Phytochemistry, Vol. 21, No. 12, pp. 2783–2813, 1982.
Printed in Great Britain.

0031-9422/82/122783-31$15.50/0

THE PHYTOCHEMISTRY OF THE ANNONACEAE

M. LEBOEUF, A. CAVÉ, P. K. BHAUMIK*, B. MUKHERJEE* and R. MUKHERJEE†‡

Laboratoire de Pharmacognosie, E.R.A. 317 C.N.R.S., Faculté de Pharmacie, 92290 Chatenay-Malabry, France; *Department of Pharmacology, B. C. Roy Postgraduate Institute of Basic Medical Sciences, Calcutta 700020, India; †Faculdade de Farmacia, Universidade Federal do Rio Grande do Sul, 90000 Porto Alegre, Brazil

(*Revised received* 1 *March* 1982)

Key Word Index—Annonaceae; alkaloids; non-alkaloidal compounds; structure; natural distribution.

Abstract—Both alkaloidal and non-alkaloidal compounds so far isolated from Annonaceous plants are reviewed. 319 secondary products have been reported from 150 species belonging to 41 genera. Due to the chemotaxonomic and pharmacological interest of some of these compounds, chemical investigations on this topic have grown considerably in the last decade.

INTRODUCTION

Annonaceae is a large family comprising *ca* 120 genera and more than 2000 species. Economically the family is of appreciable importance as a source of edible fruits; the pawpaw (*Asimina*), cherimoya, sweetsop, soursop, custard apple and ilama (*Annona*), and plants of the genera *Cananga* and *Rollinia* are grown for their edible fruits [1]. Oils from seeds of some plants may be used for the production of edible oils [2] and soap [3]; woods of some Annonaceous plants have been employed for alcohol production [4]. Fragrant flowers of ylang-ylang (*Cananga odorata*) are an important raw material for perfumery [5]. Finally, many members of this family are used in folk medicine for various purposes.

Chemical studies—and to a lesser extent pharmacological studies—on Annonaceous plants have been intensified in the last decade, though pioneering work started long ago. It is striking, however, as recently pointed out by Waterman [6], that "for its size the Annonaceae is perhaps one of the chemically least known families". Most investigations have centred upon alkaloids, but Annonaceae also produce a wide range of non-alkaloidal compounds belonging to various phytochemical groups. It is clear that the family now requires thorough phytochemical investigations in search of medicinally important as well as chemically interesting compounds. To proceed with this project, one should be aware of the complete work so far done on this family. This review has been designed to meet that need.

‡Present address: Hodag Chemical Corporation, Skokie, IL 60076, U.S.A.

BOTANICAL FEATURES OF THE ANNONACEAE

Herein only the main botanical features will be described that are characteristic of the family Annonaceae [1, 7–14].

Distribution and origin

The Annonaceae is a large family of aromatic trees, shrubs, or climbers, which occur in tropical and subtropical regions. In the tropics of the Old World, they are usually of climbing or straggling habit and occur in lowland dense evergreen forest, but in tropical America they are nearly all shrubby or arboreal and grow mostly in the open grassy plains [12]. The only genus extending into the temperate zone is *Asimina*, which occurs in North America as far north as the Great Lakes [12].

According to Takhtajan, 51 genera and *ca* 950 species are confined to Asia and Australasia, whereas in Africa and Madagascar there are 40 genera with *ca* 450 species, and on the American continent 38 genera and 740 species [7, 8]; thus, Asia together with Australasia is the basic centre of the distribution of the Annonaceae. Takhtajan views this part of the world as the native region of Annonaceae [7], whereas Walker and more recently Le Thomas hypothesize, from phytogeographical and palynological data, a South American or an African origin for the family [15].

Diagnostic features

On the basis of morphology and habitat, the Annonaceae is a very homogeneous plant family [10]. All but one species are trees or shrubs, sometimes climbing, usually evergreen, with resin canals and septate pith in the stems [1]. The leaves are alternate,

Table 1. List of genera and approximate number of species in the Annonaceae

Afroguatteria Boutique (2)
Alphonsea Hook. f. & Thoms. (30)
Ambavia Le Thomas (2)
Anaxagorea A. St. Hil. (30)
Annona L. (120)
Anomianthus Zoll. (1)
Anonidium Engl. & Diels (5)
Ararocarpus Scheff. (1)
Artabotrys R. Br. (≈ 100)
Asimina Adans. (8)
Asteranthe Engl. & Diels (2)
Atopostema Boutique (2)

Balonga Engl. & Diels (1)
Bocagea A. St. Hil. (2)
Bocageopsis R. E. Fries (3)
Boutiquea Le Thomas (1)

Cananga Hook. f. & Thoms. (2)
Cardiopetalum Schlecht. (1)
Cleistochlamys Oliv. (1)
Cleistopholis Pierre (5)
Crematosperma R. E. Fries (17)
Cyathocalyx Chapm. ex Hook. f. & Thoms. (38)
Cyathostemma Griff. (8)
Cymbopetalum Benth. (12)

Dascoclema Sincl. (1)
Dasymaschalon (Hook. f. & Thoms.) Dalla Torre & Harms (15)
Deeringothamnus Small (2)
Dennettia Bak. f. (1)
Desmopsis Safford (15)
Desmos Lour. (30)
Diclinanona Diels (2)
Dielsiothamnus R. E. Fries (1)
Disepalum Hook. f. & Thoms. (6)
Drepananthus Maing. ex Hook. f. = *Cyathocalyx* Champ. ex Hook. f. & Thoms.
Duckeanthus R. E. Fries (1)
Duguetia A. St. Hil. (70)

Ellipeia Hook. f. & Thoms. (3)
Ellipeiopsis R. E. Fries (2)
Enantia Oliv. (9)
Enicosanthum Becc. (16)
Enneastemon Exell. (15) = *Monanthotaxis* Baill.
Ephedranthus sp. Moore (4)
Exellia Boutique (1)

Fenerivia Diels = *Polyalthia* Bl.
Fissistigma Griff. (≈ 70)
Fitzalania F. Muell. (1)
Friesodielsia Van Steenis (55)
Froesiodendron R. E. Fries (2)
Fusaea (Baill.) Safford (3)

Gilbertiella Boutique (1)
Goniothalamus Hook. f. & Thoms. (115)
Guamia Merr. (1)
Guatteria Ruiz. & Pav. (≈ 250)
Guatteriella R. E. Fries (1)
Guatteriopsis R. E. Fries (4)

Haplostichanthus F. Muell. (1)
Heteropetalum Benth. (2)
Hexalobus A. DC. (5)
Hornschuchia Nees (3)

Isolona Engl. (20)

Kingstonia Hook. f. & Thoms. (1)

Letestudoxa Pellegr. (2)
Lettowianthus Diels (1)

Malmea Fries (13)
Marsypopetalum Scheff. (1)
Meiocarpidium Engl. & Diels (2)
Meiogyne Miq. (10)
Melodorum Lour. (3)
Mezzettia Becc. (7)
Mezzettiopsis Ridl. = *Orophea* Bl. Bijdr.
Miliusa Leschen ex A. DC. (40)
Mischogyne Exell. (2)
Mitrella Miq. (5)
Mitrephora Hook. f. & Thoms. (25)
Mkilua Verdc. (1)
Monanthotaxis Baill. (56)
Monocarpia Miq. (1)
Monocyclanthus Keay (1)
Monodora Dun. (20)

Neostenanthera Exell. (10)
Neouvaria Airy-Shaw (2)

Oncodostigma Diels (3)
Onychopetalum R. E. Fries (3)
Ophrypetalum Diels (1)
Oreomitra Diels (1)
Orophea Bl. (60)
Oxandra A. Rich. (22)
Oxymitra (Blume) Hook. f. & Thoms. = *Friesodielsia* Van Steenis

Pachypodanthium Engl. & Diels (4)
Papualthia Diels (20)
Petasolophus K. Schum. (1)
Phaeanthus Hook. f. & Thoms. (20)
Piptostigma Oliv. (15)
Platymitra Boerl. (2)
Polyalthia Bl. (120)
Polyaulax Backer (1)
Polyceratocarpus Engl. & Diels (5)
*Popowia** Endl. (50)
Porcelia Ruiz & Pav. (5)
Pseudannona (Baill.) Safford = *Xylopia* L.
Pseudartabotrys Pellegr. (1)
Pseudoxandra R. E. Fries (6)
Pseuduvaria Miq. (17)

Raimondia Safford (2)
Rauwenhoffia Scheff. (5)
Reedrollinsia J. Walker (1)
Richella A. Gray (22)
Rollinia A. St. Hil. (65)
Rolliniopsis Safford (5)
Ruizodendron R. E. Fries (1)

Table 1. (*Contd*)

Saccopetalum Bennett = *Miliusa* Leschen ex A. DC.	*Unona*† Hook. f. & Thoms. = *Desmos* Lour.
Sageraea Dalzell (9)	*Unonopsis* R. E. Fries (27)
Sapranthus Seem. (9)	*Uvaria* L. (150)
Schefferomitra Diels (1)	*Uvariastrum* Engl. (7)
Soala Blanco (1)	*Uvariella* Ridley = *Uvaria* L.
Sphaerocoryne Scheff. ex Ridley = *Melodorum* Lour.	*Uvariodendron* (Engl. & Diels) R. E. Fries (12)
Stelechocarpus Hook. f. & Thoms. (5)	*Uvariopsis* Engl. (12)
Stenanona Standley (2)	
Tetrameranthus R. E. Fries (2)	
Tetrapetalum Miq. (2)	*Woodiella* Merr. (1)
Thonnera De Wild. = *Uvariopsis* Engl.	
Toussaintia Boutique (1)	
Tridimeris Baill. (1)	
Trigynaea Schecht. (5)	*Xylopia* L. (≈ 100–150)
Trivalvaria Miq. (5)	*Xylopiastrum* G. Rob. = *Xylopia* L.

*African species of *Popowia* are now regarded as *Monanthotaxis*.

†Under the name *Unona*, have been described many species of Annonaceae subsequently connected with the genera *Guatteria*, *Polyalthia*, *Popowia*, *Uvaria* and *Xylopia*.

entire, exstipulate; they are often recognizable in the field by a glaucous or metallic sheen. The fragrant flowers frequently open before all the parts are fully developed; they are terminal, leaf-opposed or axillary, solitary or crowded, hermaphrodite or rarely unisexual, regular, mostly trimerous; the perianth is usually in three whorls of three (sepals persistent or deciduous; petals generally six in two series, rarely in two series of two or the inner series absent); the stamens are usually numerous, hypogenous, spirally arranged; the carpels are generally numerous and free, very rarely united in a one-celled ovary with parietal placentas. Fruiting carpels are sessile or stipitate, mostly indehiscent; the fruit is usually an aggregate of berries, but in a few genera, specially *Annona*, the berries coalesce with an edible fleshy receptacle and the fruits are worth eating. The seeds have a copious, ruminate endosperm and a minute embryo; some of the seeds develop an aril after fertilization.

Briefly, Annonaceous plants are recognized, in tropical and subtropical regions, by the alternate, exstipulate leaves, mostly trimerous flowers, numerous and often truncate free stamens, free carpels, and seeds with ruminate endosperm [1, 9–11].

Classification

The Annonaceae are characterized by a great many extremely primitive and archaic features (i.e. primitive flowers with indefinite numbers of free floral parts and spirally arranged stamens, free carpels, etc.); they are what Darwin called "living fossils", which, through some favourable circumstance, have escaped extinction and survived to the present day [7]. According to Takhtajan, Annonaceae are included within the order Magnoliales (Annonales), with the most primitive families of angiosperms: Winteraceae, Magnoliaceae, Degeneriaceae, Himantandraceae, Eupomatiaceae, Canellaceae and Myristicaceae. The Annonaceae are related to the Magnoliaceae, but noticeably more advanced. The order Magnoliales itself is allied to more advanced orders: Laurales, Piperales, Aristolochiales, Ranunculales, Papaverales [7]. As will be seen later, these phylogenetic relationships are in many cases correlated by chemotaxonomic connections. Recently, the significance of pollen characters for the phylogeny of the Annonaceae has been discussed [15].

Although its limits are well defined, the Annonaceae is notoriously difficult to divide into natural groupings of genera [8, 10, 12, 13]. Two African genera, *Monodora* and *Isolona*, have syncarpous ovaries and are separable as the subfamily Monodoroideae. The other subfamily, Annonoideae, includes all other genera and is divided variously into tribes and subtribes [8, 10, 12, 13].

Table 1 gives an alphabetical list* of accepted valid genera of Annonaceae, as understood at present [8, 14]; against each genus is shown, in parentheses, the approximate number of species. Classification is still not clear, since delimitation of genera varies in different treatments. Not all synonyms are included, but in a few cases important synonyms are given.

NON-ALKALOIDAL CONSTITUENTS OF ANNONACEAE

The non-alkaloidal constituents of Annonaceae considered here are carbohydrates, lipids, amino acids and proteins, polyphenols, essential oils, terpenes and aromatic compounds. A large number of studies have been done on the sugars, lipids and proteins contained in the fruits and seeds of certain species of *Annona*, due to their nutritional and economic importance. Readers interested in early studies are invited to consult the *Lynn Index* [16] and the works of Hegnauer [17] and of Gibbs [18] which give the original references.

