International Organization for Chemical Sciences in Development

Working Group on Plant Chemistry

CHEMISTRY, BIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF AFRICAN MEDICINAL PLANTS

Proceedings of the first International IOCD-Symposium
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Edited by

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7. Overview of the chemistry of aloes of Africa

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Introduction

The genus *Aloe* consists of more than 360 species distributed mainly in Tropical Africa, Madagascar and Southern Arabia (Mabberley 1987) and includes herbs, shrubs and trees. The leaves are fleshy, strongly cuticularized and are usually prickly at the margins. The flowers are of various colours, white, yellow, pink, greenish and red.

The bitter leaf exudates of some *Aloe* species are commercially important sources of the laxative aloe drug and are also used in the cosmetics industry as additives in shampoos, shaving and skin care creams (Leung 1970) and in the treatment of skin disorder and in particular as topical medication for the treatment of burns (Rowe *et al.* 1941). The exudate has also been used as bittering agent in alcoholic beverages. The term *aloe* is derived from the Arabic word *alloeh* which means a shining bitter substance (Tyler *et al.* 1976). Medicinally, the gel and dried leaf exudates of *Aloe* species have been used since ancient civilizations of the Egyptians, and Mediterranean peoples (Trease and Evans 1976). Egyptian copts used aloe to treat eye diseases, swellings and digestive disorders. Aloe was known to the Greeks for Alexander the Great is said to have been advised to conquer the island of Socotra near the East African shores to get aloe drug to treat his wounded soldiers (Maniche 1989). *Aloe* species still enjoy a very wide folkloric usage in many parts of the world and are also used in modern medicine. In commercial circles "Cape aloe" means the dried latex of the leaves of *Aloe ferox* Miller while "Curaçao aloe" is the latex from *Aloe vera* Miller (U.S. Pharmacopeia 1979).

Except for a few species which have been made cosmopolitan most *Aloe* species are confined to Africa and Arabia. It is therefore important for Africa that these species which have proved to be a store of diverse and interesting natural products be studied from many aspects. This paper highlights the chemistry of *Aloe* species and supplements the review by Reynolds (1985a).

The two most important analytical methods in the study of leaves and roots of *Aloe* are TLC and HPLC. Reynolds and Herring (1991) recommended for TLC of leaf components a mixture of di-isopropyl ether/*n*PrOH and water (7:5:1) followed by use of the lower layer of $CHCl_3$/EtOH/H_2O (7:3:1) to develop the

spots in a direction at right angle to the first. For root constituents we have found (Dagne *et al.* 1994) petrol/$CHCl_3$ (1:1), $CHCl_3$-EtOAc (7:3) and for analysis of leaf components EtOAc-MeOH-H_2O (77:13:10) to be quite suitable solvent systems. Developed TLC plates may be viewed under UV_{254} and UV_{366}, or sprayed with 0.5% aqueous solution of Fast Blue Salt B followed by spraying with caustic soda solution (Jork *et al.* 1990). 5-Hydroxyaloin gives characteristic violet-brown color when sprayed with 5% aqueous sodium metaperiodate (Rauwald and Beil 1993).

Reversed phase HPLC of the methanol extract of leaf exudate has proved to be one of the best methods for establishing chemical profile in *Aloe*. Whereas it is very difficult to distinguish between aloin A and B by TLC, these epimers can be easily distinguished by HPLC (Reynolds and Herring 1991). The roots of several species of *Aloe* and *Lomatophyllum* were analysed by Van Wyk *et al.* (1995b, 1995c) by TLC and HPLC for the presence of nine anthraquinones and pre-anthraquinones which are known to be characteristic constituents of roots of *Aloe*. The results support the inclusion of the genus *Lomatophyllum* in *Aloe*. Furthermore comparative studies of roots of 46 species belonging to the genera *Bulbine*, *Bulbinella* and *Kniphofia* (family Asphodelaceae) (Van Wyk *et al.* 1995a) revealed the relationships as well as differences of the two families Asphodelaceae and Aloaceae, which until recently were kept together in one family.

Constituents of *Aloe* species

The leaves and roots of *Aloe* species elaborate many interesting secondary metabolites belonging to different classes of compounds including alkaloids, anthraquinones, pre-anthraquinones, anthrones, bianthraquinoids, chromones, coumarins and pyrones. The three most important constituents of commercial aloe drug are the anthrones aloin A and B (**42**), and the chromones aloesin (**63**) and aloeresin A (**64**). We discuss below briefly each of the major classes of *Aloe* compounds.

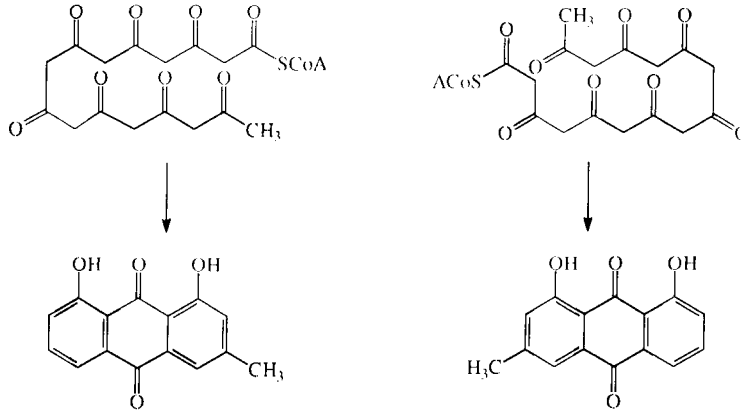
Alkaloids

The piperidine alkaloid γ-coniceine and other related hemlock alkaloids were reported to occur in seven *Aloe* species with very restricted distribution (Dring *et al.* 1984). By screening 224 *Aloe* species for alkaloids Nash *et al.* (1992) found 21% of the species positive and identified tyramine and its derivatives in 18 species. In view of the potential toxicity of many alkaloids, the authors pointed out the importance of screening for alkaloid prior to the use of *Aloe* plants as medicines.

