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A PHYTOCHEMIST IN THE AFRICAN RAIN FOREST

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Key Word Index—Annonaceae; Ebenaceae; Guttiferae; Rutaceae; African rain forest zone; secondary metabolites; chemotaxonomy; chemical ecology.

Abstract—The results of phytochemical studies carried out by the author on species of Annonaceae, Ebenaceae, Guttiferae and Rutaceae collected from within the rain forest zone of tropical Africa are reviewed. Particular attention is paid to the distribution of compounds, from both the chemotaxonomic viewpoint and with regard to possible ecological implications.

INTRODUCTION

This paper reviews the contribution made over the past fifteen years by the author and his collaborators to our understanding of the phytochemistry of species of the plant families Annonaceae, Ebenaceae, Guttiferae and Rutaceae indigenous to the rain forest zone of Africa. In particular it deals with the attempt to make a comprehensive survey in two areas, (a) the rain forest zone in Ghana, and (b) the coastal rain forest zone in the United Republic of Cameroon (Fig. 1).

Historically the association with the flora of the west African rain forest stems from the author's own doctoral studies which were concerned with the phytochemistry and chemotaxonomy of the genus *Zanthoxylum* (*Fagara*) (Rutaceae) and at a practical level dealt primarily with species of Nigerian and Ghanaian origin. From this starting point collaborative studies with the late J. B. Hall, then of the Department of Botany, University of Ghana, and his colleagues led to the expansion of these investigations to cover other genera of the Rutaceae found in Ghana. It was during the course of this development that the author's own exposure to tropical rain forests in both Africa and south-east Asia brought into focus the complexity of this ecosystem and the problems involved in attempting to use chemically diverse secondary metabolites in taxonomic studies without placing those compounds and their producers in their proper ecological context.

At this stage the opportunity arose to contribute to long-term ecological studies in rain forest in Cameroon. The Cameroonian research programme, which has been centred in the Douala-Edea Forest Reserve and more recently in the Korup Forest Reserve (Fig. 1, inset), has a number of goals. High among these have been attempts to understand the distribution of tree species in relation to physical environmental factors (in the course of which over 50 000 individual trees have been mapped and named [1]), and to explain primate food selection on the basis of plant chemistry [2–6]. The detailed information on the location and identification of individual taxa in the two Reserves has also provided an ideal reservoir of information and material for phytochemical studies. These studies have been undertaken systematically, concentrating on surveys of as many sympatric species within each plant family as possible. To date such surveys have extended to three of the families that are common elements at both Douala-Edea and Korup, the

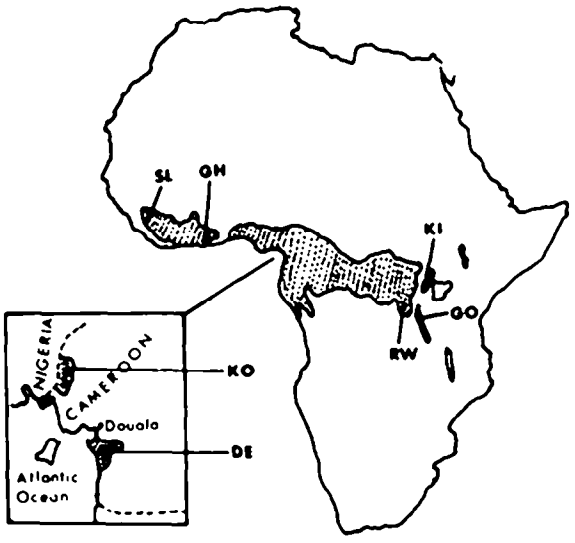


Fig. 1. Map of Africa showing rain forest zones (stippled areas). Collection sites for plant material are: GO, Gombe Reserve, Tanzania; RW, Rwanda; KI, Kibale Forest, Uganda; DE, Douala-Edea Forest Reserve, Cameroon; KO, Korup Forest Reserve, Cameroon; GH, Ghanaian rain forest zone; SL, Tiwai Island, Sierra Leone.

*Winner of the 1985 Tate and Lyle Award of the Phytochemical Society of Europe. This review was presented during a symposium of the Society held at the University College of Wales in Swansea, April 1985.

Annonaceae, Ebenaceae and Guttiferae (Table 1). Comparable investigations of other families are underway or envisaged for the future. In addition to the two areas of west Africa which have contributed the bulk of material to these investigations further samples have been obtained opportunistically from other areas, notably Sierra Leone, Nigeria, Rwanda and the gallery forests of Uganda and Tanzania (Fig. 1).

In this review I intend to discuss the types of compounds that have been encountered during investigations carried out on species of the three families noted above and the Rutaceae. It is not intended to give detailed accounts of techniques employed in isolation and structure elucidation other than where some particular feature of the work seems relevant. Such details have been covered in the original papers, which are referred to throughout the text. There will also be some discussion of the taxonomic significance in the distribution of compounds brought to light during these studies but other areas of interest will be mentioned only in passing.

COLLECTION AND DOCUMENTATION OF PLANT MATERIAL

Most of the work discussed below is concerned with the isolation of compounds from stem bark or, more rarely, root bark, heartwood and seeds. The concentration on stem bark material has arisen primarily for transport reasons, particularly in the Cameroon collection areas, which are logistically remote. It is a practical proposition to sun or oven dry ten 1 kg samples of stem bark at a remote forest camp and then transport them back to the laboratory, whereas to process the same number of 1 kg leaf samples is more difficult. Where material has to be retained at field sites after drying the simple procedure of storage in air-tight plastic bags in the dark has proved satisfactory. Seed samples can only be collected opportunistically; fortunately when fruiting does occur it is often synchronous within a species, which means that appreciable quantities of seeds become available.

A high priority has been given to collection of voucher material for all studies. This material is variously housed at the major herbaria in Edinburgh (particularly Rutaceae), Kew (all early Cameroonian material), Missouri (some later Cameroonian material) and the University of Ghana (Ghanaian Ebenaceae).

THE RUTACEAE

The Rutaceae is widely accepted as being made up of three major subfamilies together with some small, satellite groupings. All three of the large subfamilies, the Aurantioideae, Toddalioideae and Rutoideae, are pan-tropical in distribution. In Africa Aurantioideae are, apart from introduced *Citrus*, rather rare.

The genus Zanthoxylum *(subfamily Rutoideae)*

Zanthoxylum, still often referred to as *Fagara*, is a widespread genus in the forest zone of west Africa where most species, whether they be trees or lianes, are readily recognized by their very spiny barks and large compound leaves. Although the generic name *Fagara* has been widely used in Africa it now seems beyond doubt that viewed on a pan-tropical basis African taxa are congeneric with those from Asia and the Americas and that the correct generic name is therefore *Zanthoxylum* (note: not *Xanthoxylum* or *Xanthoxylon*) [7].

Both root and stem barks have proved to be rich sources of alkaloids although unlike some other *Zanthoxylum* species those in Africa seem to produce few coumarins [8]. Chemically the alkaloids can be divided into two groups.

(a) Methanol soluble quaternary amines and alkaloids, the latter based on the 1-benzyltetrahydroisoquinoline (1-BTIQ) nucleus, e.g. candicine (1), tembetarine (2), magnoflorine (3) and berberine (4) [9].