Carbohydrates

Carbohydrates were found in the fruits of *Annona cherimolia* [16], the seeds of *A. reticulata* [17] and

*The authors sincerely thank Dr. A. Le Thomas (Museum d'Histoire Naturelle, Paris) and Dr. R. S. Raghavan (Royal Botanic Gardens, Kew), for their kind help in drawing up this list.

leaves of *A. senegalensis* [19]. Reducing sugars have been obtained from pulp-peel of *A. cherimolia* [20], sucrose (**1**) from the pulp of *A. cherimolia* [20] and in the edible portion of the fruit of *A. squamosa* [21], glucose (**2**) from the fruit of *A. squamosa* [21] and the leaves of *A. muricata* [22], fructose (**3**) from the fruit of *A. squamosa* [21], starch (**4**) and pectin (**5**) from the pulp of *A. cherimolia* [16], starch (**4**) and mucilage (**6**) from the fruit of *Xylopia longifolia* [16]. Analysis of the seed coat of *Annona cherimolia* yielded uronic acid derivatives together with polymeric esters and ethyllignin [23, 24].

The sucrose (**1**), glucose (**2**) and fructose (**3**) content of the fruits of *Annona muricata* [25], and the starch (**4**) content of *A. reticulata* [26] have been determined. These sugars, along with a galactan (**7**) and a xylan (**8**) have been obtained from the seeds of *Polyalthia longifolia* [27].

Analysis of the composition of amyloid (**9**), an alkali-soluble polysaccharide, from seeds of *Annona muricata* [28], revealed that in its structure and properties, *Annona*-amyloid is intermediary between cellulose and *Tamarindus*-amyloid and it is likely that the amyloids from the species of Annonaceae all have similar intermediary constitutions. The structure of galactomannan (**10**) isolated from seeds of *Annona muricata* has been established [29] and it was found that this galactomannan is of the leguminous type, the molecules having main chains consisting of (1→4)-linked β-D-mannose residues, with side chains made of single α-D-galactose residues linked to the main chains by (1→6) bonds.

A systematic survey of scyllitol (**11**) in plants has revealed its occurrence in two of the six Annonaceae studied, namely *Annona cherimolia* [30] and *A. muricata* [31].

Lipids

Oils and fatty acids have also been isolated from fruits and/or seeds of *Annona cherimolia* [16, 20], *A. muricata* [16], *A. reticulata* [16, 17], *A. squamosa* [3, 16, 32], *Asimina triloba* [16], *Dennettia tripetala* [33], *Xylopia aethiopica* [34], *X. brasiliensis* [35], *X. longifolia* [16], and from leaves of *Annona muricata* [22] and *A. senegalensis* [36].

Constituents of the leaf wax of *Annona senegalensis* were also investigated [36]; saturated and unsaturated fatty acids, primary alcohols of C_{28}, C_{30}, C_{32}, palmitone, and yellow sesquiterpene oil, have been reported.

The possible economic importance as edible oil sources of the seeds of some Annonaceae from Zaire (*Annona muricata*, *Annona senegalensis*, *Annonidium mannii*, *Cleistopholis glauca*, *Monodora myristica*, *Pachypodanthium staudtii*, *Rollinia mucosa*) has been investigated [2]; their oil content as well as their composition of fatty acids and unsaponifiable matter have been determined. *Annona muricata*, *A. senegalensis* and *Monodora myristica* could be used to provide edible oils, if the refinery process eliminates some possibly toxic constituents of the oil of *Annona muricata* or the strong taste of the oil from *Monodora myristica* [2].

Studies on the various fatty acids contained in the oils extracted from the seeds and/or the fruits of *Anaxagorea javanica* [37], *Annona cherimolia* [38–40] *A. muricata* [41], *A. squamosa* [42], *Asimina triloba* [43, 44], *Cananga odorata* [37], *Monodora myristica* [34] and *Xylopia aethiopica* [34], show that they are semi-drying oils, in which predominate, in varying proportions, oleic and linoleic acids; saturated acids (myristic, palmitic, stearic, arachidic acids). Other unsaturated acids (palmitoleic and linolenic acids) exist only in small or trace amounts.

Glycerides of one or more hydroxylated fatty acids of unusually high MW, possessing toxic and insecticidal properties, have been reported from the seeds of several species of *Annona*, especially *A. reticulata* [45]. Furthermore, the oil-rich seeds of *Cymbopetalum penduliflorum* have been found to contain trypsin inhibitors [46].

Amino acids and proteins

From the fruit pulp of *Annona cherimolia* proteins have been isolated [20]. *Annona squamosa* [47] yielded 14 amino acids, of which citrulline and γ-aminobutyric acid predominated. The presence of large amounts of free citrulline, ornithine and arginine is peculiar and seems to be of metabolic interest [47]. Asparagine, histidine, alanine, tyrosine and lysine have been isolated from fruits of the same plant [21], whereas in the seeds 16 amino acids were detected [48, 49]. In the fruits of *Annona muricata* 11 amino acids were found, of which proline and γ-aminobutyric acid were the most important [47]. Analysis of the leaves of *Annona senegalensis* also revealed the presence of 10 amino acids [19]. Analysis of protein of the seeds of *Asimina triloba* [50] revealed that it has a relatively high content of arginine, glutamic acid, glycine and leucine [44].

The amino acids content of leaves, stem-bark and root-bark has been studied in five species of Annonaceous plants: *Annona* cv. *crassiflora*, *Annona paludosa*, *Fusaea longifolia*, *Unonopsis guatterioides* and *Xylopia longifolia* [51]: arginine, histidine, lysine and ornithine are present in relatively large quantities which may vary according to the plant organ; α, γ-diaminobutyric acid and citrulline, when present, are found only in small amounts, while citrulline is notably absent from the leaves [51].

Finally, the albumin and globulin content of the seeds of 14 species of Annonaceae was determined; among them, the seeds of seven globulin-free species usually contain high levels of albumins [52].

Polyphenols

Phenolic acids. Caffeic acid (**12**) has been found to be present in *Annona glabra* [17], *Asimina triloba* [17] and *Annona muricata*, in the latter along with *p*-coumaric acid (**13**) [17]. *p*-Hydroxybenzoic acid (**14**), *p*-coumaric acid and vanillic acid (**15**) have been extracted from the leaves of *Cananga latifolia* [53, 54].

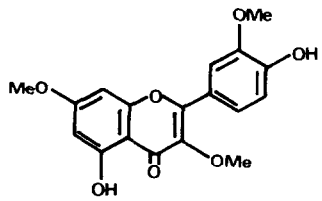
Catechins, proanthocyanidins and tannins. (+)-Catechin (**16**), (−)-epicatechin (**17**), procyanidin (**18**) and prodelphinidin (**19**) have been identified in *Annona cherimolia* [55]; procyanidin (**18**) is also present in *Annona muricata* [17], *Asimina triloba* [17] and in the trunk-bark of *Polyalthia longifolia* [56]. From the latter, a trimeric procyanidin (**20**) has also been extracted [56]. Dimeric proanthocyanidins

have been reported in the fruits of *Annona cherimolia* [57]. Tannins occur in *Alphonsea lutea* and *A. madraspatana* [58], *Annona cherimolia* [16], *A. muricata* [22], *A. reticulata* [59] and *A. senegalensis* [60], *Annonidium letestui* [61], *Artabotrys pierreanus* [61], *Asimina* sp. [18] *Bocagea* sp. [18], *Cleistopholis patens* [60], *Enantia* sp. [61], *Guatteria* sp. [18], *Hexalobus crispiflorus* [60], *Isolona campanulata* [60], *I. hexaloba, I. pilosa* and *I. zenkeri* [61], *Letestudoxa lanuginosa* [61], *Melodorum* sp. [18], *Monanthotaxis oligandra* and *M. schweinfurthii* [61], *Pachypodanthium staudtii* [61], *Rollinia* sp. [18], *Uvaria chamae* and *U. scabrida* [60], *Uvariastrum insculptum* [61], *Uvariodendron giganteum* [60, 61], *Xylopia aethiopica* [60] and *X. longifolia* [16].

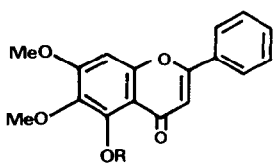
Flavonoids. Quercetin (**21**) occurs in the leaves of *Annona glabra* [17], *A. senegalensis* [19] and *Asimina triloba* [17]; quercitrin (**22**) (quercetin 3-rhamnoside) and rutin (**23**) (quercetin 3-rhamnoglucoside) in the leaves of *Annona senegalensis* [19]; rutin (**23**), nicotiflorin (**24**) (kaempferol-3-rhamnoglucoside) and an incompletely identified acylated flavonol (kaempferol *p*-coumaroylarabinoside (**25**)?) in the leaves of *Cananga latifolia* [53, 54]. Pachypodol (**26**) (quercetin 3,7,3′-trimethyl ether) has been obtained from the stem bark of *Pachypodanthium confine* [62].

Recently, Waterman *et al.* [63, 64] have isolated from the whole stem and the ripe fruit of *Monanthotaxis cauliflora* (Chipp) Verdc., syn. *Popowia cauliflora* Chipp. [64], 5,6,7-trimethoxyflavone (**27**) (baicalein trimethyl ether), 5-hydroxy-6,7-dimethoxyflavone (**28**), 5,7,8-trimethoxyflavanone (**29**), 2′-hydroxy-3′,4′,6′-trimethoxychalcone (**30**), 2′,3′,4′,6′-tetramethoxychalcone (**31**), 2′,4-dihydroxy-3′,4′,6′-trimethoxychalcone (**32**), 5,6,7,8-tetramethoxyflavanone (**33**) (kanakugin) and 2′-hydroxy-3′, 4′, 5′, 6′-tetramethoxychalcone (**34**) (kanakugiol). A common feature among the flavonoids isolated, except **32**, is the absence of B-ring substitution, a trait which may prove to have taxonomic significance [6]. A further point of note concerns the change from C-8 to C-6 substitution in the transition from chalcone or flavanone to flavone; C-8 hydroxylation, according to Harborne, is a characteristic of primitive families, and this is obviously the pattern that would be anticipated in the archaic Annonaceae [6].

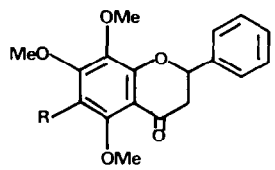
Since 1976 flavonoids of a special type have been obtained from several species of *Uvaria*. They are novel *C*-benzylated flavanones and *C*-benzylated dihydrochalcones, derived from the known flavanone pinocembrin (**35**). Some of these have demonstrated cytotoxic, antitumor and antimicrobial properties. Flavonoids isolated from *Uvaria* are listed in Table 2. The name uvaretin was originally used by Cole *et al.* [73] to designate the *C*-benzyldihydrochalcone, **42**. The same year, Hufford *et al.* [69, 70] attributed the names uvaretin and isouvaretin to the two *C*-benzylflavanones **39** and **41**; these have been later named chamanetin and isochamanetin [67]. Furthermore, chamuvarin isolated by Okorie [74] was found to be identical to uvaretin (**42**) [68]. Flavanones and chalcones are widespread in the higher plants, but the



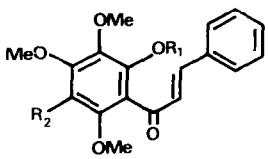
26



27 R = Me
28 R = H



29 R = H
33 R = OMe



30 $R_1 = R_2 = H$
31 R_1 = Me, R_2 = H
34 R_1 = H, R_2 = OMe

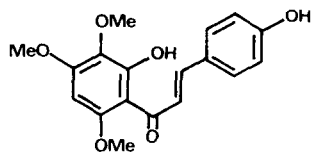


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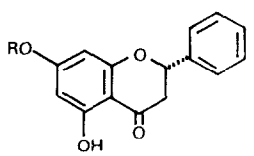
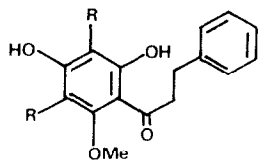
Table 2. Flavonoids of *Uvaria* species

Pinocembrin	**35**	*U. chamae*	[65–67]
Pinostrobin	**36**	*U. chamae*	[67]
Uvangoletin	**37**	*U. angolensis*	[68]
Angoletin	**38**	*U. angolensis*	[68]
Chamanetin	**39**	*U. chamae*	[65–67, 69, 70]
Chamanetin 5-methyl ether	**40**	*U. chamae*	[71, 72]
Isochamanetin	**41**	*U. chamae*	[65–67, 69, 70]
Uvaretin	**42**	*U. acuminata*	[73]
		U. angolensis	[68]
		U. chamae	[65, 67, 74, 75]
		U. kirkii	[76]
Isouvaretin	**43**	*U. angolensis*	[68]
		U. chamae	[65–67]
Dichamanetin	**44**	*U. chamae*	[71, 72]
Dichamanetin 5-methyl ether	**45**	*U. chamae*	[65, 67]
Diuvaretin	**46**	*U. chamae*	[74]
Chamuvaritin	**47**	*U. chamae*	[65, 66, 77, 78]
Uvarinol	**48**	*U. chamae*	[65, 66, 77, 78]
Vafzelin	**49**	*U. afzelii*	[79]
Uvafzelin	**50**	*U. afzelii*	[79]
Syncarpic acid	**51**	*U. afzelii*	[79]



