry of this group was reviewed (ref.3). In the last decade increasing numbers of the class have been isolated from a wide variety of living sources. As a group they represent a replenishable rather than a fossil-originated source. A new dimension of interest has been added to their chemistry as a biological resource of environmental interest when speculation has been focussed on the probable life expectation of petroleum sources and of petrochemically-derived intermediates.

The non-isoprenoid phenolic lipids have a dual aromatic and

* Generally the practice of inserting a dash above the integer representing the double-bond position has been dispensed with, but see flexirubin, structure 41.

acyclic character and partly in consequence have remained comparatively little known. They occur in several different botanical families, notably in the Anacardiaceae, and exist in tropical, sub-tropical and temperate climates in certain trees, shrubs, small plants as well in some bacterial sources. As benzenoid derivatives they are conveniently grouped for chemical purposes into the classes of phenolic acids, polyhydric, dihydric and monohydric phenols. Tables 1, 2 and 3 summarise some of the information on the naturally-occurring phenolic acids, dihydric (and polyhydric) and monohydric phenols respectively. The botanical (or biological origin), common name, main components, their molecular formulae, literature reference and country of origin have been listed. The next pages summarise some typical structures.

The cashew tree, Anacardinum occidentale, is the most widely distributed source of the phenolic lipid cashew nut-shell liquid, (CNSL), which is a by-product of industrial processing primarily to produce the cashew kernel (ref. 41, 42). Although originally indigenous to Brazil the cashew tree is now grown in many parts of the equatorial and sub-equatorial regions, including areas such as Thailand and Indonesia. Wide aspects of the cultivation of the cashew have been discussed (ref.43). The unusual nature of the raw cashew nut, an external seed of the cashew apple, is shown in Fig. 1. It is kidney-shaped and approximately 2-3 cm in length. The shell comprises some 50% of the weight of the raw nut, the kernel represents 25% and the remaining 25% consists of natural cashew nut shell liquid. This is a reddish brown liquid comprising the anacardic acids (1), (5), (6) and (7), the cardols (15), (16), (17), with R=H, a smaller proportion of 2-methylcardols (15), (16), (17) (with R= Me), cardanols (36), (37), (38), (39) and polymeric material. The kernel itself contains a rich source of protein and a glyceride oil having chiefly the component fatty acids, palmitic and oleic acids. In world production the % cashew is comparable to that of hazel and almond nuts. Table 4 gives projected estimates of the world production of cashew (ref. 43).

TABLE 1 LONG CHAIN PHENOLIC ACIDS (AND DERIVATIVES)

Botanical/ Biological origin	*Common/ Trivial Name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*†	*Country of Origin*
Anacardiaceae						
Anacardium occidentale	Cashew nut, i.e. cashew nut-shell liquid (CNSL)	Anacardic acid (C_{15}) (4 constituents)	(15:0)-Anacardic acid 2-Hydroxy-6-pentadecylbenzoic acid* 2-Hydroxy-6-[(Z)-pentadec-8-enyl]-benzoic acid 2-Hydroxy-6-[(ZZ)-pentadec-8,11-dienyl]-benzoic acid 2-Hydroxy-6-[(ZZ)-pentadec-8,11,14-trienyl]-benzoic acid	1 5 6 7	3	Brazil, Mozambique, India, Tanzania, Kenya, Nigeria, Sri Lanka, Malaysia, Indonesia etc
Anacardium giganteum Hancock	-	Anagigantic acid (C_{11})	2-Hydroxy-6-undecylbenzoic acid	cf.1	4	Brazil
Pentaspadon motleyic Hook	-	Pelandjauic acid (C_{17})	2-Hydroxy-6-[(Z)-heptadec-8-enyl] benzoic acid 2-Hydroxy-6-[(ZZ)-heptadec-8,11-dienyl]-benzoic acid	cf.5 cf.6	5	Australia
Pentaspadon officinalis Holmes	-	Pelandjauic acid (C_{17})	ditto			
Ozoroa mucronata	-	(15:0)-Anacardic acid (15:1) ditto	2-Hydroxy-6-[(Z)-pentadec-10-enyl]benzoic acid	cf.5	6	East Africa
Pistachia vera	Pistachio	(13:0),(13:1), (15:0),(15:1)-Anacardic acid	2-Hydroxy-6-[(Z)-tridec-8-enyl]benzoic acid 2-Hydroxy-6-[(Z)-pentadec-8-enyl]benzoic acid	cf.5 cf.5	7	Iran

*Previously (ref.3) termed 6-pentadecylsalicylic acid.