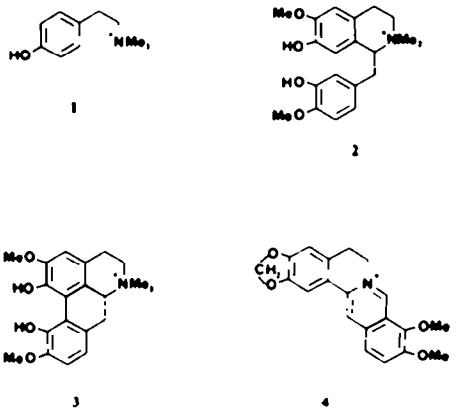


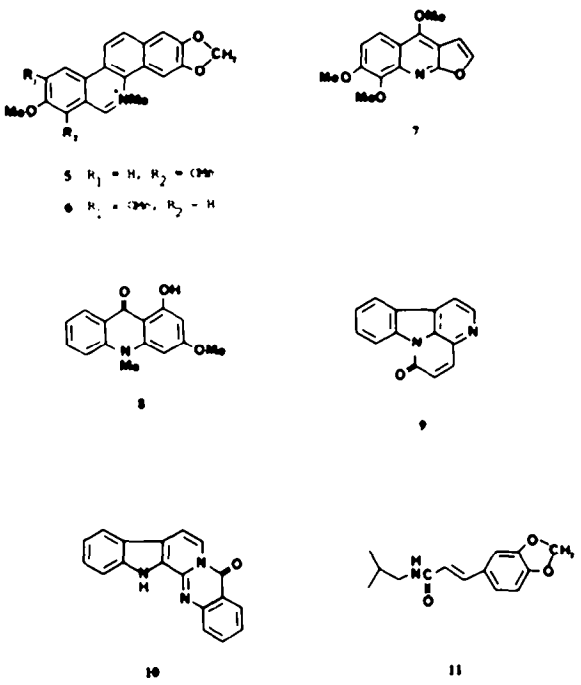
Table 1. Relative importance of Annonaceae, Ebenaceae and Guttiferae in the Douala-Edea and Korup Forest Reserves, Cameroon

Site	Measure	Annonaceae	Ebenaceae	Guttiferae
Korup	No. of species	21	15	10
	% of total individuals*	3.41	5.95	2.27
	% of total biomass	2.39	2.32	1.41
Douala-Edea	No. of species	14	11	8
	% of total individuals†	4.04	9.59	5.24
	% of total biomass	2.97	3.80	3.30

*Based on a sample of approximately 41 730 trees.
†Based on a sample of approximately 25 000 trees.

(b) Petroleum ether soluble alkaloids. These, somewhat surprisingly, include another group of 1-BTIQs, the benzophenanthridines, typified by chelerythrine (5) and nitidine (6). Others, based on anthranilic acid or tryptophan rather than phenylalanine and tyrosine precursors, are furoquinolines such as skimmianine (7), which are very common in the family as a whole [10], acridones (8), canthinones (9) and indoloquinazolines (10). The cinnamylisobutylamide derivative fagaramide (11), which has recently been shown to have molluscicidal and insecticidal properties [11], is also quite widely distributed.

Nine species have been studied by the author, primarily from Ghanaian sources but also from Nigeria, Cameroon and Kenya. The types of alkaloids isolated from each and more recent reports for other species from this area are given in Table 2. The profiles of all species analysed share a common range of quaternary 1-BTIQ alkaloids. Interesting features include the ubiquity of aporphines with the 1,2,10,11-substitution pattern (i.e. 3), whilst the alternate 1,2,9,10-pattern appears to be absent. By contrast in the benzophenanthridines the two substitution patterns (comparable to both 1,2,9,10- and 1,2,10,11-substituted aporphines) do occur (i.e. 5 and 6) and each appears to dominate in some species, although not to the complete exclusion of the other. A further interesting feature of the benzophenanthridines is their apparent concentration in external tissues of the root bark [14] whereas the other 1-BTIQs occur more generally in stem and root bark tissues. Among the remaining alkaloids the furoquinolines and amides seem to be widely distributed, perhaps ubiquitous, but others are all at present restricted to one or two species. As the distribution of alkaloid types within these taxa seems to consist either of universal or highly restricted occurrence they seem to have little chemotaxonomic value at the infrageneric level although, in the wider context of the Rutaceae as a whole and the affinities of the Rutaceae and Rutales, their occurrence may well have considerable significance [7, 10].



The Toddalioideae

The Toddalioideae is represented in Ghana by a number of rather rare species assigned to the genera *Araliopsis*, *Diphasia*, *Oricia*, *Teclea* and *Vepris*. Between 1975 and 1978 we were able to collect five of these species for examination, one from each genus. The results of that survey [15] showed three of them to be chemically similar, *D. angolensis*, *O. suaveolens* and *T. verdoorniana* all yielding acridone (8) and furoquinoline (7) alkaloids. As well as their chemical homogeneity these three taxa show

Table 2. Distribution of alkaloids in *Zanthoxylum* species of the African rain forest zone [11–13]

Species	Source	Type of alkaloid								
		AM	BTIQ	AP	BZP	AMD	QU	ACR	CAN	IND
Z. boutense	Cam	+	+	+	+	−	+	−	−	−
Z. chalybeum	Ken*	+	+	+	+	+	+	−	−	−
Z. dinklagei	Gha/Cam	−	+	+	+	−	+	−	−	+
Z. gillettii[a]	Gha/Nig/Ken*	−	+	+	+	+	+	+	−	−
Z. lemairei[b]	Gha	+	+	+	+	+	+	−	−	−
Z. leprieurii[c]	Gha/Nig/Ken	−	+	+	+	−	+	+	−	−
Z. rubescens[d]	Gha/Nig	+	+	+	+	+	+	−	−	−
Z. tessmannii	Nig/Cam	−	−	−	+	+	−	−	−	−
Z. viride	Gha/Nig	−	+	+	+	−	+	−	+	−
Z. xanthoxyloides	Nig*	−	+	+	+	+	+	−	+	−

[a] *Fagara macrophylla*; [b] *Z. parvifoliolum*; [c] *F. angolensis* and *F. benlensis*; [d] early reports of acridones can be discounted due to misidentification of plant material.

Sources: Cam = Cameroon; Gha = Ghana; Ken = Kenya; Nig = Nigeria. * denotes species indigenous to savanna round forest edges or light-gaps only.

Types of alkaloid: AM = quaternary amine; BTIQ = 1-benzyltetrahydroisoquinoline; AP = aporphine; BZP = benzophenanthridine; AMD = amide; QU = furoquinoline, pyranoquinoline; ACR = acridone; CAN = canthinone; IND = indoloquinazoline.

close morphological similarity conflicting with their generic separation. However, Hall and Swaine [16] found that from an ecological standpoint the three were very different, *O. suaveolens* being restricted to the wettest parts of the forest zone, *T. verdoorniana* to the driest parts near the savanna edge, and *D. klaineana* to an intermediate zone not overlapping with the other two. All the above observations (chemical, morphological, ecological) are interpreted as favouring the hypothesis that a wide-ranging ancestral species had differentiated into three daughter species with different ecological tolerances [15].