35 R = H
36 R = Me



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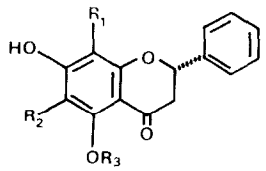

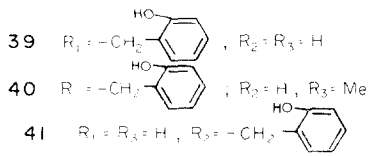

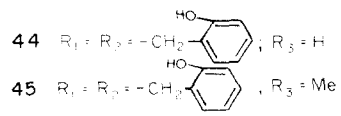

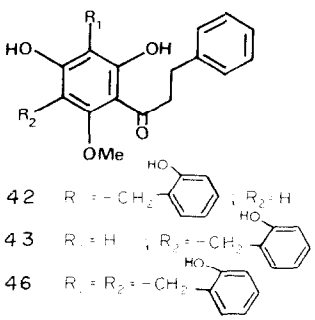

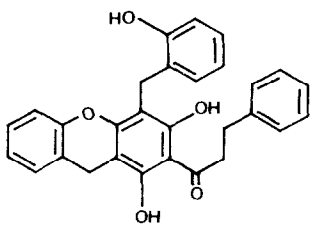

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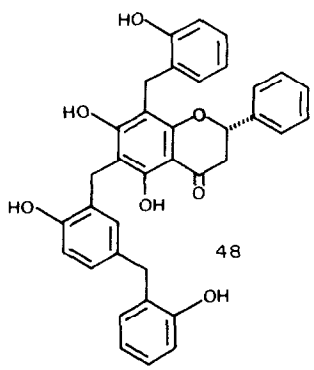
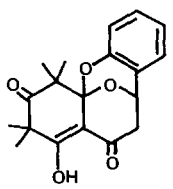


48

addition of benzyl groups is quite rare and seems to be limited in the Annonaceae, to the genus *Uvaria*. The benzyl groups presumably arise from a C_6–C_1 pathway, but the *o*-hydroxy functionality is unusual [77]. The absence of substituents on the D-ring in all these flavonoids of *Uvaria* can be linked with the previous observation concerning the flavonoids of *Popowia cauliflora* [6].

Recently, vafzelin (**49**) and uvafzelin (**50**) were isolated by Hufford *et al.* [79] from *Uvaria afzelii*, together with the known syncarpic acid (**51**). Vafzelin can rationalized as a flavanone in which the A-ring (or its triacetate precursor) is extensively methylated. Vafzelin (**49**) can be derived from the *C*-alkylation of syncarpic acid (**51**) by an *o*-hydroxycinnamoyl moiety followed by conjugate additions [79]. Uvafzelin (**50**) could be made by a similar process: the acylation of syncarpic acid by an *o*-hydroxycinnamoyl moiety, followed by the conjugate addition of syncarpic acid, and dehydration [79].



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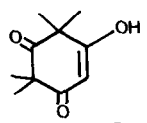

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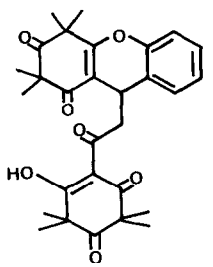


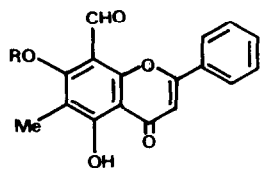
50

The *C*-benzylflavonoids of the genus *Uvaria* can be compared to the *C*-methyl *C*-formylflavonoids isolated from *Unona lawii** [80–82], which are not substituted on the B-ring either. These flavonoids are represented by: (a) three flavones: unonal (**52**) (8-formyl-5, 7-dihydroxy-6-methylflavone), unonal 7-methyl ether (**53**) and isounonal (**54**) (6-formyl-5,7-dihydroxy-8-methylflavone) [81]; (b) three flavanones: lawinal (**55**) (5,7-dihydroxy-6-formyl-8-methylflavanone), desmethoxymatteucinol (**56**) (5,7-dihydroxy-6,8-dimethylflavanone) and desmethoxy-matteucinol 7-methyl ether (**57**) [80]; and (c) two dibenzoylmethanes **58** and **59** [81]; **58** was shown to exist in the cyclic hemiketal forms **60** and **61** (isomeric 2,5-dihydroxyflavanones), but **59** exists only in the ring opened enolic form [82]. Unonal 7-methyl ether (**53**) is the only dehydration product of (**59**), whereas both unonal (**52**) and isounonal (**54**) are produced from (**58**); these data strongly support the biogenetic scheme: flavanone → 2-hydroxyflavanone → flavone [82], i.e. **55** → **58** → **60** → **52**, **58** → **61** → **54** and **58** → **59** → **53**.

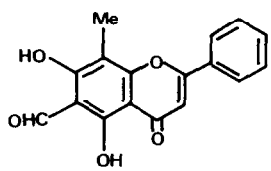
Essential oils

A large number of Annonaceae are fragrant due to the presence of essential oils. The constituents of these oils are usually either well-known monoterpenes and sesquiterpenes or aromatic compounds. Leaves of *Annona muricata* [22] and *A. senegalensis* [36], fruits of *Xylopia longifolia* [16] and *X. striata*

* *Unona lawii* Hook. f. & Thoms. is synonymous to *Desmos lawii* (Hook. f. & Thoms.) Safford.



52 R = H
53 R = Me



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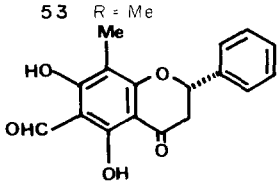

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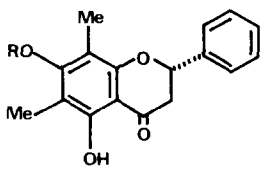
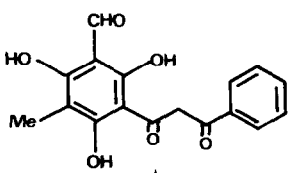


56 R = H
57 R = Me



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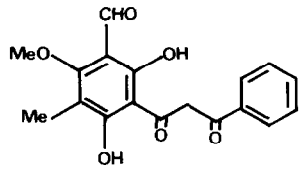

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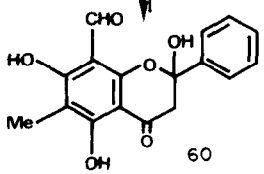

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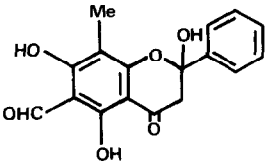


61

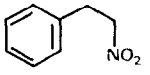
[83], yielded essential oils. Dried fruits of *Xylopia aethiopica* [83, 84] and *X. brasiliensis* [35] produce an agreeable, spicy, fragrant, essential oil.

The most widely studied essential oil is ylang-ylang oil obtained from the flowers of *Cananga odorata*. It is of considerable economic importance due to its widespread use in perfumery [5]. A very large number of constituents has been identified [5, 16, 85–90]. In *Annona squamosa*, essential oil from seeds contains α-pinene and caryophyllene [16], whereas the predominant terpenes in the fruit peel oil are α- and β-pinenes, limonene, β-farnesene, *trans*-ocimene [91], and in the leaves α-pinene, caryophyllene and a cadalenous sesquiterpene [92].

Methyl salicylate has been reported in the volatile oil from *Hexalobus crispiflorus* [16]; constituents of essential oils from *Monodora grandiflora*, *Monodora myristica* and *Popowia capea* were also investigated [16]. As the fruit of *Xylopia aethiopica* is commonly used in tropical Africa as a substitute for pepper, its essential oil has been extensively studied [93–95]. Among the hydrocarbons, β-pinene is the most prominent. Of the oxygenated constituents, cuminal and cineole are present in a rather high concentration, but terpinen-4-ol is the major constituent in the oil [95]. However, in the essential oil from the fruit of *Xylopia discreta*, cineole seems to be the most abundant constituent [17].

A sweet smelling oil obtained from the fruits and seeds of *Dennettia tripetala*, which retained the taste and fragrance of the fruit and seeds, yielded a mixture of sesquiterpenes [33].

The pungent and fragrant principle, which resides in the seeds, was identified as β-phenylnitroethane (**62**) [33, 96]. In spite of its close relationship with



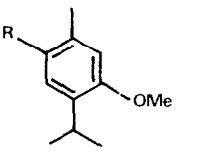
62

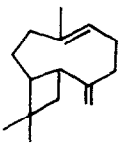
phenylalanine, an ubiquitous precursor, this nitro compound seems to be a rare natural substance [97] and so far it has been found only in two Lauraceae, *Aniba canelilla* and *Ocotea pretiosa* [98]. This illustrates relationship between Annonaceae and Lauraceae [97]. Analgesic [99] and antibacterial [100] properties were reported for the essential oil from *Miliusa tomentosa**; its main component is cineole [17]. Preliminary investigation of the volatile oil from *Polyalthia longifolia* showed the presence of five constituents, mostly azulenes [101], and an antimicrobial activity of this oil was reported [102, 103].

Terpenes

Monoterpenes. Camphor (**63**) and borneol (**64**) have been found in the roots and bark of *Annona squamosa*, along with an oxygenated unidentified monoterpene, $C_{10}H_{14}O$ [104]. An investigation of the root bark of *Uvaria chamae* has led to the isolation of a novel *C*-benzylated monoterpene, chamanen (**65**), together with thymoquinol dimethyl ether, **66** [78, 105]. The presence of an *o*-hydroxybenzyl group in the molecule of chamanen recalls the special structure of the *C*-benzylated flavonoids of *Uvaria* (see above).

Sesquiterpenes. Leaves of *Annona senegalensis* yielded a sesquiterpene mixture which was reported to possess larvicidal properties [36]. Bohlmann and Rao [106] isolated from roots of *Annona squamosa*, β-caryophyllene (**67**), accompanied by several kaurane type diterpenes (see below). Two novel sesquiterpenes, yingzhaosu A (**68**) and yingzhaosu B (**69**), were isolated from roots of *Artabotrys uncinatus* [107, 108]. An unidentified sesquiterpene lactone, $C_{15}H_{20}O_3$, probably of the eudesmanolide type, has recently been reported from *Annona cherimolia* [109]. *Cymbopetalum penduliflorum* yielded a tetracyclic unoxygenated sesquiterpene, ishwarane (**70**) [110]. While that work was in progress, Govindachari *et al.* [111] reported the isolation of ishwarane and of





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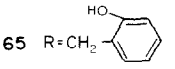
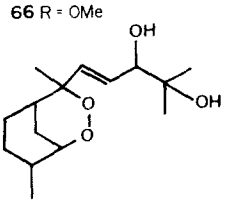


66 R = OMe



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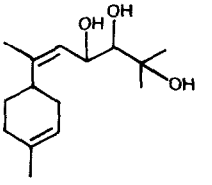

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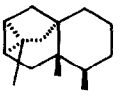


70

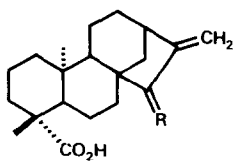
the related sesquiterpenone ishwarone from *Aristolochia indica*; this is interesting due to the chemotaxonomic relations between Annonaceae and Aristolochiaceae. Finally, nitrogenous sesquiterpenes of a special type, containing an indole nucleus, have been observed in Annonaceae of the genus *Polyalthia*. They will be discussed under alkaloids (see below).

Diterpenes. Ca 20 kaurane diterpenes have been reported in several *Annona* species and in *Xylopia aethiopica*. They are listed in Table 3, which also includes stachanoic acid (the stachane skeleton is closely related to that of kaurane). It should be pointed out that xylopic acid, isolated by Ekong and Ogan [84] from the dried fruits of *Xylopia aethiopica*, was shown to be 15β-acetoxy-(−)-kaur-16-en-19-oic acid (**71**). The structure (**88**) tentatively assigned later [112] for xylopic acid, must be discarded since structure **71** was confirmed by X-ray analysis [113]. Xylopic acid was found to have antimicrobial properties [114]. Extraction of the stem bark of *Polyal-*

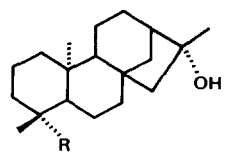
Saccopetalum tomentosum Hook. f. & Thoms. is synonymous to *Miliusa tomentosa* (Roxb.) J. Sinel.