†The references are a guide to further information rather than a chronology of discovery.

Botanical/ Biological origin	*Common/ Trivial Name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Basidiomycetes						
Merulius	Merulinic acids	(15:1),(17:1)-Anacardic acid	2-Hydroxy-6-[(Z)-heptadec-10-enyl]benzoic acid	cf.5	8	Europe
		(15:1),(17:1)-4-hydroxyanacardic acid	2-Hydroxy-6-[(Z)-14-hydroxypentadec-8-enyl] benzoic acid	8		
		(15:1)-14-hydroxy anacardic acid	2,4-Dihydroxy-6[(Z)-pentadec-8-enyl]benzoic acid	9		
			2,4-Dihydroxy-6[(Z)-heptadec-10-enyl]benzoic acid	10		
Araceae Philodendron scandens		(17:3)-4-hydroxy-anacardic acid	2,4-Dihydroxy-6[heptadecatrienyl]benzoic acid	cf.10	9	Scandinavia
Ginkgoaceae Gymnospermae	Ginkgo biloba (Maidenhair tree)	Ginkgolic acid (C_{15})	2-Hydroxy-6-[(Z)-pentadec-8-enyl]benzoic acid	cf.5	10	China, Europe, Japan
		Ginkgolinic acid (C_{14})	2-Hydroxy-6-tetradecylbenzoic acid	cf.1		China
Compositae Chrysanthemum frutescens	Marguerite	Frutescin and relatives (C_6)	Methyl 2-methoxy-6-(hexa-2,4-diynyl)benzoate	11	11	Europe, North America
		Demethyl-frutescin (C_5)	Methyl 2-methoxy-6-(penta-2,4-diynyl)benzoate	12		
Lichens Sphaerophorin cetraria	Depsides	Microphyllinic acid		13	12	Worldwide

TABLE 2 LONG CHAIN DIHYDRIC PHENOLS

Botanical/ Biological origin	*Common/ Trivial name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Anacardiaceae						
Anacardium occidentale	Cashew nut-shell liquid (CNSL)	Cardol (R=H) (4 constituents)	1,3-Dihydroxy-5-pentadecylbenzene	14	3	As for anacardium occidentale (Table 1)
			1,3-Diydroxy-5-[(Z)-pentadec-8-enyl] benzene	15	13	
			1,3-Dihydroxy-5-[(ZZ)-pentadec-8,11-dienyl]benzene	16		
			1,3-Dihydroxy-5-[(ZZ)-pentadec-8,11,14-trienyl]benzene	17		
		2-Methylcardol (R=Me) (4 constituents)	As for cardol, e.g. 1,3-Dihydroxy-2-methyl-5-pentadecylbenzene	cf.14-17		
Rhus vernicifera	Japanese lac Chinese lac	Urushiol	1,2-Dihydroxy-3-pentadecylbenzene	18	14	China, Korea, Japan
			1,2-Dihydroxy-3-[(Z)-pentadec-8-enyl] benzene	19	15	
			1,2-Dihydroxy-3-[(ZZ)-pentadec-8,11-dienyl]benzene	20		
			1,2-Dihydroxy-3-[(ZZZ)-pentadec-8,11,13-trienyl]benzene	21		
			1,2-Dihydroxy-3-[(ZZ)-pentadec-8,11,14-trienyl]benzene	22		
Rhus toxicodendron radicans	Poison ivy	Urushiol	As for Japanese lac except (21) not present	-	16	North America
Rhus toxicodendron diversilobum	Poison oak	Urushiol	As for poison ivy	-	16	North America
Smodingium argutum			Related to urushiol		*	South Africa
Anacardium semecarpus	Indian marking nut (BNSL)	Bhilawainol	Related to urushiol	-		India

* C.P. Gorst-Allman, P.S. Steyn, T. Heyl, M.J. Wells and D.M.C. Fourie, S. Afr. J. Chem., 1987, 40, 82.