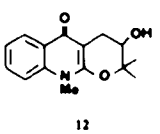
The remaining two species in that original survey showed somewhat different chemical profiles. Both lacked acridones, *A. soyauxii* (= *tabouensis*) being rich in furoquinolines and also yielding linear pyranoquinolines such as ribalinine (**12**), indoloquinazolines (**10**) and the protolimonoid flindissol (**13**), whereas *V. heterophylla* (= *T. sudanica*) gave only furoquinolines. When the survey was widened to take in populations of *O. suaveolens* and *A. tabouensis* from Nigeria and Cameroon respectively significant differences in chemical profiles were found. *O. suaveolens* from Nigeria gave primarily the angular pyranoquinoline oricine (**14**) with only traces of acridones and no furoquinolines. *A. soyauxii* from Cameroon did not appear to contain **13** and gave the enantiomer of **12**.

In the case of *O. suaveolens* a possible explanation for the variation of alkaloid chemistry was proposed relating it to Janzen's hypothesis [17] that sympatric species would select for maximum differentiation in secondary metabolic profiles in order to maximise the 'detoxification problems' faced by a herbivore in any given ecosystem. In Ghana *O. suaveolens* and *D. klaineana* do not overlap in habitats and are chemically similar. However, in Nigeria *O. suaveolens* occurs in a drier zone where it is sympatric with *D. klaineana* and this may have provided the stimulus for a change of emphasis in the preferred alkaloid-producing biogenetic matrix of *O. suaveolens* so that chemical diversity is maximized.

Since 1978 a number of further reports have been published on west and central African species of Toddalioideae indicating that the range of compounds found in the original Ghanaian survey were typical and also bearing out Hall's contention [15] that the generic characters used within this group are unsatisfactory and that it is perhaps better to consider most of these taxa as part of a single large genus, comparable to *Zanthoxylum*. For example, prenylated furoquinolines, limonoids and acridones have been found in other species of *Teclea* [18, 19], furoquinolines, pyranoquinolines, indoloquinazolines and limonoids in *Vepris* spp. [20–22], pyranoquinolines and limonoids in *Oriciopsis* [23] and acridones, furoquinolines and pyranoquinolines in *Oricia* [24]. A full listing of isolated alkaloids are available in the recent review by Mester [12].

One particularly interesting find has been a group of pyranoquinolone dimers, isolated independently from *Vepris louisii* collected in Cameroon and *Oricia renieri* collected in Rwanda. In all a total of four compounds have been isolated, vepridimerines A (**15**) and B (**16**) based on two pyrano-2-quinolone units and vepridimerines C (**17**) and D (**18**) based on one pyrano-2-quinolone and one pyrano-4-quinolone unit. The dimers were characterized primarily by means of high-field ^{1}H NMR [25]. The analogous paraensidimerines, differing only in the absence of the methoxy substituents, occur in a South American species of Rutaceae, *Euxylophora paraensis* [26], and their structures have been confirmed by X-ray analysis. The vepridimerines are part of a now quite extensive group of dimeric alkaloids found in the Rutaceae that appear to be formed by Diels–Alder type cycloaddition reactions [27]. None of these alkaloids are optically active, suggesting that they arise *via* a non-enzymatic mode of formation.

One further species from the Toddalioideae has been examined, *Fagaropsis angolensis*, a large deciduous tree of dry, predominantly evergreen, forest in East Africa. The stem bark, collected in Uganda, yielded three unusual benzophenanthridine alkaloids, the 6-acetonyl derivatives of dihydrochelerythrine (**19**), dihydronitidine (**20**) and dihydrosanguinarine (**21**), and the limonoids rutaevin (**22**) and limonin diosphenol (**23**) [28]. These metabolites have proved most useful in resolving the confused taxonomic position of *Fagaropsis* and place it among the small group of rutaceous taxa (others are *Zanthoxylum*, *Phellodendron* and *Toddalia*) capable of synthesizing 1-BTIQ alkaloids. These taxa, irrespective of their previous placement in either the Rutoideae or Toddalioideae, are probably best considered together in the systematics of the Rutaceae. It is suggested that they represent the remains of the proto-rutaceous chemical type and as such reflect the evolution



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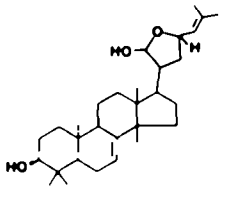

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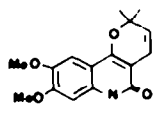

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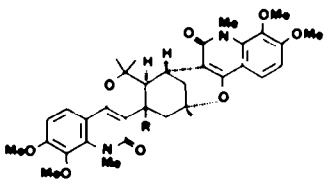

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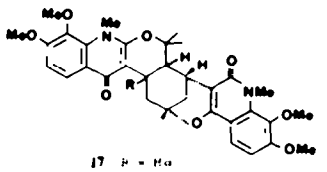
16 R = H



17 R = Me

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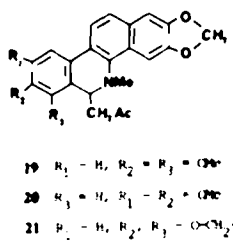
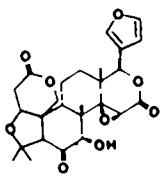


19 R_1 = H, R_2 = R_3 = OMe

20 R_3 = H, R_1 = R_2 = OMe

21 R_1 = H, R_2, R_3 = OCH_2O



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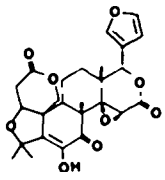

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of the Rutales from the 1-BTIQ-rich families of the Ranales, such as the Berberidaceae and Papaveraceae [10, 28–30]. They do not support the opposing view [28] that *Fagaropsis* has its closest allies among the Aurantioideae.

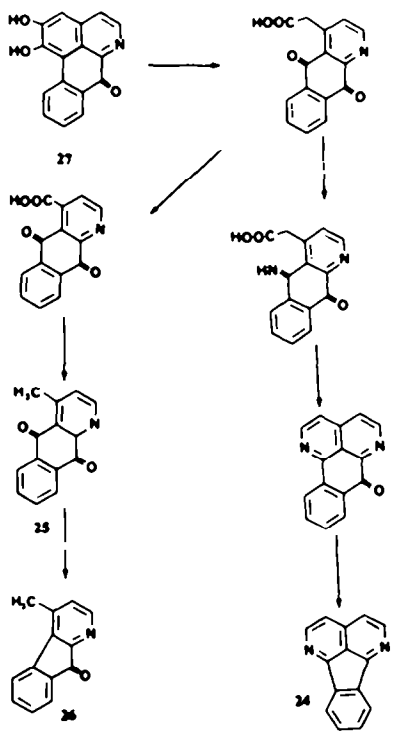
THE ANNONACEAE

The Annonaceae make a very significant contribution to the tree flora of the west African rain forest [31]. In both Douala-Edea and Korup Forest Reserves the family is conspicuous for the number of species of tree and liane that are present, although very few of these species could be classified as common with the result that the contribution of the family to total biomass is lower than would be anticipated from the number of species (Table 1). The chemistry of the family was comprehensively reviewed by Leboeuf *et al.* in 1982 [32]. That review illustrated the propensity of the Annonaceae for the production of 1-BTIQ alkaloids, a feature which is typical of the supposedly primitive families of the Ranales. However, the chemical profile of the Annonaceae suggested by that review has clearly been strongly biased by the excellent and extensive work done by Cavé, Leboeuf and their students which has been specifically directed toward the 1-BTIQ alkaloids. By contrast our investigations, which have been more general in their interest, reveal a much greater variation in secondary metabolite profiles in the family in which 1-BTIQ alkaloids do not dominate in the manner that might have been anticipated. Indeed, among the alkaloids isolated simple indole derivatives have proved to be quite widespread, whilst a whole range of non-alkaloidal compounds including sesquiterpenes, diterpenes, triterpenes, flavonoids, styrenes and phenylpropenes have been found.