Table 3. Kaurane diterpenes from Annonaceae

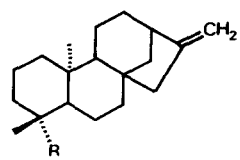
15β-Acetoxy-(−)-kaur-16-en-19-oic acid (xylopic acid)	**71**	*Xylopia aethiopica*	[84, 112–114]
(−)-Kaur-16-en-15-hydroxy-19-oic acid	**72**	*X. aethiopica*	[115]
15-Oxo-(−)-kaur-16-en-19-oic acid	**73**	*X. aethiopica*	[115]
(−)-Kauran-16α-ol	**74**	*Annona senegalensis*	[116, 117]
		Xylopia aethiopica	[115]
(−)-Kauran-16α, 19-diol	**75**	*X. aethiopica*	[115]
(−)-Kaur-16-en-19-ol	**76**	*Annona squamosa*	[106]
(−)-Kaur-16-en-19-yl acetate	**77**	*A. squamosa*	[106]
(−)-Kaur-16-en-19-al	**78**	*A. squamosa*	[106]
(−)-Kaur-16-en-19-oic acid	**79**	*A. glabra*	[118, 119]
		A. senegalensis	[116, 117]
		A. squamosa	[120]
		Xylopia aethiopica	[115]
(−)-Kauran-17-ol-19-al	**80**	*Annona squamosa*	[106]
(−)-Kauran-17-acetoxy-19-al	**81**	*A. squamosa*	[106]
19-Nor-(−)-kauran-4α-ol-17-oic acid	**82**	*A. senegalensis*	[116]
Methyl-19-nor-(−)-kauran-4α-ol-17-oate	**83**	*A. senegalensis*	[117]
(−)-Kauran-19-al-17-oic acid	**84**	*A. senegalensis*	[116]
Methyl-(−)-kauran-19-al-17-oate	**85**	*A. senegalensis*	[117]
(−)-Kauran-17, 19-dioic acid	**86**	*A. senegalensis*	[116]
Stachanoic acid	**87**	*A. senegalensis*	[117]
Two unidentified diterpenes		*A. senegalensis*	[117]
Four unidentified diterpenes		*Xylopia aethiopica*	[114]



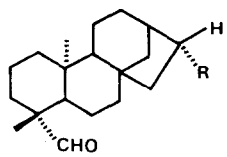
71 R = β-OAc, α-H
72 R = β-OH, α-H
73 R = O



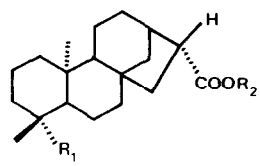
74 R = Me
75 R = CH_2OH



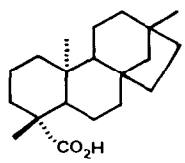
76 R = CH_2OH
77 R = CH_2OAc
78 R = CHO
79 R = COOH



80 R = CH_2OH
81 R = CH_2OAc



82 R_1 = OH ; R_2 = H
83 R_1 = OH ; R_2 = Me
84 R_1 = CHO ; R_2 = H
85 R_1 = CHO ; R_2 = Me
86 R_1 = COOH ; R_2 = H



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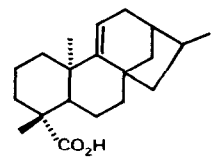
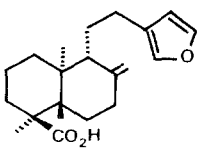


88

thia fragrans yielded polyalthic acid (**89**), a new diterpene acid with a labdane skeleton [121]. The structures of two new diterpenes with a clerodane skeleton isolated from *Annona coriacea* have been established as (**90**) and (**91**) [122]. From the same species was isolated annonalide (**92**), a new diterpene lactone with a pimarane skeleton [123]. Its configuration was erroneously assigned by ^{13}C NMR [124] and revised later by chemical correlations and single crystal X-ray analysis [125, 126].



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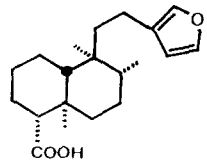

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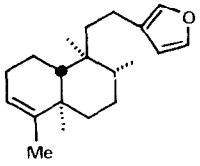

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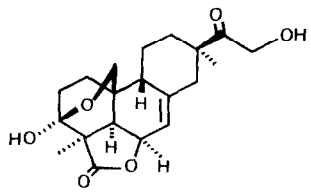
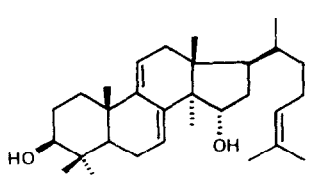


92

Triterpenes, sterols and saponins. Phytochemical screening tests have revealed the presence of sterols and terpenes in *Enantia* sp., *Isolona hexaloba*, *I. pilosa*, *I. zenkeri* [61], and of saponins in *Goniothalamus subevenius* [127], and in *Cleistopholis patens*, *Hexalobus crispiflorus*, *Uvaria chamae* and *U. scabrida* [60]. Friedelin (**93**) has been found in the leaves of *Annona squamosa* [128], an unidentified triterpene in the stem bark of *Uvaria rufa* [129], taraxerol (**94**) in *Uvaria scandens* [130] and in *Uvaria sorzogonensis*, together with glutenol (**95**), glutenone (**96**) and three unidentified triterpenes [131].

Sitosterol (**97**) has been frequently isolated: from leaves of *Annona muricata* [22] and *A. senegalensis* [19], from seeds, root and bark of *A. squamosa* [16, 104], from *Asimina triloba* [43], *Dennettia tripetala* [33], *Duguetia eximia* [132], *Polyalthia longifolia* [56], and from *Fusaea longifolia* [133] and *Onychopetalum amazonicum* [134] where it co-occurs with stigmasterol (**98**). Quantities of sitosterol (**97**), stigmasterol (**98**), campesterol (**99**), and cholesterol (**100**), were reported in fruits and seeds of *Annona cherimolia* [40, 135] and in seeds of *A. muricata* [41]. The cholesterol content of the fruits of several species of *Annona* has been determined [136].

A new triterpene, polycarpol (**101**), has been discovered by Cavé *et al.* [137, 138] simultaneously in the bark of *Polyalthia oliveri* and *Meiocarpidium lepidotum* which later was found to be present also in several other Annonaceae: *Isolona campanulata* [139], *Pachypodanthium confine* [Bévalot, F., Leboeuf, M. and Cavé, A., unpublished results], *Polyalthia suaveolens* [140], *Fusaea longifolia*, *Unonopsis guatterioides* and *Xylopia longifolia* [51]. So far polycarpol does not seem to have been isolated from plants belonging to families other than Annonaceae, despite systematic research in various species belonging to neighbouring families (Lauraceae, Monimiaceae, Menispermaceae) [Bévalot, F., Leboeuf, M. and Cavé, A., unpublished results]; this triterpene may be a useful chemotaxonomic marker.



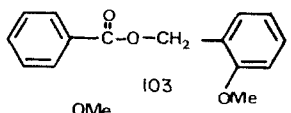
101

Polyprenols. Several long-chain polyprenols (C_{45}–C_{70}) were identified in leaves of *Anaxagorea brevipens* and *Annona reticulata* [141]. The C_{60}-polyprenol was the main component in the polyprenol mixture isolated from *Anaxagorea brevipens* [141].

Aromatic compounds

From the root bark of *Uvaria chamae*, four aromatic constituents were isolated [74, 78, 105]: benzyl benzoate (**102**), *o*-methoxybenzyl benzoate (**103**), *o*-methoxybenzyl benzyl ether (**104**), and di-*o*-methoxybenzyl ether (**105**). From the stem bark of *Uvaria ovata* [142], benzyl 2,3,6-trimethoxybenzoate (**106**) was obtained, and 1,2,3,4,6,7-hexamethoxyxanthone (**107**) from the roots of *Uvaria kirkii* [76].

Several propenylbenzene and vinylbenzene derivatives have been recorded from Annonaceous plants. Asarone (**108**), *trans*-isoelemicin (**109**) and *trans*-isomyristicin (**110**) occur in the bark of *Guatteria gau-*



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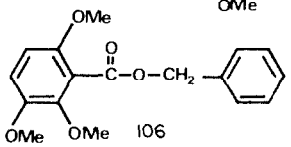

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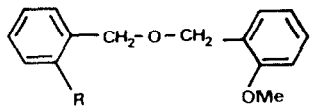
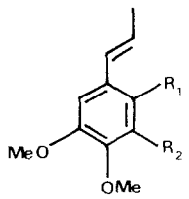
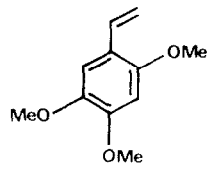


104 R=H
105 R=OMe



108 R_1=OMe; R_2=H
109 R_1=H; R_2=OMe
110 R_1=R_2=OMe



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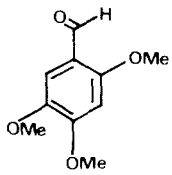

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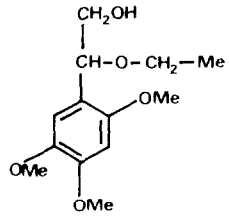
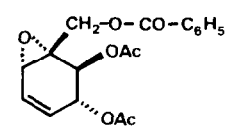


113

meri [143]; 2,4,5-trimethoxystyrene (**111**) in *Pachypodanthium confine* [144], *P. staudtii* [145, 146] and *Duguetia eximia* [132]. In addition, asaraldehyde (**112**) was isolated from *Pachypodanthium staudtii* [146] and *Guatteria gaumeri* [143] and a new aromatic compound pachysontol (**113**) from *Pachypodanthium staudtii* [146].

Three shikimate-derived metabolites, senepoxide (**114**), seneol (**115**) and pipoxide (**116**) were reported in Annonaceae. Senepoxide (**114**) and seneol (**115**) were discovered by Polonsky *et al.* [147] in the fruits of *Uvaria catocarpa*, and the stereoselective synthesis of **114** has been recently reported [148]. Pipoxide (**116**) was isolated from another species of *Uvaria*, *U. purpurea*, by Holbert *et al.* [149] who described its revised structure, **116**, by NMR measurements and X-ray crystallography and carried out the total synthesis. Senepoxide, pipoxide and crotepoxide (the latter not from Annonaceae) belong to a group of highly oxygenated cyclohexane epoxides. They are not aromatic, because the aromatic ring has been further oxidized to an epoxide, and they display an interesting spectrum of biological activity [149].

Goniothalamin (**117**), a biologically active styryldihydropyrone, previously obtained from the Lauraceous *Cryptocarya caloneura* [150], was isolated from the bark of *Goniothalamus andersonii* and its distribution in *G. andersonii*, *G. macrophyllus*, *G. malayanus* and *G. velutinus* was studied [151]. Styryl-2-pyrones have earlier been reported as constituents of Lauraceae and Piperaceae, and their occurrence in Annonaceae may be of taxonomic significance for the genus *Goniothalamus* [151]. Extracts from the bark of an un-named *Polyalthia* species yielded altholactone (**118**), a novel tetrahydrofuro-pyran-5-one [152]; it is biogenetically related to a number of α-pyrones of the Lauraceae, Annonaceae and Piperaceae and in formal terms can be regarded as an oxygenated and cyclized derivative of the lactone goniothalamin (**117**) [152]. Finally, only one lignan-type compound seems to have been recorded from an Annonaceous plant: the neolignan (**119**), isolated by Gottlieb *et al.* [153] from *Duguetia surinamensis*. This unique example of lignan occurring in the Annonaceae is noteworthy, as it is in sharp contrast to the large number of such aromatic compounds present in the neighbouring Eupomatiaceae, Lauraceae and Magnoliaceae [154].



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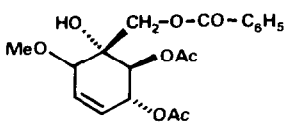

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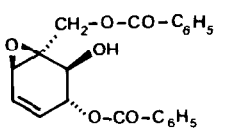

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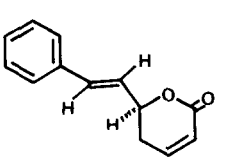

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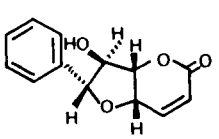

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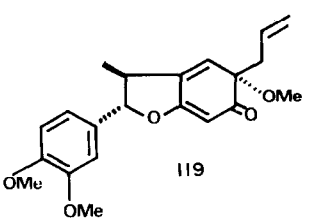
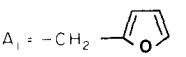


119

Miscellaneous compounds

Polyacetylenic compounds. Sixteen diacetylenes, **120–135**, were isolated by Bohlmann *et al.* [155] from the roots of *Alphonsea ventricosa*. All are closely related and are probably formed in the plant by condensation of C_{18}-acids with pyruvate [155]. The structures of **122**, **123** and **135** have been later confirmed by synthesis [156].



$A_2 = -CH_2-CO-CH_2-CHOH-CH_2OCOMe$

$A_3 = -CH_2-CO-CH_2-CHOH-CH_2OH$

$A_4 = -CH_2-CHOH-CH_2-CHOH-CH_2OH$

$R_1 = -(CH_2)_6-(C{\equiv}C)_2-CH_1{=}CH-(CH_2)_2-CH{=}CH_2$

$R_2 = -(CH_2)_6-(C{\equiv}C)_2-(CH_2)_4-CH{=}CH_2$

$R_3 = -(CH_2)_6-(C{\equiv}C)_2-CH_1 = CH-(CH_2)_3-Me$

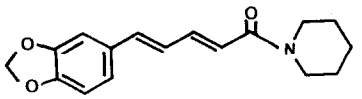
$R_4 = -(CH_2)_6-(C{\equiv})_2-(CH_2)_5-Me$

120	A_1–R_1	**128**	A_3–R_1
121	A_1–R_2	**127**	A_3–R_2
122	A_1–R_3	**130**	A_3–R_3
123	A_1–R_4	**131**	A_3–R_4
124	A_2–R_1	**132**	A_4–R_1
125	A_2–R_2	**133**	A_4–R_2
126	A_2–R_3	**134**	A_4–R_3
127	A_2–R_4	**135**	A_4–R_4

Vitamins and carotenes. Vitamins B_1 (**136**) and B_2 (**137**) were reported in the fruit pulp of *Annona cherimolia* [157]. Vitamin C (ascorbic acid, **138**) content was determined in the fruit pulp of *Annona cherimolia* [20, 157], *A. muricata* [158], *A. reticulata* [159] and *A. squamosa* [158]. Carotene (**139**) (or carotenoids) were isolated from the fruits of *Annona cherimolia* [157], *A. reticulata* [159], *A. sericea* and *A. squamosa* [160].