Botanical/ Biological origin	*Common/ Trivial name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Melannorrhea usitata Wall	Burmese lac tree	Thitsiol	1,2-Dihydroxy-4-pentadecylbenzene and corresponding unsaturated constituents as for urushiol	23	17	Burma
			1,2-Dihydroxy-4-heptadecylbenzene and corresponding unsaturated constituents as for urushiol	cf.23	***	
			1,2-Dihydroxy-3-(10-phenyldecyl)benzene	24	18	
			1,2-Dihydroxy-3-(12-phenyldodecyl)benzene	25		
Gluta renghas	-	Glutarenghol	1,2-Dihydroxy-3-[(Z)-heptadec-10-enyl]-benzene *	cf.19	19	
Semecarpus heterophylla	Renghas fruit	Renghol	As for glutarenghol		20	
Semecarpus vernicifera	Formosan lac	Laccol	As for glutarenghol		21	Formosa
			1,2-Dihydroxy-3-[(ZZ)-heptadec-10,13,16-trienyl]benzene *	cf.22		
Rhus succendanea	Indochinese lac Vietnam	-	-			Vietnam
Proteacae						
Grevillea pyramidalis	-	A cardol monoene	1,3-Dihydroxy-5-[(Z)-pentadec-10-enyl]-benzene	cf.15	22	N.W. Australia
Grevillea banksii	-	-	1,3-Dihydroxy-5-undecylbenzene (C_{11}), C_{13} and C_{15} analogues	cf.14	23	Australia
			1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl]-benzene **	cf.15		
			1,3-Dihydroxy-5-[(Z)-pentadec-10-enyl]-benzene **	cf.15		

*Stereochemistry not known for certain

** " " " " " (but probably z)

*** ref. 85

Botanical/ Biological origin	*Common/ Trivial name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Grevillea hilliana	-	-	Similar to G. banksii and C_{17}, C_{19} analogues with unsatn. at 10 position*	cf.15	23	Australia
Grevillea pteridifolia	-	-	Similar to G. banksii but with (17:0)*		23	Australia
Grevillea robusta	Grevillol	-	1,3-Dihydroxy-5-tridecylbenzene	cf.14	23	Australia
Cardwellia sublimis Hakea persihana Opisthiolepis heterophylla	-	-	Many related components to the above		23	Australia
Persoona elliptica	Persoonal	-	1,3-Dihydroxy-5-[(Z)-undec-3-enyl]-benzene	cf.15	24	Australia
Hakea trifurcata Hakea amplexicaulis	-	-	1,3-Dihydroxy-5-[(Z)-heptadec-8-enyl]-benzene	cf.15	25	Australia
			1,3-Dihydroxy-5-[(ZZ)-heptadec-8,11-dienyl]-benzene	cf.16		
			1,3-Dihydroxy-5-pentadecylbenzene	14		
Graminae						
Cereale secale	Rye	-	1,3-Dihydroxy-5-pentadecylbenzene (C_{15}), C_{17},C_{19},C_{21},C_{25}*	14	28	Europe
			Monoenes corresponding to above			
			C_{13},C_{15},C_{17},C_{19},C_{21},C_{23} dienes corresponding to above*	cf.15		
Graminae	Barley grains	-	1,3-Dihydroxy-5-alkylbenzenes (C_{25},C_{27},C_{29}, C_{31})	cf.16	29	UK

*Position and sterochemistry of double bonds not known.