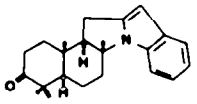
Alkaloids

A number of 1-BTIQ-derived alkaloids have been isolated from species collected in either the Ghanaian or the Cameroonian forests: *Enantia chlorantha* (berberines, 7-methoxyaporphines) [P. G. Waterman, unpublished], *Greenwayodendron* (*Polyalthia*) *suaveolens* [33] (aporphines, 7-oxygenated aporphines), *Monanthotaxis* (*Popowia*) *cauliflora* [34] (aporphines, 7-oxygenated aporphines, berberines), *Cleistopholis patens* [35] (oxoaporphines), *Uvaria ovata* [36] and *Cleistopholis staudtii* [37] (both bis-1-benzylisoquinolines). By contrast extensive studies of the barks of a number of other species, notably *Uvaria angolensis*, *Xylopia aethiopica*, *X. acutiflora*, *X. quintasii* and *Uvariastrum zenkeri*, have failed to reveal any 1-BTIQ alkaloids. The most interesting of the 1-BTIQs isolated have been the alkaloids from *C. patens* root bark [35], eupolauridine (**24**) and its mono- and di-N-oxides, cleistopholine (**25**) and onychine (**26**). It is suggested [38] that these alkaloids are actually the products of catabolism of a 1,2-dihydroxyoxoaporphine (**27**) precursor through fission of the 1,2-bond (Scheme 1). It is important to note that these alkaloids appear to be restricted to the root bark. The stem bark by contrast yields only oxoaporphines and non-alkaloidal compounds.

The major isolates of *Greenwayodendron suaveolens* collected in the Korup Forest Reserve were a group of neutral or weakly basic nitrogenous compounds made up of an indole nucleus linked through N-1 and C-2 to a sesquiterpene moiety, giving pentacyclic products of which greenwayodendrin-3-one (**28**) is a typical example [33]. These compounds were subjected to extensive high-field NMR investigations in which all protons were assigned and the structure of **28** was subsequently verified by X-ray analysis. Polyveoline (**29**) in which the linkage between sesquiterpene and indole involves C-2 and C-3 of the latter was also isolated [33]. Both **29** and a number of tetracyclic indolosesquiterpenes have been recorded from



Scheme 1. Possible route to the 'aporphinoids' of *Cleistopholis patens* from 1,2-dihydroxyoxoaporphine (**27**).



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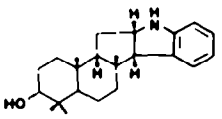

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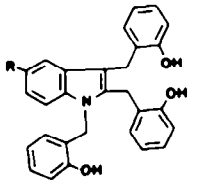
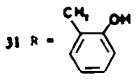
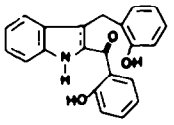


30 R = H

31 R = 



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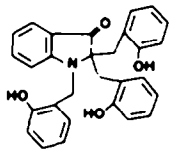

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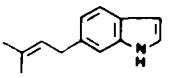


34

the allied species *Greenwayodendron* (*Polyalthia*) *oliveri* [32]. A discussion of the stereochemistry, analytical spectroscopy and nomenclatural confusion that exists among this group of alkaloids, which remain unique to these two species, has recently been published [39].

Another rich source of indole derivatives has been the stem bark of *Uvaria angolensis* collected in the Gombe Reserve in Tanzania. This material yielded [40–42] four compounds in which the indole nucleus was substituted at C-2, C-3, and in some cases N-1 and C-6, with *o*-hydroxybenzyl, or in one case *o*-hydroxybenzoyl, substituents. The structures of the uvarindoles A (**30**) and B (**31**) were easily resolved from ^{1}H and ^{13}C NMR studies [40, 41]. The presence of an *o*-hydroxybenzoyl moiety in uvarindole C (**32**) followed from the UV and MS and its placement at C-2 from the comparative shielding of the ^{13}C NMR resonance for C-2 and deshielding of that for C-3 of the indole nucleus due to the effect of the benzoyl carbonyl [40]. The final compound, uvarindole D (**33**), gave spectral characteristics notably different from the other compounds and was tentatively identified from UV and NMR evidence as a dihydroindole-3-one with gem *o*-hydroxybenzyl substituents at C-2 and another at N-1 [40, 41]. This was later confirmed by an X-ray study [42]. Although Nigerian material of this species had previously been found to be the source of a number of similarly benzylated flavonoids [32] indole derivatives had not been reported.

A further indole, 6-(3,3-dimethylallyl)indole (**34**), occurs in the seeds of *Monodora myristica* collected in Cameroon [43]. Although this was the only compound isolated and characterized other nitrogenous compounds, possibly dimers based on **34**, are also present. A whole range of similar prenylated and diprenylated indoles have recently been found in another west African species, *Hexalobus crispiflorus* [44].

Sesquiterpenes

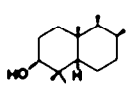
Sesquiterpenes have been recorded from very few Annonaceae [32], although those that have, such as yingzhaosu A and B and ishwarone, are often somewhat unusual. Their sporadic occurrence and chemical diversity is well illustrated by our own investigations which have revealed their presence in species of three genera, *Greenwayodendron*, *Cleistopholis* and *Uvaria*.

No free sesquiterpenes have yet been reported from *Greenwayodendron* species but their presence in the form of the indolosesquiterpenes (**28**, **29**) is obvious. The parent sesquiterpene moiety that is incorporated into the alkaloids is presumed to be of the drimane (**35**) type [39]. In *U. angolensis* the major sesquiterpenes are common bicyclic derivatives of cadinane but these are accompanied by C_{22} compounds formed by the addition of an *o*-hydroxybenzyl unit to a sesquiterpene with subsequent linkage between sesquiterpene and the phenolic hydroxy group to give a benzopyran. These compounds, which are exemplified by uvarisesquiterpene-C (**36**), are still under investigation (for a preliminary report see ref. [45]).

Whilst the root bark of *C. patens* yielded a number of alkaloids the stem bark gave only one, the common oxoaporphine liriodenine, but also gave two sesquiterpenes. These have been characterized [35] as the acyclic farnesoic acid methyl ester (**37**), which bears an obvious affinity to insect juvenile hormone, and its monocyclic derivative (**38**). These sesquiterpenes were obtained in appreciable yield from stem bark samples collected in both Ghana and Sierra Leone but no traces were detected in root bark. Similar sesquiterpenes also occur in another Cameroonian species, *C. glauca* [J. T. Etse and P. G. Waterman, unpublished].