Cyanogenic glucosides. The occurrence of cyanogenic compounds was recorded in *Anaxagorea luzonensis*, *Annona cherimolia*, *A. chrysophylla*, *A. muricata*, *A. reticulata*, *A. squamosa*, *Artabotrys suaveolens* and *Cananga odorata* [17, 18] and in *Rollinia emarginata* [161].

Non-alkaloidal nitrogen heterocycles. From the dried fruit of *Xylopia brasiliensis* the amide piperine (**140**) was isolated [34]. Nicotinic acid (**141**) occurs in the fruit pulp of *Annona cherimolia* [157]. Squamolone was first reported in 1972 from *Annona squamosa* as 4-oxoperhydro-1, 3-diazepin-2-one (**142**) [162], but in 1980 it was found to be 1-carbamoyl-2-pyrrolidinone (**143**) instead and an unequivocal synthesis of squamolone (**143**) and of its isomer, **142**, was carried out [163]. Zincpolyanemine (**144**) has been recently isolated from *Polyalthia nemoralis*, a medi-



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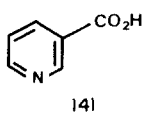

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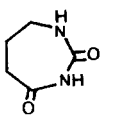

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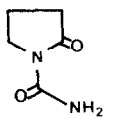

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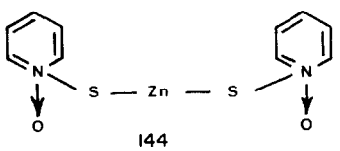

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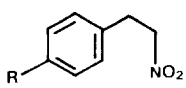


62 R=H
145 R=O-primeverose

cinal herb effective in treating hepatitis and malaria [164].

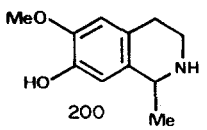
Two nitro compounds were isolated from Annonaceous plants: first β-phenylnitroethane (**62**) from the fruits of *Dennettia tripetala* [33, 96], then 4-(-2-nitroethyl)phenol *O*-primeveroside (**145**) by Forgacs *et al.* [165, 166] from the leaves and stems of *Annona squamosa*. Lastly, the heavy odour of butter which is exhaled by flowers of *Polyalthia canangioides* var. *angustifolia* is due to the presence of diacetyl **146** [167].

ALKALOIDS OF ANNONACEAE

Almost all these alkaloids possess an isoquinoline-derived structure and they are considered here in the following order: simple isoquinolines; benzyltetrahydroisoquinolines; bisbenzylisoquinolines and bisbenzyltetrahydroisoquinolines; protoberberines and tetrahydroprotoberberines; aporphinoids *sensu lato*, including aporphines *sensu stricto*, 7-substituted aporphines, oxoaporphines, phenanthrenes ('open aporphines'); miscellaneous isoquinoline-type alkaloids. The few alkaloids devoid of an isoquinoline skeleton are considered later. In this review, only structures and sources are discussed. Other details of these alkaloids are available elsewhere [168–175]. The annual series edited since 1971 by the Chemical Society of London [176] can also be consulted. It is to be noted that phytochemical screening tests have revealed the presence of alkaloids in a number of Annonaceae, without having led to the isolation and identification of these alkaloids.

Simple isoquinolines

Salsolinol (**200**), a simple tetrahydroisoquinoline, was reported in *Annona reticulata*, together with dopamine (**201**), its biogenetic precursor [177], and the only example of isoquinolone described in Annonaceae seems to be corydaldine (**202**), isolated from the stem bark of *Enantia polycarpa* [178].



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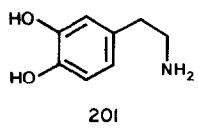

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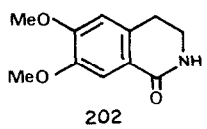
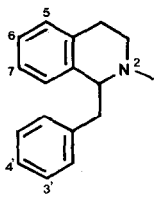


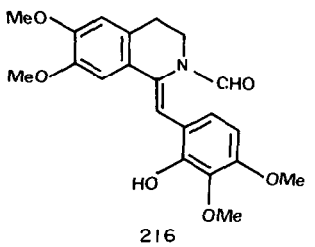
202

Table 4. Occurrence of benzyltetrahydroisoquinolines in Annonaceae

Anomuricine	**203**	*Annona muricata*	[181, 182]
Anomurine	**204**	*Annona muricata*	[181, 182]
Armepavine	**205**	*Xylopia pancheri*	[185]
Coclaurine	**206**	*Annona muricata*	[182]
		Annona reticulata	[177]
		Xylopia papuana	[186]
N-Demethylcolletine	**207**	*Xylopia pancheri*	[185]
Higenamine	**208**	*Annona squamosa*	[187, 188]
Laudanine	**209**	*Xylopia pancheri*	[185]
Laudanosine	**210**	*Monodora angolensis*	[189]
O-Methylarmepavine	**211**	*Annona squamosa*	[128]
		Xylopia pancheri	[185]
N-Methylcoclaurine	**212**	*Xylopia pancheri*	[185]
N-Nor-*O*-methylarmepavine	**213**	*Xylopia pancheri*	[185]
		Xylopia buxifolia	[190]
N-Oxy-*O*-methylarmepavine	**214**	*Xylopia pancheri*	[185]
Reticuline	**215**	*Annona cherimolia*	[191]
		Annona glabra	[118, 119, 192]
		Annona montana	[193]
		Annona muricata	[179, 180, 182]
		Annona reticulata	[194, 195, 196]
		Annona squamosa	[197]
		Xylopia pancheri	[185]
		Xylopia papuana	[186]
Polycarpine	**216**	*Enantia polycarpa*	[178, 183]



	2	5	6	7	3'	4'
203	H	OH	OMe	OMe	—	OMe
204	H	OMe	OMe	OMe	—	OMe
205	Me	—	OMe	OMe	—	OH
206	H	—	OMe	OH	—	OH
207	Me	—	OMe	OH	—	OMe
208	H	—	OH	OH	—	OH
209	Me	—	OMe	OMe	OH	OMe
210	Me	—	OMe	OMe	OMe	OMe
211	Me	—	OMe	OMe	—	OMe
212	Me	—	OMe	OH	—	OH
213	H	—	OMe	OMe	—	OMe
214	*N*-oxy	—	OMe	OMe	—	OMe
215	Me	—	OMe	OH	OH	OMe



216

Scheme 1. Benzyltetrahydroisoquinolines from Annonaceae.

Benzyltetrahydroisoquinolines

Thirteen benzyltetrahydroisoquinolines, **203–215**, were isolated from some species of *Annona* and *Xylopia* and from *Monodora angolensis* (Table 4; Scheme 1). The most frequently occurring benzyltetrahydroisoquinoline is reticuline (**215**). The alkaloid isolated by Meyer in 1941 [179] from *Annona muricata* under the name 'muricinine' was later identified to be reticuline by Santos *et al.* [180]. Anomuricine (**203**) and anomurine (**204**) from *Annona muricata* [181, 182] are special in that they are substituted at C-5.

In spite of its peculiar structural features, polycarpine (**216**) (1-benzylidene *N*-formyltetrahydroisoquinoline), isolated from the stem-bark of *Enantia polycarpa* [178, 183], is listed herein. Murugesan and Shamma [184] postulated that polycarpine must be derived biogenetically from the protoberberinium salt palmatine; they proposed a new hypothetical biogenetic route from protoberberinium salts to aporphines via benzylisoquinoline amides such as polycarpine, without involving phenolic oxidative coupling [184].

Bisbenzylisoquinolines and bisbenzyltetrahydroisoquinolines

Eleven bisbenzyltetrahydroisoquinolines **217–227** and one quaternary bisbenzylisoquinoline (**228**) were isolated from the genera *Crematosperma*, *Guatteria*, *Isolona*, *Phaeanthus*, *Popowia* and *Uvaria* (Table 5; Scheme 2). The extracted bisbenzyltetrahydroisoquinolines are of various structural types; it may be noted that phlebicine (**227**) possesses a rather rare structural pattern, which seems to be otherwise present only in the Lauraceae and Menispermaceae.

Protoberberines and tetrahydroprotoberberines

Protoberberines. To date, only five protoberberines, **230–234**, were recorded from Annonaceae exclusively in the genus *Enantia* (Table 6; Scheme 3). In addition, berberine (**229**) has been reported from *Xylopia polycarpa* in 1855 [16], but this doubtful occurrence has not been confirmed in later investigations. To this protoberberine group is added staudine (**235**), discovered in *Pachypodanthium staudtii* [210, 211]. Staudine is an alkaloid of a new structural type, which exists in a zwitterionic form; it results from the combination of jatrorrhizine, a protoberberine alkaloid, and of a 2, 4, 5-trimethoxystyrene unit, through the vinyl side chain of the latter. This styrene compound is known to accompany staudine in the plant [145, 146].

Tetrahydroprotoberberines. There are 10 tetrahydroprotoberberines, **236–245**, described in the Annonaceae. Most are 1, 2, 9, 10-substituted, a few only are 1, 2, 10, 11-substituted (Table 7; Scheme 4). The structures **236** and **242** given here for the two alkaloids isolated from *Schefferomitra subaequalis* [217] namely aequaline and schefferine, are those that have been corrected by Brochmann-Hanssen *et al.* [218] and by Pai *et al.* [219]: aequaline is actually identical to discretamine, while schefferine has the same structure as kikemanine and (−)-corydalmine. In addition, discretinine (**238**) isolated by Schmutz [220] from *Xylopia discreta* was later identified as corypalmine [218].

Proaporphines

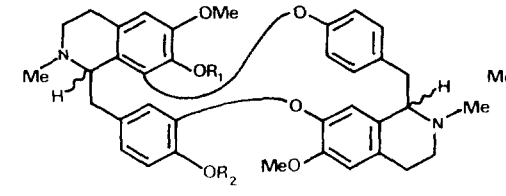
There seem to be few proaporphines in the Annonaceae. Only four representatives, **246–249**, of this group of isoquinoline alkaloids have been reported in a small number of species (Table 8; Scheme 5). It is to be noted that (+)-glaziovine (**247**) and (−)-*N*-methylcrotsparine (**247**) are enantiomers.

Aporphinoids

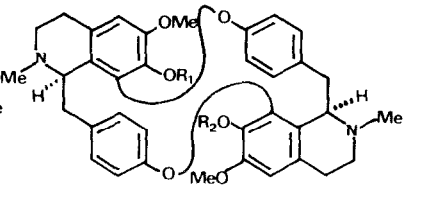
Aporphines sensu stricto. Fifty aporphines *sensu stricto* (noraporphines, aporphines, quaternary aporphines), **250–300**, were isolated from many genera of Annonaceae (Table 9; Scheme 6). They have very different structures and none is 8-substituted. Anonaine (**251**) is the most frequently cited aporphine, since it has been reported in 18 species belonging to nine genera. The structure of artabotrinine (**253**) was not elucidated [229]. Actual structures of four aporphines are still to be confirmed: danguyelline (**259**) [190], *O*-demethylpurpureine (**260**) [227] and xyloguyelline (**298**) [190] are 2-hydroxy-3-methoxy-substituted or vice-versa; suaveoline (**295**) is 2-hydroxy-10-methoxy-substituted or vice-versa [229, 230], but the latter hypothesis is doubtful (catecholic aporphine). Recently, two original alkaloids, guattescidine (**301**) and guattescine (**302**), were isolated from *Guatteria scandens* [231]. They are the first

Table 5. Occurrence of bisbenzylisoquinolines and bisbenzyltetrahydroisoquinolines in Annonaceae

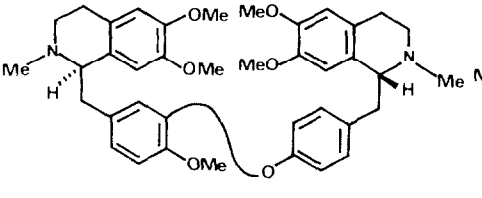
Chondrofoline	**217**	*Uvaria ovata*	[198]
Curine	**218**	*Isolona pilosa*	[199, 200]
Cycleanine	**219**	*Isolona hexaloba*	[200]
Dauricine *O*-methyl ether	**220**	*Popowia* cv. *cyanocarpa*	[201]
O, *O*-Dimethylcurine	**221**	*Guatteria megalophylla*	[202]
Isochondodendrine	**222**	*Guatteria megalophylla*	[202]
		Isolona hexaloba	[200]
		Isolona pilosa	[199, 200]
Limacine	**223**	*Phaeanthus aff. macropodus*	[203]
12′-*O*-Methylcurine	**224**	*Guatteria megalophylla*	[202]
Norcycleanine (7-*O*-methyl-isochondodendrine)	**225**	*Isolona hexaloba*	[200]
Phaeanthine	**226**	*Phaeanthus ebracteolatus*	[204–206]
		Phaeanthus aff. macropodus	[203]
Phlebicine	**227**	*Crematosperma polyphlebum*	[207]
Phaeantharine	**228**	*Phaeanthus ebracteolatus*	[206, 208, 209]



217 R_1 = Me ; R_2 = H ; 1-S, 1′-S
218 R_1 = R_2 = H, 1-R, 1′-R
221 R_1 = R_2 = Me ; 1-R, 1′-R
224 R_1 = H, R_2 = Me, 1-R, 1′R



219 R_1 = R_2 = Me
222 R_1 = R_2 = H
225 R_1 = Me, R_2 = H



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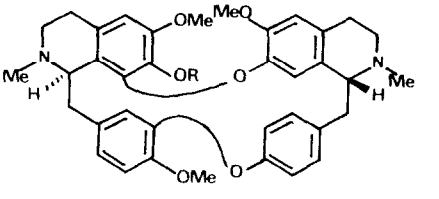
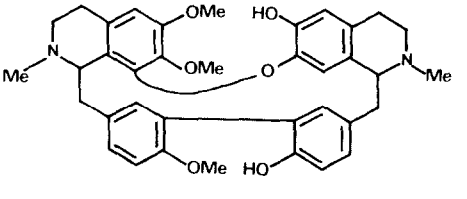


223 R = H
226 R = Me



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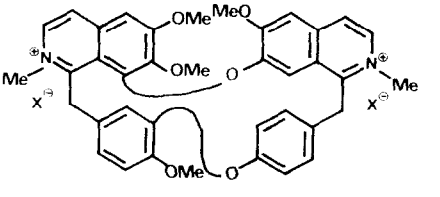
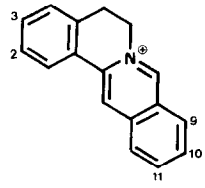


228

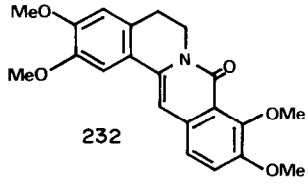
Scheme 2. Bisbenzylisoquinolines and bisbenzyltetrahydroquinolines from Annonaceae.