Botanical/ Biological origin	*Common/ Trivial name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Triticum						
Triticum vulgare	Wheat bran phenols	-	1,3-Dihydroxy-5-nonadecylbenzene 1,3-Dihydroxy-5-heneicosylbenzene	cf.14 cf.14	27	United States
Myrisinaceae						
Rapanea laetevirens	-	-	1,3-Dihydroxy-alkylbenzenes		30	
Anacardiaceae						
Mangifera indica	Mango	-	1,3-Dihydroxy-5-[(Z)-heptadec-2-enyl]-benzene	cf.14	31	India
Araceae						
Philodendron scandens	-		1,3-Dihydroxy-5-[heptadec-8,11,14-trienyl] benzene 2,4-Dihydroxy-6-[heptadecatrienyl]benzoic acid	cf.17	9	Scandinavia
Gymnospermae						
Ginkgo biloba	-	Bilobol	1,3-Dihydroxy-5-[(Z)-pentadec-8-enyl]-benzene	15	10	China, Japan, Europe
Melastomaceae						
Miconia sp.	Miconidin	-	1,4-Dihydroxy-2-methoxy-6-pentylbenzene	26	32	Brazil
Zingiberaceae						
Zingiber officinale Roscoe	Gingerol	-	1-Hydroxy-2-methoxy-4-(5-hydroxy-3-oxodo-decyl)benzene*	27	35	Japan
	Shogaol		1-Hydroxy-2-methoxy-4-(3-oxo-dec-4-enyl) benzene*	28		
	Zingerone		1-Hydroxy-2-methoxy-4-(3-oxobutyl)benzene	29		
Algae						
Cystoseria spinosa (var. squarrosa)	Brown algae	Alkenyl hydroquinon			33	Italy

*Gingerol and shogaol are shown as C_{10} compounds in Cancer Letters, 1987, 36, 221-331.

Botanical/ Biological origin	*Common/ Trivial name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Cystophora torulosa	Brown algae	-	1,3-Dihydroxy-5-[(ZZZZ)-heptadec-5,8,11,14-tetraenyl]benzene	30	34	Australia
			1,3,5-Trihydroxy-2-[(ZZZZ)-octadec-1-oxo-6,9,12,15-tetraenyl]benzene	31		
Sorghum bicolor	Sorghum (natural host)	-	5-Methoxy-3-[(Z,Z)-pentadec-8,11,14-trienyl]-1,2,4-trihydroxybenzene	42	*	N. America
Bacterial						
Mycobacterium leprae	α- and β-leprosol	-	1-Hydroxy-3-methoxy-4,6-dimethyl-5-heptadecylbenzene (and C_{15} analogue)	32	36	Europe
			1,3-Dihydroxy-2,6-dimethylpentadecylbenzene	33		
Bacterium pseudomonas sp. B-9004	-	2,5-dialkyl resorcinol	1,3-Dihydroxy-5-hexyl-2-propylbenzene	34	37	Japan
Lepidoptera						
Anagasta kueniella	Insect source	-	2-[(Z)-octadec-1-oxo-8-enyl]-1,3-dioxo cyclohexane and 4-hydroxy analogue of the above	35	38	Western Europe