Diterpenes

Whereas sesquiterpenes appear to be sporadically distributed in the Annonaceae diterpenes seem to have a



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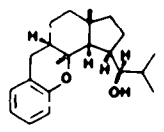

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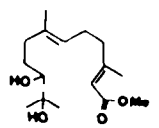

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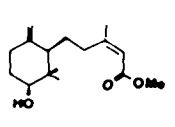

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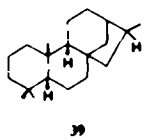
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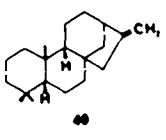
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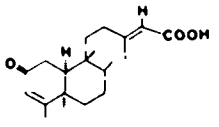
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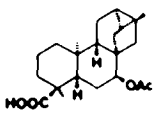
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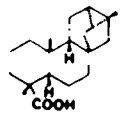
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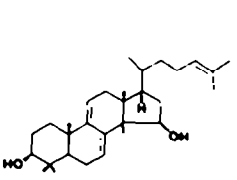
narrow distribution, primarily from species of *Annona* and *Xylopia*, but they occur extensively within these genera. One rich source of kaurane (**39**) and kaur-16-ene (**40**) diterpenes is *X. aethiopica* a large tree, widespread in tropical Africa and with a fruit that finds use as a condiment. In the course of our survey of Annonaceae we have been able to examine the barks of three species to date, *X. aethiopica* [46], *X. quintasii* [47] and *X. acutiflora* [48, 49]. From each a number of diterpenes have been isolated, the majority belonging to either the **39** or **40** structural types. However, in each case these have been accompanied by one major diterpene belonging to another skeletal type. Thus, examination of material from Cameroon revealed *X. aethiopica* stem bark to contain 2-oxokolav-3,13-dien-15-oic acid (**41**), *X. quintasii* yielded 7β-acetoxytrachyloban-18-oic acid (**42**) and *X. acutiflora* the diterpene dimer acutifloric acid (probable structure **43**). This last compound is presumably formed by a Diels–Alder condensation between the 15-oxokaur-16-en-19-oic acid (**44**) which is present in the bark extracts and a bicyclic labdatriene such as **45** (Scheme 2). No labdanes have yet been isolated from this plant.

A further interesting development has been the recent isolation of trachyloban-19-oic acid (**46**) from the stem bark of *X. aethiopica* originating in Sierra Leone [50]. This material did not contain any of the kolavane previously isolated from this species. It should be noted that the carboxylic acid group on C-4 is in this case in the more common axial (C-19) configuration whereas in the trachylobane from *X. quintasii* it is equatorial.

Despite a thorough investigation none of these *Xylopia* species has yielded any alkaloids. This is in direct contrast to investigations on *Xylopia* species originating in Asia and South America where berberine and aporphine alkaloids have commonly been found [32].

Triterpenes

In comparison with other groups of terpenes the search for triterpenes in the Annonaceae has been rather unrewarding [32]. The only two compounds of interest that have arisen to date are polycarpol (**47**) and uvariastrol (**48**). Polycarpol was initially isolated from two African species, *Greenwayodendron* (*Polyalthia*) *oliveri* and *Meiocarpidium lepidotum* and has since been isolated from a number of other species world-wide [32]. A survey for **47** in species from supposedly closely allied families such as Lauraceae, Monimiaceae and Menispermaceae has proved negative suggesting that it is unique to the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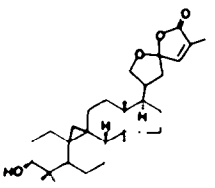
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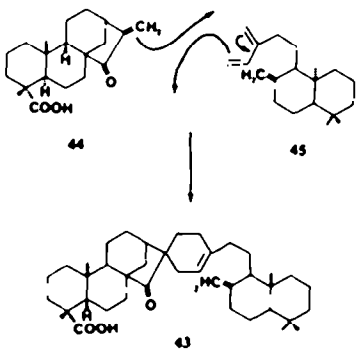
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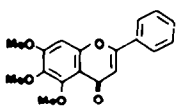
Scheme 2. Route to acutifloric acid (**43**).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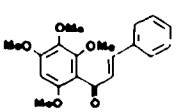
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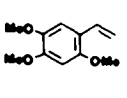
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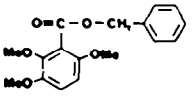
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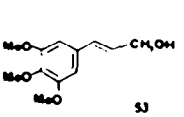
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Annonaceae and therefore has some value as a chemotaxonomic marker [32].

A further source of **47** is the small rain forest tree *Uvariastrum zenkeri* which has also yielded another novel triterpene, uvariastrol (**48**) [51]. The identity of **48** as a cycloartane was easily established by spectroscopic means and the structure of the spiro-fused tetrahydrofuran–furanone system in the side chain derived from MS, ^1H and ^{13}C NMR studies. Uvariastrol remains the only triterpene found in the Annonaceae based on a cycloartane nucleus and the only one in which elements of the C-17 side-chain have been oxidized and cyclized.

Flavonoids

Comparatively few flavonoids have been isolated from the Annonaceae and relatively little has been done on the examination of flavonoid glycosides [32]. One exception has been the stem bark and seeds of the liane *Monanthotaxis* (*Popowia*) *cauliflora* which has yielded a range of flavones, flavanones and chalcones [52, 53] typified by baicalein trimethyl ether (**49**) and 2',3',4',6'-tetramethoxychalcone (**50**). A characteristic of most of the simple flavonoids isolated from the family to date is the absence of substitution on the phenylalanine-derived B-ring.

A survey of the leaves of many Annonaceae from the Douala-Edea Forest Reserve [4] revealed that most contained condensed tannins, more specifically procyanidin tannins. None of the other proanthocyanins were detected in any of the leaf hydrolysates from species included in the survey.

A fascinating sub-group of flavonoids are those from *Uvaria* and *Desmos* species, in which a simple flavonoid nucleus has been substituted in the acetate-derived ring by either one-carbon units (Me or CHO) or, more commonly, by *o*-hydroxybenzyl units. These compounds have attracted particular attention because of their cytotoxicity [32] and much work has been done on the distribution of these compounds in west African species. Flavonoids of this type were also isolated in our study on *U. angolensis* from Tanzania [41], although they were less in evidence than were the analogously benzylated indoles.

Miscellaneous

In addition to the major groups of compounds discussed above our work on the Annonaceae has yielded some other compounds. Most notable was 2,4,5-trimethoxystyrene (**51**) which was obtained in high yield from the stem bark of *Pachypodanthium staudtii* [54]. This simple compound occurs as large discrete crystals on the inner surface of the stem bark and the sample used for initial studies was isolated pure with a pair of forceps! Styrenes are quite possibly of universal distribution in the genus, being found in both bark and seeds of three species [32; K. Panichpol, unpublished]. Simple benzyl benzoates are widespread in *Uvaria* [32] and include a number of highly substituted derivatives such as 2',3',6'-trimethoxybenzoate (**52**) from Ghanaian material of *U. ovata* [55]. Fruits of Annonaceae are often aromatic and this is generally due to the presence of a monoterpene-rich volatile oil. However, the fruit of *Uvariodendron connivens*, another understorey tree from the Cameroonian forests, is a good source of phenylpropenes, including cinnamyl alcohol derivatives such as **53** [56], which, it is interesting to note, do not have the same ring substitution pattern as **51**.