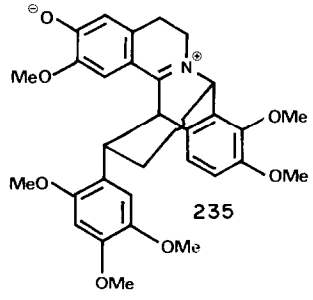
Table 6. Occurrence of protoberberines in Annonaceae

Alkaloid	Formula	Sources
Berberine	**229**	*Xylopia polycarpa* [16]
Columbamine	**230**	*Enantia chlorantha* [212]
		Enantia polycarpa [213]
Jatrorrhizine	**231**	*Enantia chlorantha* [212]
		Enantia polycarpa [213]
Oxypalmatine	**232**	*Enantia polycarpa* [178]
Palmatine	**233**	*Enantia chlorantha* [212, 214]
		Enantia pilosa [215]
		Enantia polycarpa [178, 213, 216]
Pseudopalmatine	**234**	*Enantia polycarpa* [178]
Staudine	**235**	*Pachypodanthium staudtii* [210, 211]



	2	3	9	10	11
229	OCH_2O		OMe	OMe	—
230	OH	OMe	OMe	OMe	—
231	OMe	OH	OMe	OMe	—
233	OMe	OMe	OMe	OMe	—
234	OMe	OMe	—	OMe	OMe





Scheme 3. Protoberberines from Annonaceae.

members of a new class of aporphinoids as they are 6a-methyl substituted and they cannot be regarded as oxoaporphines, since ring B is not aromatic.

Dehydroaporphines. No 6a, 7-dehydroaporphine seems to have been reported in Annonaceae as yet.

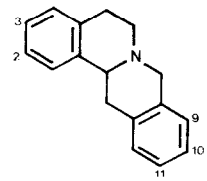
7-Substituted aporphines. Ca 25 7-substituted aporphines were isolated from Annonaceae, most of them discovered only recently and not yet described in other families (Table 10; Scheme 7). Among these 7-substituted aporphines, four types may be defined. The most numerous, **303–322**, are C-7 oxygenated aporphines (substituted by an alcoholic hydroxyl or an *O*-methyl ether group).

Norpachystaudine (**323**) and pachystaudine (**324**) [210] are to date the only two known examples of aporphines twice substituted at C-7 and C-4 (no 4-substituted aporphine has been reported in Annonaceae). Recently, melosmidine (**325**) and melosmine (**326**), the two first members of the new class of 7, 7-dimethylaporphines, have been discovered in *Guatteria melosma* [241]. Finally, two original alkaloids, duguecalyne (**327**) and duguenaine (**328**) were isolated from stem-bark of *Duguetia calycina* [248]. As in the case of melosmidine and melosmine, the C-7 is substituted by a carbon group, but here this group is engaged in an oxazinic ring formation between C-7 and the aporphine nitrogen.

It may be pointed out that the 7-hydroxy or 7-methoxy aporphines are never substituted at C-11 and very rarely at C-3. Moreover, the *trans*-configuration between H-6a and H-7 is found only among alkaloids of the Annonaceae, but members of this plant family may also produce *cis*-alkaloids, particularly norushinsunine (**311**) and ushinsunine (**322**) which

Table 7. Occurrence of tetrahydroprotoberberines in Annonaceae

Alkaloid	Formula	Sources
Aequaline	**236**	*Mitrella kentii* [221]
(cf. discretamine)		*Schefferomitra subaequalis* [217–219]
Coreximine	**237**	*Annona montana* [286]
		Annona muricata [182]
		Asimina triloba [222]
Corypalmine	**238**	*Pachypodanthium confine* [223]
(discretinine)		*Pachypodanthium staudtii* [210]
10-Demethylxylopinine	**239**	*Duguetia calycina* [224]
Discretamine	**236**	*Duguetia calycina* [224]
(aequaline)		*Xylopia buxifolia* [190]
		Xylopia discreta [220]
Discretine	**240**	*Pachypodanthium staudtii* [210]
		Xylopia discreta [220]
Discretinine	**238**	*Xylopia discreta* [218, 220]
(cf. corypalmine)		
Isocorypalmine	**241**	*Pachypodanthium confine* [223]
		Pachypodanthium staudtii [225]
Kikemanine	**242**	*Polyalthia oligosperma* [226]
(schefferine)		
Schefferine	**242**	*Schefferomitra subaequalis* [217–219]
(cf. kikemanine)		
Stepholidine	**243**	*Monanthotaxis cauliflora* [64]
Tetrahydropalmatine	**244**	*Pachypodanthium confine* [223]
Xylopinine	**245**	*Polyalthia oligosperma* [226]
		Xylopia buxifolia [190]
		Xylopia discreta [220]

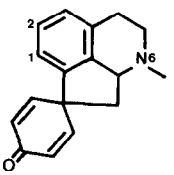


	2	3	9	10	11
236	OMe	OH	OMe	OH	—
237	OH	OMe	—	OMe	OH
238	OMe	OH	OMe	OMe	—
239	OMe	OMe	—	OH	OMe
240	OMe	OH	—	OMe	OMe
241	OH	OMe	OMe	OMe	—
242	OMe	OMe	OMe	OH	—
243	OH	OMe	OMe	OH	—
244	OMe	OMe	OMe	OMe	—
245	OMe	OMe	—	OMe	OMe

Scheme 4. Tetrahydroprotoberberines from Annonaceae.

Table 8. Occurrence of proaporphines in Annonaceae

Alkaloid	Formula	Sources
Crotsparine (norglaziovine)	**246**	*Monodora angolensis* [189]
Glaziovine	**247**	*Annona purpurea* [227] *Uvaria chamae* [228]
N-Methylcrotsparine	**247**	*Isolona zenkeri* [200]
Pronuciferine	**248**	*Isolona pilosa* [199, 200] *Uvaria chamae* [228] *Xylopia buxifolia* [190]
Stepharine	**249**	*Annona muricata* [182] *Annona purpurea* [227]



	1	2	6
246	OH	OMe	H
247	OH	OMe	Me
248	OMe	OMe	Me
249	OMe	OMe	H

Scheme 5. Proaporphines from Annonaceae.

Table 9. Occurrence of aporphines in Annonaceae

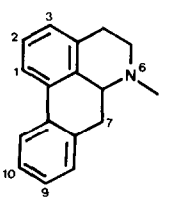
Alkaloid	Formula	Sources
Anolobine	**250**	*Annona glabra* [118, 119] *Annona squamosa* [197] *Asimina triloba* [222] *Schefferomitra subaequalis* [217]
Anonaine	**251**	*Annona cherimolia* [191] *Annona glabra* [118, 119] *Annona montana* [193, 286] *Annona reticulata* [59, 194–196] *Annona squamosa* [104, 197, 232, 233] *Cananga odorata* [234] *Enantia polycarpa* [178] *Isolona campanulata* [139] *Isolona pilosa* [200] *Mitrella kentii* [221] *Polyalthia emarginata* [226] *Polyalthia oliveri* [138] *Pseuduvaria* sp. [235] *Pseuduvaria* cv. *grandifolia* [235] *Schefferomitra subaequalis* [217, 235] *Xylopia brasiliensis* [236] *Xylopia pancheri* [185] *Xylopia papuana* [186]
Artabotrine (cf. isocorydine)	**252**	*Artabotrys suaveolens* [229, 230]
Artabotrinine	**253**	*Artabotrys suaveolens* [229]

Table 9. (*Contd*)

Alkaloid	Formula	Sources
Asimilobine	**254**	*Anaxagorea dolichocarpa* [237] *Anaxagorea prinoides* [237] *Annona glabra* [118, 119] *Annona montana* [286] *Asimina triloba* [222] *Melodorum punctulatum* [238] *Mitrella kentii* [221] *Monanthotaxis cauliflora* [64] *Popowia* cv. *cyanocarpa* [201] *Schefferomitra subaequalis* [217] *Uvaria chamae* [228]
Buxifoline	**255**	*Xylopia buxifolia* [190]
Caaverine	**256**	*Isolona pilosa* [199, 200] *Isolona zenkeri* [200]
Calycinine	**257**	*Duguetia calycina* [224]
Corydine	**258**	*Annona squamosa* [104, 233] *Xylopia danguyella* [190]
Danguyelline	**259**	*Xylopia danguyella* [190]
O-Demethylpurpureine	**260**	*Annona purpurea* [227]
Dicentrine	**261**	*Duguetia* sp. [239]
Glaucine	**262**	*Alphonsea ventricosa* [240] *Annona squamosa* [104, 233] *Pseuduvaria* cv. *dolichonema* [235] *Uvaria chamae* [228]
9-Hydroxy-1,2-dimethoxynoraporphine	**263**	*Monanthotaxis cauliflora* [64]
Isoboldine	**264**	*Annona glabra* [118, 119] *Annona montana* [286] *Enantia polycarpa* [178] *Guatteria melosma* [241] *Monodora* cv. *brevipes* [189, 242] *Polyalthia acuminata* [251] *Schefferomitra subaequalis* [217] *Uvaria chamae* [228] *Xylopia danguyella* [190]
Isocorydine	**252**	*Annona purpurea* [227] *Annona squamosa* [104] *Artabotrys suaveolens* [229, 230] *Asimina triloba* [222]
Isopiline	**265**	*Enantia polycarpa* [178, 244]
Laurelliptine (norisoboldine)	**266**	*Isolona pilosa* [199, 200] *Monanthotaxis cauliflora* [64] *Monodora tenuifolia* [245]
Laurolitsine (norboldine)	**267**	*Xylopia papuana* [186]
Laurotetanine	**268**	*Xylopia danguyella* [190]
Lirinidine	**269**	*Isolona zenkeri* [200]
Magnoflorine	**270**	*Enantia polycarpa* [178]
Menisperine (*N*-methylisocorydine)	**271**	*Enantia polycarpa* [178]
N-Methylactinodaphnine	**272**	*Annona glabra* [192]
N-Methylasimilobine	**273**	*Xylopia buxifolia* [190]
N-Methylcorydine	**274**	*Polyalthia oliveri* [138]
N-Methyllaurotetanine	**275**	*Enantia polycarpa* [178]
O-Methylpukateine	**276**	*Duguetia calycina* [224]
Norcorydine	**277**	*Annona squamosa* [233] *Popowia* cv. *cyanocarpa* [201] *Xylopia danguyella* [190] *Xylopia pancheri* [185]
Norglaucine	**278**	*Alphonsea ventricosa* [240] *Duguetia* sp. [239] *Pseuduvaria* cv. *dolichonema* [235]

Table 9. (*Contd*)

Alkaloid	Formula	Sources
Norisocorydine	**279**	*Annona squamosa* [233]
		Xylopia danguyella [190]
Norisodomesticine	**280**	*Xylopia danguyella* [190]
Norlaureline	**281**	*Guatteria elata* [246]
Nornantenine	**282**	*Xylopia danguyella* [190]
Nornuciferine	**283**	*Annona glabra* [118, 119]
		Enantia polycarpa [178]
		Isolona campanulata [139]
		Isolona pilosa [199, 200]
		Pseuduvaria sp. [235]
		Pseuduvaria cv. *grandifolia* [235]
		Xylopia buxifolia [190]
Noroconovine	**284**	*Polyalthia oligosperma* [226]
Norpredicentrine	**285**	*Pseuduvaria* cv. *dolichonema* [235]
Norpurpureine	**286**	*Annona purpurea* [227]
Norstephalagine	**287**	*Xylopia buxifolia* [190]
Nuciferine	**288**	*Monanthotaxis cauliflora* [64]
Obovanine	**289**	*Duguetia calycina* [224]
Polygospermine	**290**	*Polyalthia oligosperma* [226]
Purpureine	**291**	*Annona purpurea* [227]
Puterine	**292**	*Duguetia calycina* [224]
		Guatteria elata [246]
Roemerine	**293**	*Annona glabra* [118, 119]
		Annona squamosa [233]
		Cananga odorata [234]
		Guatteria modesta [247]
		Isolona pilosa [199, 200]
		Xylopia pancheri [185]
		Xylopia papuana [186]
Sparsiflorine	**294**	*Monodora angolensis* [189]
Suaveoline	**295**	*Artabotrys suaveolens* [229, 230]
Thaliporphine	**296**	*Uvaria chamae* [228]
Wilsonirine	**297**	*Monodora angolensis* [189]
		Popowia cv. *cyanocarpa* [201]
Xyloguyelline	**298**	*Xylopia danguyella* [190]
Xylopine	**299**	*Annona squamosa* [128]
		Duguetia calycina [224]
		Xylopia brasiliensis [236]
		Xylopia buxifolia [190]
		Xylopia discreta [220]
		Xylopia pancheri [185]
		Xylopia papuana [186]
Zenkerine	**300**	*Isolona pilosa* [199, 200]
		Isolona zenkeri [199, 200]
Guattescidine	**301**	*Guatteria scandens* [231]
Guattescine	**302**	*Guatteria scandens* [231]