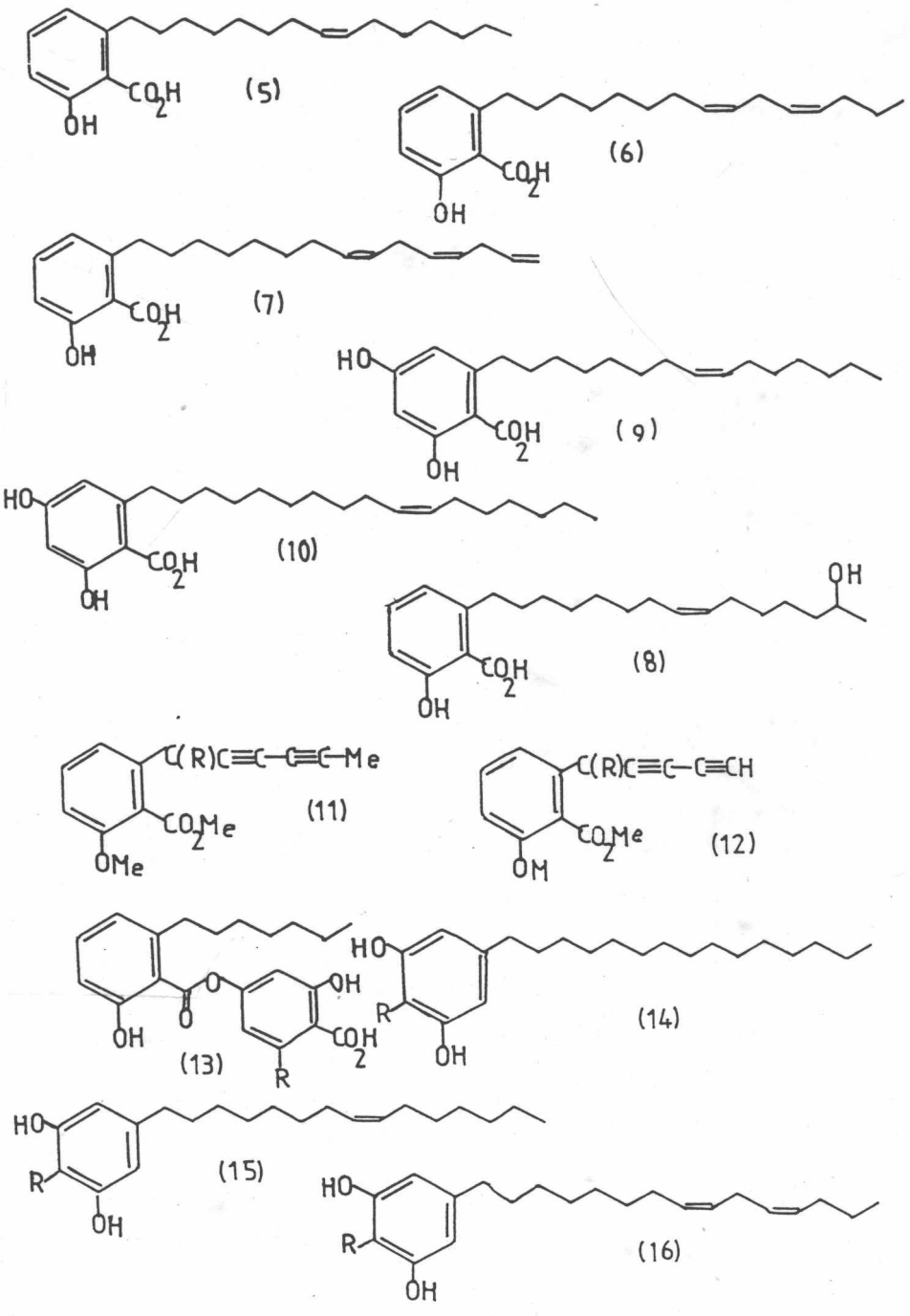
* M. Chang, D.H. Netzly, L.G. Butler and D.G. Lynn, J. Amer. Chem. Soc., 1986, 108, 7858.

TABLE 3 LONG CHAIN MONOHYDRIC PHENOLS

Botanical/ Biological origin	*Common/ Trivial Name*	*Main Component (side chain)*	*Formula*	*Structure*	*Ref.*	*Country of Origin*
Anacardiacae						
Anacardium occidentale	Cashew nut-shell liquid	Cardanol (C_{15}) (4 constituents)	3-Pentadecylphenol 3-[(Z)-pentadec-8-enyl]phenol 3-[(ZZ)-pentadec-8,11-dienyl]phenol 3-[(ZZ)-pentadec-8,11,14-trienyl]phenol	36 37 38 39	3	As for anacardium occidentale (Table 1)
Campnospermum auriculata	-	Campnospermanol	3-[(Z)-nonadec-2-oxo-9-enyl]phenol	40	39	Australia, Solomon Islands
Ginkgoaceae Gymnospermae	Ginkbo biloba (Maidenhair tree)	Ginkgol	3-[(Z)-pentadec-8-enyl]phenol	37	10	China, Europe, Japan
Bacterial Cytophaga Flexibacter elegans	Flexirubin, gliding bacterium	-	2'-n-Dodecyl-3'-hydroxy-5'-methylphenyl* 1-[3"-Methyl-4"-hydroxyphenyl-1"]heptadeca-1(E),3(E),5(E),7(E),9(E),11(E),-13(E),15(E)-heptaenyl-17-oate	41	40	Europe

[*2-Dodecyl-3-hydroxy-5-methylphenyl 17-(4-hydroxy-3-methylphenyl)heptan dec-2(E), 4(E), 6(E), 8(E), 10(E), 12(E), 14(E), 16(E)-oate]