General comments on the phytochemistry of the Annonaceae

Table 3 lists the major isolates found in the annonaceous species from the African forest zone studied by ourselves and by Cavé and his colleagues. The

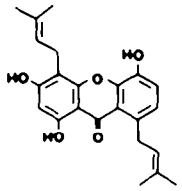
Table 3. Types of secondary metabolites isolated from the barks of Annonaceae from Cameroon

Species	Constituents	
	non-alkaloidal	alkaloidal
Cleistopholis glauca	sesquiterpenes/phenylpropenes	?
*C. patens**	sesquiterpenes	oxoaporphines/'aporphinoids'
C. staudtii	—	bis-1-btiq
Enantia chlorantha	—	aporphines/berberines
Greenwayodendron suaveolens	triterpenes	aporphines/berberines/ indolosesquiterpenes
Isolona campanulata	triterpenes	aporphines
I. hexaloba	?	bis-1-btiq
Monanthotaxis cauliflora	flavonoids	aporphines/berberines
Pachypodanthium confine	styrenes/triterpenes	aporphines/berberines
P. staudtii	styrene	aporphines/berberines
Uvaria angolensis†	benzylated flavonoids benzylated sesquiterpenes	benzylated indoles
Uvariopsis zenkeri	triterpenes	–
Xylopia acutiflora	diterpenes	—
X. aethiopica	diterpenes	—
X. quintasii	diterpenes	—

*Investigated material from Ghana and Sierra Leone.

†Indoles and sesquiterpenes from Tanzanian material only.

metabolic profiles exhibited among these taxa are strikingly diverse with different genera apparently highly specific in their capacities to produce very different types of metabolites. In some cases that diversity is seen within a genus, good examples being in *Cleistopholis* and *Hexalobus* in which some species are specifically bis-benzylisoquinoline producers and others produce rather different alkaloid types. In its diversity the Annonaceae tends to be more extreme than the other families that we have studied in depth. The reason for this greater degree of diversity is unknown but could possibly reflect the archaic nature of the family, in which individual genera have been long separated from one another and during that separation chemical diversification has become more pronounced.



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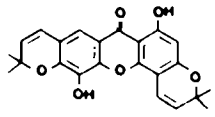

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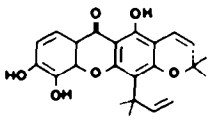

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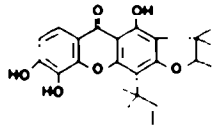

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THE GUTTIFERAE

The Guttiferae (*sensu stricto*) are represented in the Cameroonian forests by five genera, *Garcinia*, *Mammea*, *Pentadesma*, *Allanblackia* and *Symphonia*, and make an important contribution to the biomass in both of the study sites (Table 1). A sixth genus, *Calophyllum*, has been introduced and is found growing close to the coast. The allied Hypericaceae is represented by *Psorospermum*, *Vismia* and *Endodesmia*. To date work has concentrated on just two of thes genera, *Garcinia* and *Mammea*.

Garcinia

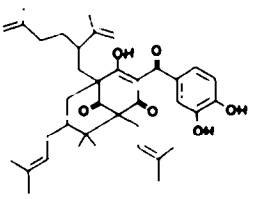
Garcinia is a large genus of about 400 species found as shrubs, understorey trees or trees of the canopy in the rain forests of the old world, with a major concentration of species in south-east Asia and secondary centres in India and west Africa [57]. In all we have managed to collect stem barks from ten species from Cameroon and one from Gombe, Tanzania. In addition we have examined fruit and seeds from *G. kola*, the stem bark of which has been reported on by other workers. From these studies three different types of metabolite have been obtained, xanthones and the allied benzophenones, biflavonoids and lactones.

Xanthones, variously oxygenated and with prenyl and more rarely geranyl substituents, appear to occur widely in the Guttiferae [58]. However, this has not been the case among the west African species examined for xanthones. These have been isolated from the stem barks of only five of the eleven species, in each case a single compound in low concentration ($< 0.01\%$) being reported. Xanthones have not been found in any other plant part in this survey but amounts of material for analysis have often been small.

With the exception of 4,8-di(3,3-dimethylallyl)-1,3,5-trihydroxyxanthone (**54**) from *G. quadrifaria* [59] all of the xanthones have been 1,3,5,6-tetraoxygenated. Rheediaxanthone-A (**55**) occurs in two species, *G. densivenia* [60] and *G. staudtii* [59]; in the former having initially been erroneously assigned the alternative all linear annulation due to misinterpretation of the shifts caused in the ^{1}H NMR spectrum on peracetylation [60, 61]. The remaining two compounds, macluraxanthone (**56**) from *G. ovalifolia* [62] and isorheediaxanthone-B (**57**) from *G. polyantha* [63] both carry 1,1-dimethylallyl substituents. Whilst easily characterized as xanthones complete structural assignment of these compounds has often proved problematical because of paucity of material and difficulty in interpretation of ^{1}H NMR data from acetylated derivatives, a procedure which has been widely employed to locate the substituents *ortho* to positions of acetylation. Improvements in sensitivity and advent of the INEPT technique in ^{13}C NMR have proved most valuable in resolving structural problems, particularly those involving assignment of the position of a single prenyl substituent at C-2 or C-4 of the 1,3-oxygenated A-ring [63].

Xanthones are thought to be formed by cyclization of benzophenones which have themselves been formed from a phenylalanine-derived C_6C_1-unit and three acetate units. In some species highly prenylated benzophenones do themselves occur, either with or without xanthones. Two compounds are particularly common, xanthochymol (**58**) and isoxanthochymol (**59**), sometimes occurring in quite significant amounts, i.e. 0.56 % of **58** in the stem bark of *G. ovalifolia* [62]. One or both of these have been found in five of the west African species to date [63, 64]. The only other benzophenone obtained has been kolanone (**60**) which is an antibacterial principal present in the fruit pulp and seeds of *G. kola* [65]. This is of particular interest as the seeds of this species are chewed by many people in west Africa and are sold as an item of commerce.