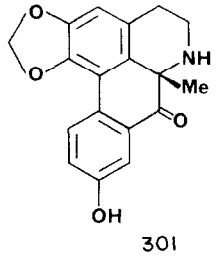


	1	2	3	6	9	10	11
250	OCH_2O		—	H	OH	—	—
251	OCH_2O		—	H	—	—	—
252	OMe	OMe	—	Me	—	OMe	OH

Scheme 6. (*Contd over page*)

Scheme 6. (*Contd*)

	1	2	3	6	9	10	11
253*							
254	OMe	OH	—	H	—	—	—
255	OCH_2O		OMe	H	OMe	—	—
256	OH	OMe	—	H	—	—	—
257	OCH_2O		—	H	OMe	—	OH
258	OH	OMe	—	Me	—	OMe	OMe
259	OMe	OH ↔	OMe	H	—	OMe	OH
260	OMe	OMe ↔	OH	Me	OMe	OMe	—
261	OCH_2O		—	Me	OMe	OMe	—
262	OMe	OMe	—	Me	OMe	OMe	—
263	OMe	OMe	—	H	OH	—	—
264	OH	OMe	—	Me	OH	OMe	—
265	OH	OMe	OMe	H	—	—	—
266	OH	OMe	—	H	OH	OMe	—
267	OMe	OH	—	H	OH	OMe	—
268	OMe	OMe	—	H	OH	OMe	—
269	OH	OMe	—	Me	—	—	—
270	OH	OMe	—	$(Me)_2$	—	OMe	OH
271	OMe	OMe	—	$(Me)_2$	—	OMe	OH
272	OCH_2O		—	Me	OH	OMe	—
273	OMe	OH	—	Me	—	—	—
274	OH	OMe	—	$(Me)_2$	—	OMe	OMe
275	OMe	OMe	—	Me	OH	OMe	—
276	OCH_2O		—	Me	—	—	OMe
277	OH	OMe	—	H	—	OMe	OMe
278	OMe	OMe	—	H	OMe	OMe	—
279	OMe	OMe	—	H	—	OMe	OH
280	OMe	OH	—	H	OCH_2O		—
281	OCH_2O		—	H	—	OMe	—
282	OMe	OMe	—	H	OCH_2O		—
283	OMe	OMe	—	H	—	—	—
284	OMe	OMe	OMe	H	—	OMe	OH
285	OMe	OH	—	H	OMe	OMe	—
286	OMe	OMe	OMe	H	OMe	OMe	—
287	OCH_2O		OMe	H	—	—	—
288	OMe	OMe	—	Me	—	—	—
289	OCH_2O		—	H	—	—	OH
290	OMe	OMe	OMe	H	—	OCH_2O	
291	OMe	OMe	OMe	Me	OMe	OMe	—
292	OCH_2O		—	H	—	—	OMe
293	OCH_2O		—	Me	—	—	—
294	OH	OMe	—	H	—	OH	—
295	OMe	OMe†	—	Me	—	OH†	OH
296	OH	OMe	—	Me	OMe	OMe	—
297	OH	OMe	—	H	OMe	OMe	—
298	OMe	OH ↔	OMe	H	OCH_2O		—
299	OCH_2O		—	H	OMe	—	—
300	OH	OMe	—	H	—	OMe	—



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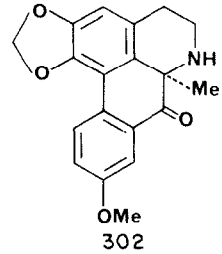


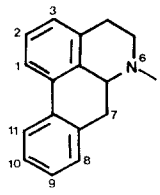
302

*Unidentified aporphine (artabotrinine).
†In **295**, these substituents may be reversed.

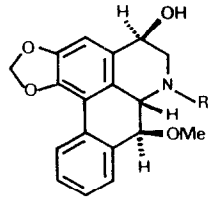
Scheme 6. Aporphines from Annonaceae.

Table 10. Occurrence of 7-substituted aporphines in Annonaceae

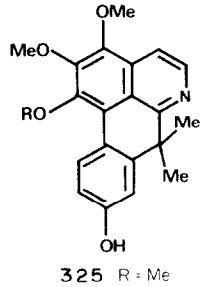
Alkaloid	Formula	Sources
Anaxagoreine	**303**	*Anaxagorea dolichocarpa* [237]
		Anaxagorea prinoides [237]
Duguetine	**304**	*Duguetia* sp. [239]
Guatterine	**305**	*Guatteria psilopus* [250]
		Pachypodanthium confine [223]
		Polyalthia suaveolens [249]
Guatterine *N*-oxide	**306**	*Pachypodanthium confine* [223]
N-Methylpachypodanthine	**307**	*Pachypodanthium staudtii* [210]
N-Methylpachypodanthine *N*-oxide	**308**	*Polyalthia oliveri* [138]
Noroliveridine	**309**	*Polyalthia oliveri* [138]
Noroliverine	**310**	*Polyalthia suaveolens* [249]
Noroliveroline	**310bis**	*Polyalthia acuminata* [251]
Norushinsunine (michelalbine)	**311**	*Annona cherimolia* [191]
		Annona glabra [118, 119]
		Annona reticulata [195, 196]
		Annona squamosa [197]
		Asimina triloba [223]
		Melodorum punctulatum [238]
		Polyalthia acuminata [251]
Oliveridine	**312**	*Enantia pilosa* [252]
		Isolona campanulata [139]
		Polyalthia oliveri [138, 253]
		Polyalthia suaveolens [249]
Oliveridine *N*-oxide	**313**	*Enantia pilosa* [252]
Oliverine	**314**	*Enantia pilosa* [252]
		Isolona campanulata [139]
		Polyalthia oliveri [138, 253]
		Polyalthia suaveolens [249]
Oliverine *N*-oxide	**315**	*Enantia pilosa* [252]
		Isolona campanulata [139]
Oliveroline	**316**	*Pachypodanthium confine* [223]
		Polyalthia oliveri [138]
		Polyalthia suaveolens [249]
Oliveroline *N*-oxide	**317**	*Polyalthia oliveri* [138]
Pachyconfine	**318**	*Pachypodanthium confine* [223]
Pachypodanthine	**319**	*Pachypodanthium staudtii* [210, 254]
		Polyalthia oliveri [138]
		Polyalthia suaveolens [249]
Polyalthine	**320**	*Polyalthia suaveolens* [249]
Polysuavine	**321**	*Polyalthia suaveolens* [249]
Ushinsunine	**322**	*Cananga odorata* [234]
Norpachystaudine	**323**	*Pachypodanthium staudtii* [210]
Pachystaudine	**324**	*Pachypodanthium staudtii* [210]
Melosmidine	**325**	*Guatteria melosma* [241]
Melosmine	**326**	*Guatteria melosma* [241]
Duguecalyne	**327**	*Duguetia calycina* [248]
Duguenaine	**328**	*Duguetia calycina* [248]



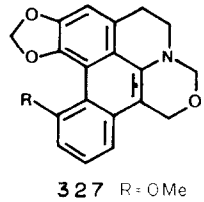
	1	2	3	6	7	9	10
303	OMe	OH	—	H	OHα	—	—
304	OCH_2O		—	Me	OHβ	OMe	OMe
305	OCH_2O		OMe	Me	OHβ	—	—
306	OCH_2O		OMe	*N*-oxy	OHβ	—	—
307	OCH_2O		—	Me	OMeβ	—	—
308	OCH_2O		—	*N*-oxy	OMeβ	—	—
309	OCH_2O		—	H	OHβ	OMe	—
310	OCH_2O		—	H	OMeβ	OMe	—
310bis	OCH_2O		—	H	OHβ	—	—
311	OCH_2O		—	H	OHα	—	—
312	OCH_2O		—	Me	OHβ	OMe	—
313	OCH_2O		—	*N*-oxy	OHβ	OMe	—
314	OCH_2O		—	Me	OMeβ	OMe	—
315	OCH_2O		—	*N*-oxy	OMeβ	OMe	—
316	OCH_2O		—	Me	OHβ	—	—
317	OCH_2O		—	*N*-oxy	OHβ	—	—
318	OMe	OH	—	Me	OHβ	—	—
319	OCH_2O		—	H	OMeβ	—	—
320	OCH_2O		OMe	Me	OHβ	OMe	—
321	OCH_2O		—	Me	OMeβ	OH	—
322	OCH_2O		—	Me	OHα	—	—



323 R = H
324 R = Me



325 R = Me
326 R = H

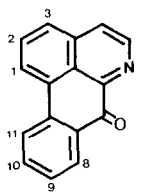


327 R = OMe
328 R = H

Scheme 7. 7-Substituted aporphines from Annonaceae.

Table 11. Occurrence of oxoaporphines in Annonaceae

Alkaloid	Formula	Sources
Atherospermidine	**329**	*Enantia polycarpa* [178]
		Guatteria psilopus [250]
Lanuginosine (oxoxylopine)	**330**	*Annona squamosa* [128]
		Enantia pilosa [252]
		Polyalthia emarginata [226]
		Polyalthia oliveri [138]
		Xylopia brasiliensis [236]
		Xylopia buxifolia [190]
		Xylopia lemurica [257]
Liriodenine	**331**	*Annona cherimolia* [191]
		Annona glabra [118, 119, 258]
		Annona montana [193, 286]
		Annona reticulata [195, 196, 259]
		Annona squamosa [197]
		Asimina triloba [222]
		Cananga latifolia [54]
		Cananga odorata [234]
		Enantia pilosa [252]
		Enantia polycarpa [178]
		Fusaea longifolia [133]
		Guatteria modesta [247]
		Isolona campanulata [139]
		Melodorum punctulatum [238]
		Mitrella kentii [221]
		Pachypodanthium staudtii [210, 225]
		Polyalthia emarginata [226]
		Polyalthia nitidissima [235]
		Polyalthia oliveri [138]
		Pseuduvaria sp. [235]
		Pseuduvaria cv. *grandifolia* [235]
		Schefferomitra subaequalis [235]
		Uvariopsis guineensis [260]
		Xylopia brasiliensis [236]
		Xylopia buxifolia [190]
		Xylopia pancheri [185]
		Xylopia vielana [261]
Lysicamine (oxonuciferine)	**332**	*Enantia chlorantha* [212]
		Enantia polycarpa [178]
		Polyalthia suaveolens [249]
O-Methylmoschatoline	**333**	*Duguetia eximia* [132]
		Enantia chlorantha [212]
		Guatteria subsessilis [256]
Oxoanolobine	**334**	*Guatteria melosma* [241, 262]
Oxoglaucine (*O*-methylatheroline)	**335**	*Annona purpurea* [227]
Oxolaureline (lauterine)	**336**	*Guatteria elata* [263]
Oxopukateine	**337**	*Duguetia eximia* [132]
Oxopurpureine	**338**	*Annona purpurea* [227]
Oxoputerine	**339**	*Duguetia calycina* [224]
		Duguetia eximia [132]
		Guatteria elata [263]
Oxostephanine	**340**	*Polyalthia suaveolens* [249]
Subsessiline	**341**	*Guatteria subsessilis* [255, 256]
No name ('compound D')	**342**	*Guatteria melosma* [241]



	1	2	3	8	9	10	11
329	OCH_2O		OMe	—	—	—	—
330	OCH_2O		—	—	OMe	—	—
331	OCH_2O		—	—	—	—	—
332	OMe	OMe	—	—	—	—	—
333	OMe	OMe	OMe	—	—	—	—
334	OCH_2O		—	—	OH	—	—
335	OMe	OMe	—	—	OMe	OMe	—
336	OCH_2O		—	—	—	OMe	—
337	OCH_2O		—	—	—	—	OH
338	OMe	OMe	OMe	—	OMe	OMe	—
339	OCH_2O		—	—	—	—	OMe
340	OCH_2O		—	OMe	—	—	—
341	OMe	OMe	OMe	—	OH	—	—
342	OH*	OMe	OMe*	—	—	—	—

*In **342**, these substituents may be reversed.

Scheme 8. Oxoaporphines isolated from Annonaceae.