Formulae of Some Non-isoprenoid Phenolic Lipids



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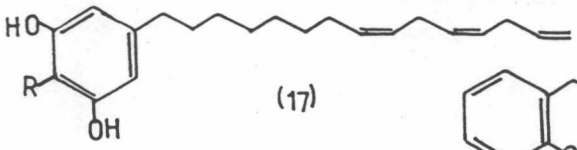

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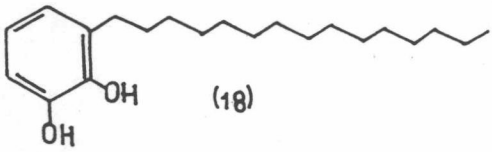

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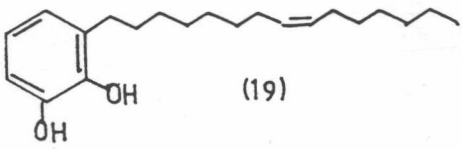

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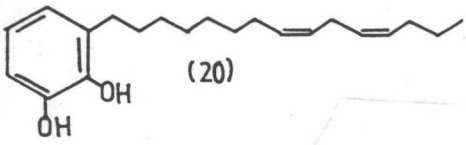

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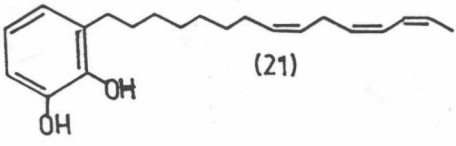

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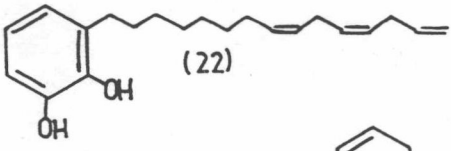

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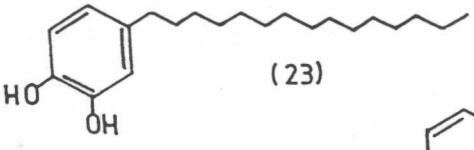

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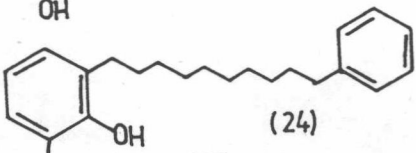

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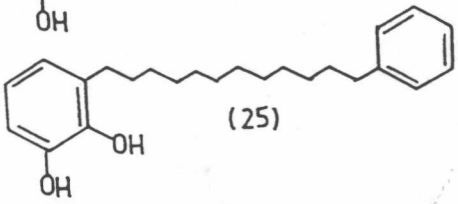

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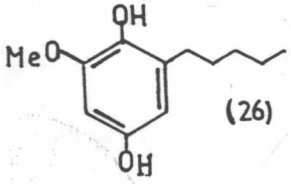

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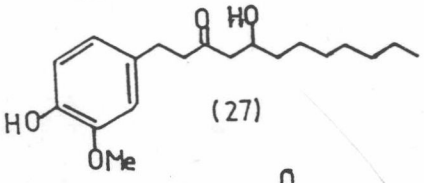

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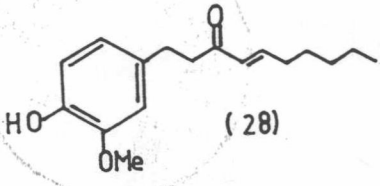

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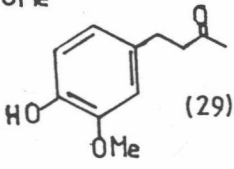

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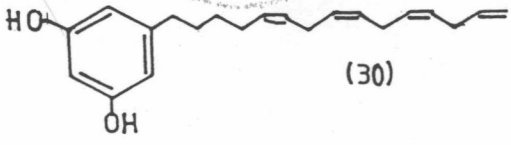

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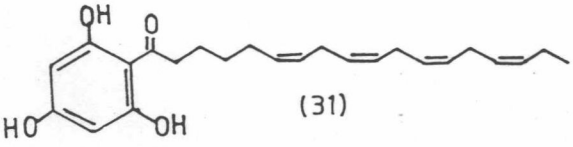


(31)