The most widespread group of metabolites from the *Garcinia* species studied are the biflavonoids, found in seven of the ten west African species and in *G. huillensis* from Gombe [64]. As well as being most common they are usually also present in highest amounts, in *G. mannii* stem bark reaching the extraordinary level of 10 % of the dry weight [66]. The biflavonoids can be divided into two groups, the flavanone/flavone dimers (**61**) and the biflavanones (**62**), one or other of which tend to dominate in each of the speices [64]. Characterization of these compounds is difficult; successful procedures generally involve field-desorption and chemical ionization MS and permethylation, although care has to be taken with this procedure as ring-opening to give a chalcone-containing biflavonoid (**63**) must be expected. ^{1}H NMR spectra are generally poorly resolved at room temperature due to compounds existing in several conformations but considerable improvements can be achieved by working at



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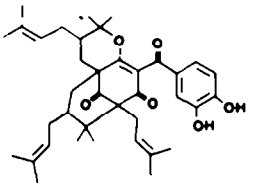

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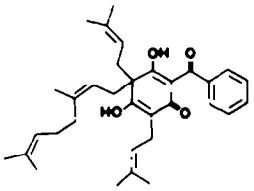

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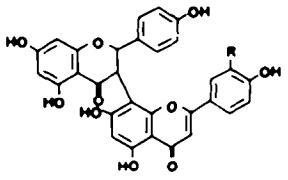

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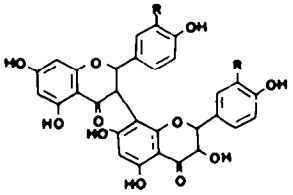

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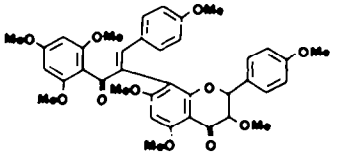

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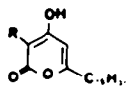
elevated temperatures (120°) using DMSO-d_6 as solvent [66, 67].

Garcinia conrauana, a tree species with a particularly large fruit, is markedly different in its chemistry from the other west African species. Initial examination of the bark of individuals collected in the Douala-Edea Reserve gave a compound $C_{20}H_{34}O_3$ characterized as the novel lactone, conrauanalactone (**64**) [68]. Later examination of seeds from Douala-Edea and stem bark from Korup gave, as well as **64**, its 3-prenylated derivative **65** [69]. Yields of these lactones were high; from 0.4 to 0.8% [68, 69]. The only compound allied to **64** and **65** that has been found in these surveys has been the tetrahydrofuranone lactone **66**, based on a C_{21} chain rather than the C_{20} chain of **64**, which was obtained in trace amounts from the bark of *G. mannii* [69].

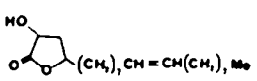
The chemotaxonomic significance of xanthone and biflavonoid distribution has been explored in a review [64] which used as its systematic basis the taxonomy proposed by Engler in 1925. There is clearly a correlation in xanthone production by taxa that are considered to be closely allied in Engler's system (Table 4). Whilst the available data is less definitive it also seems possible that biflavonoid production, or relative abundance of biflavanones and mixed flavanone/flavone dimers, may also show correlation [64]. The importance of xanthone profiles may also be extended to the tribal level. For example, the four genera of the Clusioideae tribe Garciniaea (*Garcinia*, *Allanblackia*, *Rheedia* and *Pentaphalangium*) all yield similar xanthones and all except *Rheedia* are recorded as containing biflavonoids. By contrast members of the tribe Clusieae have yet to yield biflavonoids and xanthones are only known from *Tovomita*.

One final point concerning the chemistry of *Garcinia* species. It is obvious that the thick, latex-rich, stem barks of *Garcinia* species, and by inference their secondary metabolites, provide a potent defensive barrier against wood-boring beetles. Where bark was removed for analysis the exposed wood immediately became the target



64 R = H

65 R = $CH_2CH{=}C(CH_3)_2$



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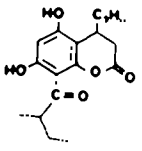

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Table 4. Distribution of secondary metabolites among *Garcinia* species from Cameroon

Subgenus Species	Xanthones*	Biflavonoids† a	Biflavonoids† b	Benzophenones	Pyrones
Rheediopsis					
G. ovalifolia	1356	–	–	+	–
G. polyantha	1356	–	–	+	–
G. staudtii	1356	–	–	+	–
Tetraphalangium					
G. conrauana	–	–	+ +	–	+
Xanthochymus					
G. densivenia	1356	+	+ +	–	–
G. quadrifaria	135	+	+ +	–	–
Tagamanthera					
G. afzelii	–	+ +	+	–	–
G. mannii	–	+ +	+	+	(+)
G. punctata	–	+ +	+ +	–	–
Paragarcinia					
G. kola	–	+ +	+	+	–

*The numbers in this column refer to oxygenation patterns of xanthones.
†a = biflavanones, b = flavone/flavanone dimers ('+ +' indicates the major component).

for attack, often resulting in the rapid death of the tree. This group of trees would seem to have considerable potential for a study of the defensive properties of bark secondary metabolites.

Mammea africana

Mammea africana is a large forest tree found in both Cameroon Reserves and is often a significant element in the flora. Both it and its central American counterpart, *M. americana*, have attracted interest as sources of 4-aryl and 4-alkyl-5,7-dihydroxycoumarins (neoflavonoids) substituted at C-6 and C-8 with isopentenyl units of various types; 3,3-dimethylallyl, 3-methylbuteryl, 2-methylbuteryl. When a large sample of seeds became available an analysis confirmed the presence of these compounds but gave an additional compound with the characteristics of a dihydro-5,7-dihydroxycoumarin with 4-*n*-pentyl and 8-(2-methylbuteryl) substituents (**67**). This dihydromammea coumarin was initially characterized by comparison with synthetically prepared 4-substituted coumarins, making particular use of ^{13}CNMR, a technique that was found to be of general value in resolving problems relating to the identity of the various side chains of the mammea coumarins [70]. The configuration of the C-4 *n*-pentyl moiety was tentatively assigned as axial on the basis of ^{1}HNMR coupling constants and this was confirmed by an X-ray crystallography study [71].

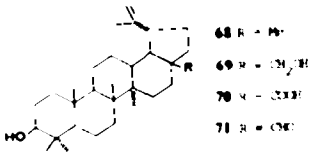
One general point of interest concerns the distribution of bark metabolites among the major species of Guttiferae in the Douala-Edea Forest Reserve. Here four species are common, *Mammea africana* (major bark compounds, neoflavonoids), *Garcinia conrauana* (lactones), *G. mannii* (biflavanones) and *G. ovalifolia* (benzophenones and xanthones). Between these four species the total range of types of guttiferous secondary metabolites encountered in all of the west African species studied occur. In this respect the picture found here is comparable to that seen among the Ghanaian Toddalioideae in which sympatric species exhibit maximum secondary metabolite diversity within the constraints laid down by the metabolic capabilities of the taxa.

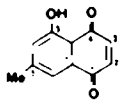
THE EBENACEAE

The final family to be considered in this review is the Ebenaceae which, in terms of tropical rain forest species, can be considered as synonymous with the very large and complex genus *Diospyros*. The complexity of this genus is well illustrated by reference to the ordination work carried out in the Douala-Edea Forest Reserve where, in four transect lines, a total of eleven different species were recognized, many of them characteristic of individual transects where they were common whilst they were not to be found at all on neighbouring transects. The coastal forests of Cameroon are recognized as being a centre of diversification for this remarkable genus [72].

In all a total of eighteen African species have been examined; in every case the stem bark and often the wood as well [73, 74]. These species have originated from three sources, the two Cameroon Reserves and the Ghanaian rain forest zone. The typical chemical characteristic of all samples analysed has been the presence, in varying amounts, of the three triterpenes lupeol (**68**), betulin (**69**) and betulinic acid (**70**). Other triterpenes were uncommon, perhaps the most interesting being the rarely isolated fourth member of the lupeol to betulinic acid sequence, betulinaldehyde (**71**), which was obtained from *D. canaliculata* [73]. In none of the species studied were either oleane or ursane pentacyclic triterpenes found although both these types were present in Asian species of *Diospyros* [75] examined in the same survey.