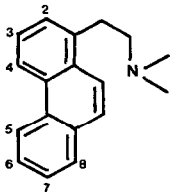
were also recorded in Lauraceae, Magnoliaceae and Menispermaceae [237, 243, 249]. Lastly, it is solely in the Annonaceae that C-7 methoxylated aporphines occur [243]. It is also of interest to note that several *N*-oxides of these alkaloids have been isolated and they do not seem to be artefacts.

Oxoaporphines. Fourteen oxoaporphines, **329–342**, were isolated from various Annonaceous plants, liriodenine (**331**) being ubiquitous (Table 11; Scheme 8). From the structural point of view, these oxoaporphines are rarely substituted at positions 3, 9, 10 and 11; oxostephanine (**340**) is a rare example of an 8-substituted aporphine. The molecular structure, **341**, of subsessiline [255] described herein, is a revision of the original one proposed during the extraction from *Guatteria subsessilis* [256]. The structure of the oxoaporphine (**342**) isolated from *Guatteria melosma* is not yet fully elucidated (1-hydroxy-2, 3-dimethoxyoxoaporphine, or 1,2-dimethoxy-3-hydroxy-oxoaporphine).

Phenanthrenes. Ten members, **343–352**, belonging to the limited group of aminoethylphenanthrene derivatives ('open aporphines') have been found in the Annonaceae (Table 12; Scheme 9). None possess substituents on C-5 and C-6 (corresponding to positions 10 and 11 of the aporphines). On the other hand, the

Table 12. Occurrence of phenanthrenes in Annonaceae

Alkaloid	Formula	Sources
Atherosperminine	**343**	*Annona montana* [193]
		Annona muricata [180, 182]
		Duguetia calycina [224]
		Enantia chlorantha [212]
Argentinine	**344**	*Annona montana* [193]
		Enantia chlorantha [212]
		Monodora angolensis [189]
Methoxyatherosperminine	**345**	*Meiocarpidium lepidotum* [264]
Methoxyatherosperminine *N*-oxide	**346**	*Meiocarpidium lepidotum* [264]
Methoxy-8-uvariopsine	**347**	*Uvariopsis guineensis* [260]
Noratherosperminine	**348**	*Duguetia calycina* [265]
Noruvariopsamine	**349**	*Uvariopsis guineensis* [260]
Uvariopsamine	**350**	*Uvariopsis guineensis* [260]
Uvariopsamine *N*-oxide	**351**	*Uvariopsis guineensis* [260]
Uvariopsine	**352**	*Uvariopsis congolana* [267]
		Uvariopsis guineensis [260]
		Uvariopsis solheidii [266]



	N	2	3	4	7	8
343	$(Me)_2$	—	OMe	OMe	—	—
344	$(Me)_2$	—	OH	OMe	—	—
345	$(Me)_2$	OMe	OMe	OMe	—	—
346	*N*-oxy*	OMe	OMe	OMe	—	—
347	$(Me)_2$	—	OCH_2O		OMe	OMe
348	H, Me	—	OMe	OMe	—	—
349	H, Me	—	OMe	OMe	OMe	OMe
350	$(Me)_2$	—	OMe	OMe	OMe	OMe
351	*N*-oxy*	—	OMe	OMe	OMe	OMe
352	$(Me)_2$	—	OCH_2O		OMe	—

*In **346** and **351**, *N*-oxy means the *N*-oxide of the $N(Me)_2$ compounds.

Scheme 9. Phenanthrenes isolated from Annonaceae.

four phenanthrenes **347**, **349**, **350** and **351**, extracted from *Uvariopsis guineensis* [260], are all, strangely enough, substituted at C-8.

Miscellaneous isoquinoline-type alkaloids

Three isoquinoline-type alkaloids may be recorded herein. Fusein (**353**) was isolated from trunk-wood of the Amazonian *Fusaea longifolia* [129]. The amide group clearly differentiates fuseine from all other aporphines, and it was thought that 5-oxoaporphines, such as fuseine, might arise by the oxidation of aporphines and function as intermediates in the biosynthesis of aristolochic acids [133]. Investigation of the bark of *Schefferomitra subaequalis* [217, 268] afforded a lactam alkaloid which was found to be identical to aristolactam B2, **354**, previously reported from *Aristolochia argentina*; it is structurally related to aristolochic acids. Probovatine, **355**, recently isolated from trunk-bark of *Duguetia obovata*, was thought to be a spirodienone related to the proerythrinadienone group [269]. But it was recently shown [270] by X-ray crystal analysis that probovatine in fact belongs to the morphinanedienone group and is identical to sebiferine earlier isolated from *Litsea sebifera*, Lauraceae.

Another morphinanedienone, pallidine **355bis**, has very recently been found in the aerial parts of *Desmos tiebaghiensis* [271]. Sebiferine and pallidine seem to be the only two examples of morphinanedienones reported so far in the Annonaceae.

Non-isoquinoline alkaloids

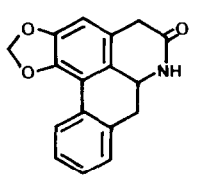
Surprisingly, caffeine (**356**) has been found to be one of the major constituents of *Annona cherimolia* seeds [272]. Similarly, quinidine (**357**) and hydroquinidine (**358**) were reported in the bark of *Enantia polycarpa* [215, 273] and quinidine (**357**) in the bark of *Enantia pilosa* [215], but these unexpected quinoline alkaloids were not found again by other workers [178, 213, 252].

From the stem bark of *Cananga odorata* was isolated an alkaloid named canangine [234]; its identity with eupolauridine, **359**, a new naphthyridine alkaloid recently isolated from *Eupomatia laurina*, was later established [274]. Occurrence of eupolauridine in both *Eupomatia laurina* and *Cananga odorata* may be of taxonomic significance, since several authors have included *Eupomatia* in Annonaceae before considering it as the sole genus of the family Eupomatiaceae [18].

Investigation of the trunk wood of *Onychopetalum amazonicum* [134] yielded the structurally new alkaloid onychine, 1-aza-4-methylfluorenone, **360**, and it was suggested [134] that its biosynthesis involves phenylalanine and mevalonate in an interesting pathway leading to the pyridine nucleus.

Recently the isolation of two new alkaloids of an unusual type, namely annomontine (**361**) and methoxyannomontine (**362**), from the stem and root bark of *Annona montana*, was reported [275, 286]. They are the first examples of a new class of pyrimidine-β-carboline alkaloids, composed by an harman moiety linked to 2-aminopyrimidine.

A last group of alkaloids occurring in the Annonaceae consists of isoprenylindoles and sesquiterpenylindoles. The simplest compound in this series



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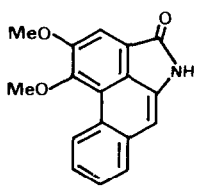

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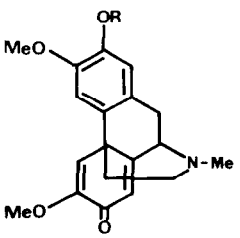
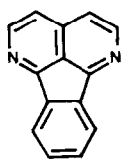


355 R = Me
355bis R = H



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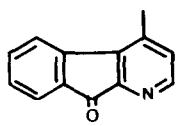

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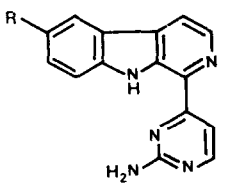


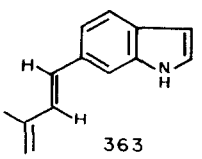
361 R = H
362 R = OMe

is the isoprenylindole (**363**), 6-(*trans*-3-methylbuta-1,3-dienyl)-indole, isolated from the seeds of *Monodora tenuifolia* [276]; the *trans*-configuration of the isoprenyl side chain was assigned later [277] while the synthesis of **363** was being carried out [277]. 3,6-Bis(γ, γ-dimethylallyl)-indole (**364**) was reported [278] as the main alkaloid in the stem bark of *Uvaria elliotiana*; **364** is the first naturally occurring indole substituted only by two unlinked isoprenoid units [278].

Lastly, since 1976, several original sesquiterpenylindoles have been discovered in two species of African *Polyalthia*, *P. oliveri* and *P. suaveolens*. First, from *Polyalthia oliveri* was isolated the structurally novel indolosesquiterpene polyalthenol (**365**) [138, 279]. A hypothetical biogenetic scheme was proposed on the assumption of a drimanic pyrophosphate having trapped tryptophan, with extrusion of dehydroalanine or serine, and the resultant indolosesquiterpene having undergone acid-catalysed rearrangement [279]. A polyalthenol-related indolosesquiterpene has been provisionally identified in *Isolona campanulata*, but its total structure has not been fully established [139]. *Polyalthia suaveolens* yielded seven sesquiterpenylindoles: first, polyalthenol (**365**) together with two isomers, isopolyalthenol (**366**) and neopolyalthenol (**367**) [140] and a novel indolosesquiterpene polyveoline **368**, from a Congolese *Polyalthia suaveolens* [249, 280, 281]; second, three other new indolosesquiterpenes, polyavolensine (**369**), polyavolensinol (**370**) and polyavolensinone (**371**), isolated from a Nigerian *P. suaveolens* [282]; but these last three compounds were not found in the species from Congo [140, 281].

CONCLUSION

The above survey indicates that the literature on Annonaceae has grown considerably in the last decade and a vast field is now open to the chemist, taxonomist and pharmacologist for in-depth investigations. Of more than 2000 species classified in 120 genera, only 150 species (*ca* 7%) belonging to 41 genera (*ca* 33%) have been investigated so far. Moreover, some of the studies involved are of early origin, very fragmentary, and incomplete. In view of this, any attempt to draw valid chemotaxonomic conclusions would be futile. However it is apparent that both non-alkaloidal and alkaloidal compounds show relationships amongst some species of the same



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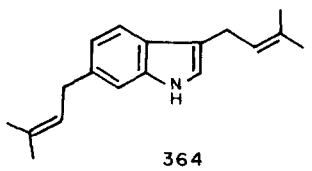

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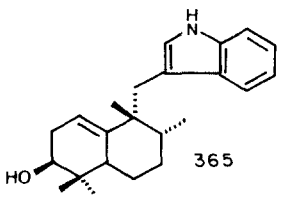

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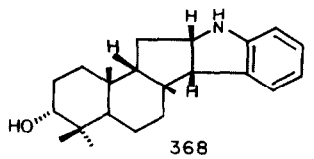

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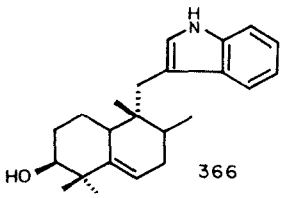

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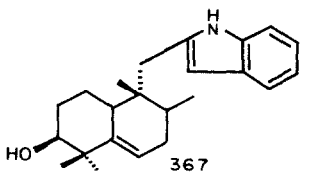

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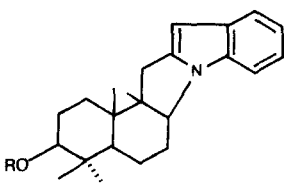
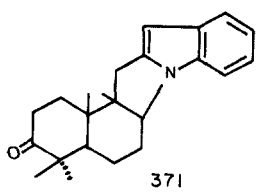


369 R = Ac
370 R = H



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genus or of different genera, and amongst Annonaceous species and species belonging to phylogenetically related families such as those of Magnoliales, Laurales, Piperales, Aristolochiales. In this connection, among the non-alkaloidal components, the flavonoids elaborated by the genus *Uvaria* and the diterpene derivatives of the kaurane series occurring in the genera *Annona* and *Xylopia* are worth mentioning. The same applies to ishwarane, present in *Cymbopetalum* and in *Aristolochia*, and to goniothalamin, found in *Goniothalamus* and in *Cryptocarya*.

Among the alkaloidal components, it is interesting that isoquinolines—which have all been found to have benzylisoquinolines as *in vivo* precursors [169]—are the main alkaloidal constituents of the Annonaceae. Aporphinoids are the largest class of compounds occurring in this family and, excepting *Phaeanthus* and *Onychopetalum*, are common to all the Annonaceous alkaloid-containing plants so far investigated. Besides biogenetic implications, the isolation of isoquinolines is also significant from the chemotaxonomic point of view. Many species elaborate aporphines with their corresponding oxoaporphines, which supports the view that oxoaporphines are formed in plants from corresponding aporphines. This fact also favours the establishment of chemotaxonomic relationships between the species of the Annonaceae. Further support is also provided with the isolation of the same alkaloid(s) from different species of the same genus (for example, xylopine in *Xylopia*), or by the occurrence of the same alkaloid or alkaloids with similar substitution patterns in species belonging to different genera of the family (e.g. 7β-substituted aporphines in *Enantia, Guatteria, Isolona, Pachypodanthium* and *Polyalthia*).

Moreover, some of the alkaloidal and non-alkaloidal constituents of Annonaceae are pharmacologically important, either individually (e.g. *C*-benzylated flavanones: cytotoxic and antimicrobial properties [65–79]; diterpenes: antitumor activity [117]; oliveroline: antiparkinsonian properties [283]; liriodenine: antitumor, antibacterial, and antifungal activities [258, 284], or because they belong to a group which is known to produce many medicinal compounds (e.g. isoquinoline alkaloids). Ethnopharmacological and chemical studies on Annonaceous plants are as yet not advanced enough to ascertain whether the various folk medicinal uses known are supported by the pharmacological activites of the constituents.

Acknowledgement—One of us (B.M.) thanks I.F.S. (Sweden) for a research grant.

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