Formulae of Some Non-isoprenoid Phenolic Lipids

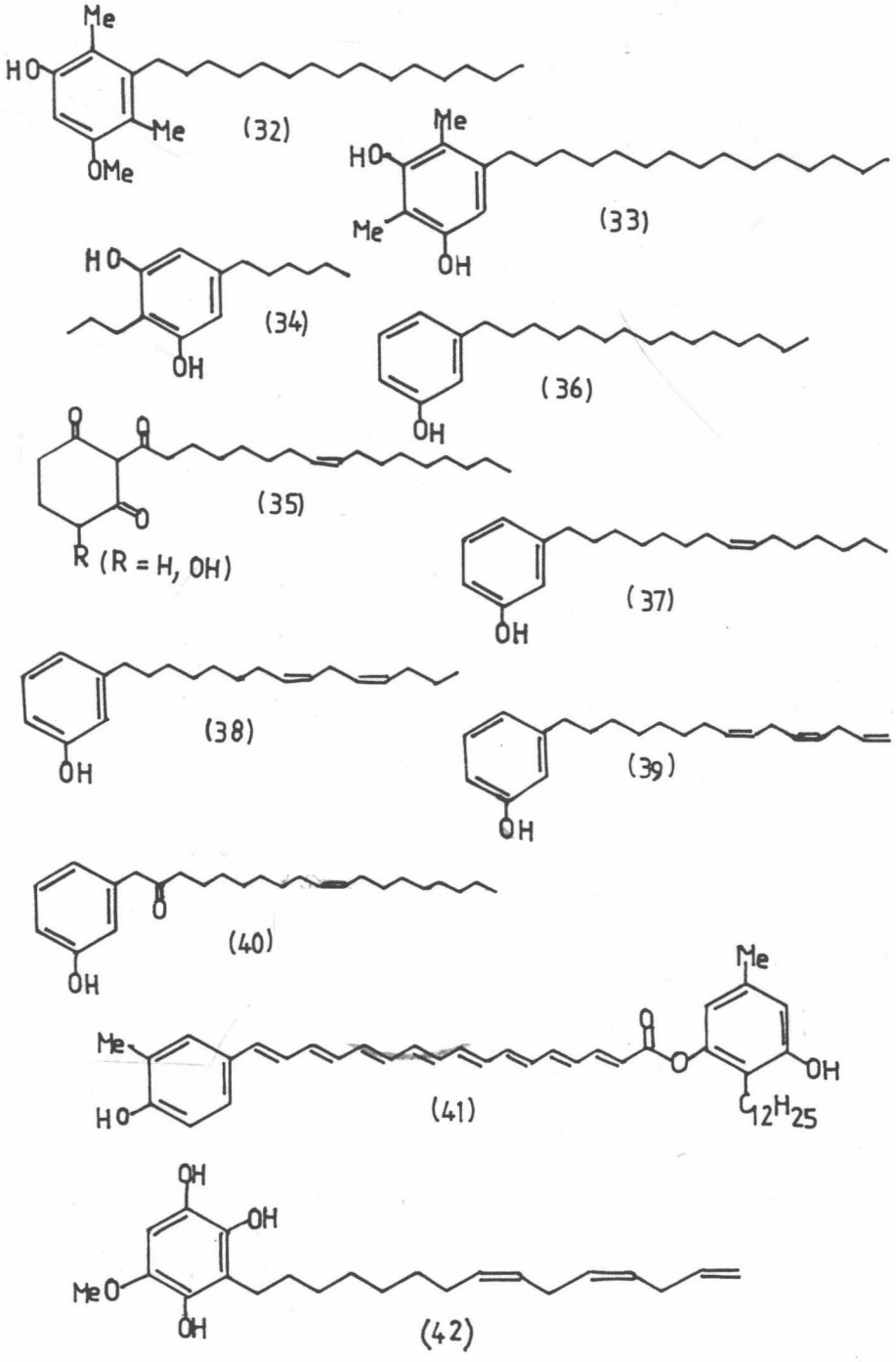
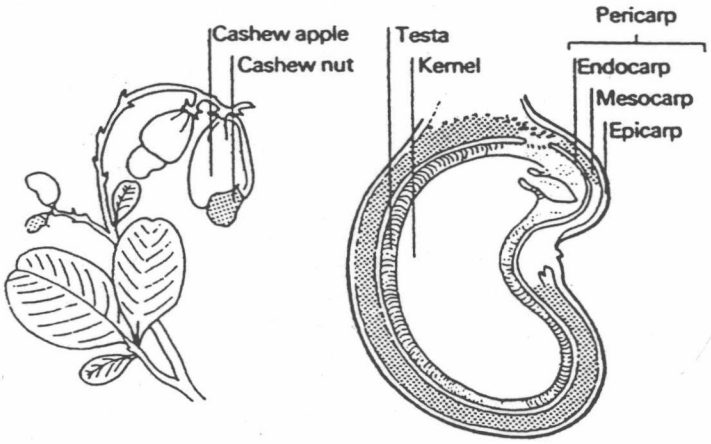