The other widespread group of metabolites obtained from *Diospyros* are the naphthoquinone dimers, most commonly those based on 7-methyljuglone (**72**). In all these were obtained from eleven of the African species surveyed, the most common individual compound being diospyrin (**73**). It has been suggested that these dimers might be artefacts formed through non-enzymatically





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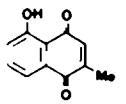

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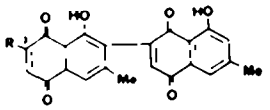

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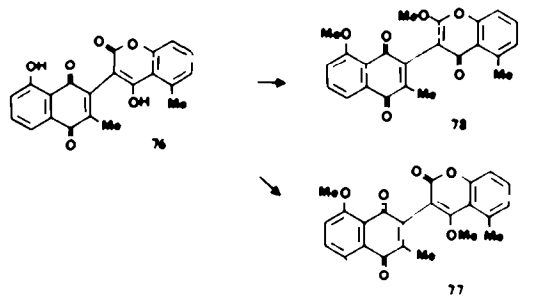


76 78 77

Scheme 3. Methylation of canaliculatin (76).

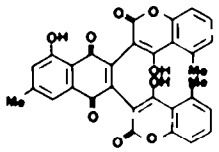
controlled, perhaps light-induced, oxidative coupling of the monomers but the fact that different species produce different dimers indicates that the process is not random. In addition to the various dimers of 7-methyljuglone and more rarely of its 2-methyl analogue plumbagin (74) two of the African species analysed have produced somewhat unusual derivatives.

Diospyros mannii collected in Cameroon yielded the typical naphthoquinones 72 and 73 and in addition a dimer carrying a methoxy group in place of one of the positions on the quinone nucleus not involved in the linkage. The assignment of the methoxy moiety to C-3' (75) rather than C-2' stemmed from the effect that substitution had on the resonance position of the hydrogen-bonded 5'-hydroxyl signal in the ^{1}H NMR spectrum [74]. The possibility that 75 might be an artefact produced by methanol extraction was tested by treatment of 73 with methanol under conditions more rigorous than those used in the extraction procedure. This failed to reveal any trace of 75.

Somewhat more unusual were two compounds isolated from the bark of *D. canaliculata*, one of the most widespread of African species and an 'ecological transgressor', that is a species found across a range of habitats [72]. The first unusual compound to be encountered from this species was recognized as plumbagin linked to a C_{10}-unit (naphthoquinones are C_{11}). The second unit was assigned a 4,7-dihydroxycoumarin nucleus with a methyl substituent on the aromatic ring and had to be linked to C-3 of plumbagin (74) through C-3 of the coumarin. The structure of this compound (trivial name canaliculatin) was assigned as 76 with the coumarin methyl substituent fixed at C-5 on the basis of NMR and MS analysis and the preparation of the corresponding methyl ether (77) and the tautomeric pyranone (78) (Scheme 3). Coincident with the characterization of 76 a similar naphthoquinone-coumarin trimer, ismailin (79), had been isolated from an Asian species, *D. ismailii* [76, 77]. Both 76 and 79 have been synthesized from their naphthoquinone and 5-methylcoumarin precursors [77] using the method first reported by Jurd [78]. The biosynthetic route to these compounds is presumed to be entirely polyketide in nature, arising through separately formed naphthoquinine and 5-methylcoumarin units.

A derivative of 76 obtained in small amounts from *D. canaliculata* was the pentacyclic compound cyclocanaliculatin (80) which was readily recognized by the loss of a methyl resonance and addition of a methylene resonance in the NMR spectrum and by the absence of tautomerism in the coumarin unit [77].

A summary of the distribution of naphthoquinones among over twenty African and Asian species included in our survey is given in Table 5. The homogeneity in secondary metabolism in *Diospyros* is quite striking, the only major differentiation being in the preferred positions on dimerization in the naphthoquinones and the occasional replacement of 7-methyljuglone by plumbagin as the primary monomer. This comparative homogeneity, when contrasted to the heterogeneity in the secondary chemistry of the Annonaceae and diversity in the Guttiferae and Toddalioideae, would seem to reflect the relative modernity of *Diospyros* and possibly recent species radiation.



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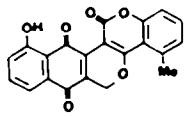

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Table 5. Distribution of naphthoquinones and triterpenes among African and Asian *Diospyros* species investigated

Type of compounds	African species	Asian species
Number of species investigated	18	9
Triterpenes		
lupanes	18	9
glutene	1	—
cerin	1	—
taraxeranes	—	3
oleananes	—	1
ursanes	—	2
Naphthoquinones		
plumbagin type	1	2
plumbagin dimers	—	1
7-methyljuglone type	—	1
2-2′-dimers	2	—
2-3′-dimers	—	1
2-6′-dimers	6	1
3-8′-dimers	—	1
6-8′-dimers	3	2

CONCLUDING COMMENTS

The preceding discussion was intended to illustrate the diversity of chemistry in given taxonomic groups where studies have been largely confined to two relatively small areas of rain forest. In terms of an understanding of the phytochemistry of Cameroonian forests, despite all of the effort that has been put in probably no more than 15% of the tree species of the two study areas have yet been studied in any depth and some of the most important families such as the Euphorbiaceae, Caesalpiniaceae, Olacaceae and Sterculiaceae, remain virtually untouched. Has this been worth doing and is it worth continuing? I would say it is on at least four counts. (1) The study of plants from these forests has provided training for a large number of young phytochemists. The wide variety of structure elucidation problems that beset the researcher still offers one of the best vehicles for teaching a range of skills in isolation technology, spectroscopic techniques and synthetic chemistry. (2) Used sensibly the data obtained from these investigations can often, although not always, make a meaningful contribution to resolving taxonomic problems. The value of this chemotaxonomic tool can often be best appreciated in cases such as the study of the Ghanaian Toddalioideae, where the ecological characteristics of each species are also well understood. (3) The chemical diversity and number of novel compounds that can be obtained remain surprisingly large. Furthermore with the recent strides that have been made in developing more sensitive tests for biological activity we are now in the position of being able to broaden areas over which biological testing can be achieved, even when amounts of material isolated are low. (4) Finally, it will only be possible to accurately gauge the impact of secondary metabolite profiles in ecosystems on the overall functioning of those ecosystems when data pools of the kind we are trying to develop are achieved. From more general surveys with very limited chemical goals it has already been established that chemical profiles of different forest areas can be extraordinarily variable [4] and can profoundly influence the feeding behaviour and sustainable biomass of herbivorous mammals [6, 79] and host selection and developmental processes in insects [80]. The impact of secondary metabolism on the whole ecosystem and the extent to which ecosystem pressures can and do cause changes in secondary metabolism are areas that we at present know little about although we speculate a great deal. The understanding of secondary metabolism dynamics at the ecosystem level must be a goal for many groups of scientists, not only the phytochemist but also the ecologist, the conservationist, the agronomist and the forester.

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