Fig 1. **(left) Diagrammatic view of a cashew branch; (right) cross-section of a cashew nut**



(Adapted from ref. 3 by kind permission of the Roy. Soc. Chem.)

Table 4

Estimated World Production of Raw Cashew Nuts (1000 tons) excluding home consumption

Year	World	Mozambique	Tanzania	India	Brazil	Kenya	Madagascar
1955	125	54	18	47	2	2	-
1960	160	63	37	50	2	5	-
1955	280	119	65	80	4	8	-
1970	370	115	110	95	31	13	1
1975	470	166	115	110	44	22	5
1980	535	145	122	130	84	30	10
1985	750	215	135	130	207	35	15
1990	910	235	222	130	229	40	20
1995	1,000	255	240	140	260	45	25
2000	1,120	300	250	150	284	50	30
2005	1,260	350	280	175	290	50	40

(By kind permission of J.G. Ohler (ref. 43), Royal Tropical Institute, Amsterdam)

3.2 Phenolic Acids

In this group (Table 1) the members are long chain salicylic acids having in general C_{13}, C_{15}, and C_{17} alkyl groups with varying levels of unsaturation. During the last decade several new anacardic acids have been isolated from the sources Ozoroa Mucronata and Pistachia vera. From the fungal Merulius species

long chain orsellinic acids have been obtained, the first naturally-occurring members of this class to be found.

Conjugated acetylenic C_5 and C_6 derivatives have been discovered in species from Compositae. The lichens contain as building units for the depsides a number of shorter side chain anacardic acids. Microphyllinic acid is an ester of 2-hydroxy 6-(2-oxoheptyl)benzoic acid with the corresponding orsellinic acid analogue.

3.3 Dihydric Phenols

This class, some of which are listed in Table 2, comprises 1,2-dihydroxy 1,3-dihydroxy and 1,4-dihydroxybenzenes with alkyl and alkenyl side chains. The group has a wider distribution than the phenolic acids probably because the precursor orsellinic acids (see section on biosynthesis) are more readily decarboxylated than the anacardic acids. In recent years Myrisinaceae, Melastomaceae and numerous other living sources in addition to the Anacardiaceae, Graminae, Protaceae, have been found to contain a variety of dihydric phenols. Outstandingly, a diverse range has been uncovered in many species from Australia (ref. 23). Very largely the compounds are homologous variants of the cardols from cashew having C_{11}, C_{13} C_{17} side chains. The occurrence of 5-alkyl and alkenylresorcinols in rye (Cereale secale) (ref. 28) is reminiscent of the related wheat bran phenols where only the saturated compounds have been found (ref. 27) as with barley (ref 29). The role of these compounds and their possible significance in nutrition has yet to be explained. Among the catechols, the urushiols (18), (19), (20), (21) and (22) in Rhus vernicifera and Rhus toxicodendron have been well studied in the extensive research of Majima (ref. 14). Japanese lac from Rhus vernicifera is probably the oldest known cultivated source of phenolic lipid, having been used since the 6th century. The structures and composition of lacs from other countries have been less studied. Alkylcatechols with a terminal phenyl group in the side chain bearing a superficial resemblance to flexirubin from bacterial sources, have been isolated from the Burmese lac tree (ref. 18). An unusual member of the catechol family is gingerol (ref. 35) from the rhizome of the ginger plant.

Highly unsaturated alkyl resorcinols and a phloroglucinol