Anthraquinones and pre-anthraquinones

Several free anthraquinones occur in roots and leaves of *Aloe* species. Aloe-emodin (**1**) is a typical leaf constituent and is wide spread in the genus. Chrysophanol (**10**) occurs both in roots (Yagi *et al.* 1977a) and leaves (Dagne and Alemu 1991) while nataloe-emodin (**6**) has so far been reported only from leaves (Conner *et al.* 1987). The anthraquinones in leaves may be present as O-glycosides as is the case in compounds **2** and **7**. The anthraquinones, physcion and emodin which are oxygenated at the 6 position are not found in *Aloe*. Aloesaponarin I (**8**), aloesaponarin II (**9**), desoxyerythrolaccin (**12**), helminthosporin (**3**), isoxanthorin (**5**) and laccaic acid D methyl ester (**14**) were isolated first from roots of *A. saponaria* (Yagi *et al.* 1974) but have recently been shown to occur in roots of many other *Aloe* species (Dagne *et al.* 1994).

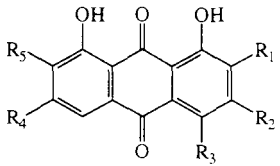
Thus two main types of anthraquinones are present in the roots of *Aloe*, these are 1,8-dihydroxyanthraquinone (*e.g.* chrysophanol, aloe-emodin) and 1-hydroxy-8-methylanthra-quinone (*e.g.* aloesaponarin I). Whereas anthraquinones of the former type are known to occur both in leaves and roots, those that belong to the latter type are confined only to roots. In a recent study of the roots of 172 species of *Aloe*, Van Wyk *et al.* (1995a) detected 1,8-dihydroxy-anthraquinones in almost all and 1-hydroxy-8-methylanthraquinones in 129 *Aloe* species. As shown in Figure 7.1. these two types of anthraquinones appear to be derived through two parallel biogenetic routes of the polyketide pathway, differing by the way the octaketide chain folds (Leistner 1973).



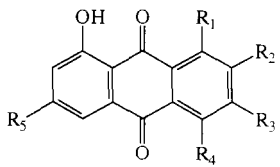
1,8-Dihydroxyanthraquinones
e.g. Chrysophanol

1-Hydroxy-8-methylanthraquinones
e.g. Aloesaponarin I

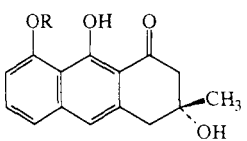
Fig. 7.1. Two folding mechanisms of octaketides leading to 1,-dihydroxy- and 1-hydroxy-8-methyl-anthraquinones.

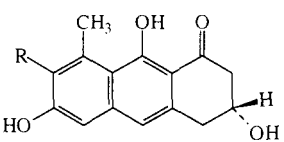


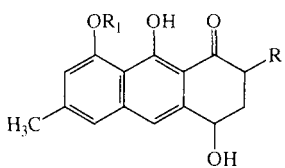
	R_1	R_2	R_3	R_4	R_5	
(**1**)	H	CH_2OH	H	H	H	Aloe-emodin
(**2**)	H	CH_2O-Rha	H	H	H	Aloe-emodin-11-O-rhamnoside
(**3**)	H	H	OH	CH_3	H	Helminthosporin
(**4**)	H	CH_2OH	H	H	OH	7-Hydroxyaloe-emodin
(**5**)	OCH_3	H	OH	CH_3	H	Isoxanthorin
(**6**)	H	CH_3	H	H	OH	Nataloe-emodin
(**7**)	H	CH_3	H	H	O-Glc	Nataloe-emodin-2-O-glucoside

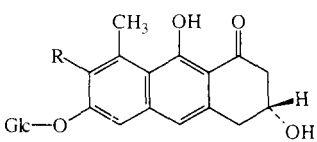


	R_1	R_2	R_3	R_4	R_5	
(**8**)	CH_3	$COOCH_3$	OH	H	H	Aloesaponarin I
(**9**)	CH_3	H	OH	H	H	Aloesaponarin II
(**10**)	H	H	H	H	CH_3	Chrysophanol
(**11**)	CH_3	H	H	H	CH_3	Chrysophanol-8-methyl ether
(**12**)	CH_3	H	OH	H	OH	Desoxyerythrolaccin
(**13**)	H	H	H	OH	CH_2OH	1,5-Dihydroxy-3-hydroxymethyl-anthraquinone
(**14**)	CH_3	$COOCH_3$	OH	H	OH	Laccaic acid D-methyl ether
(**15**)	OCH_3	OH	H	H	CH_3	Nataloe-emodin-8-methyl ether







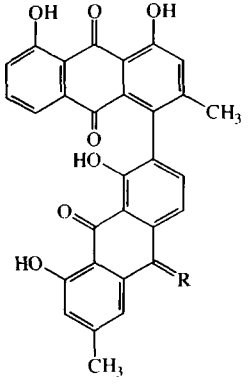


(**16**) R=CH_3 Aloechrysone
(**17**) R=H Prechrysophanol

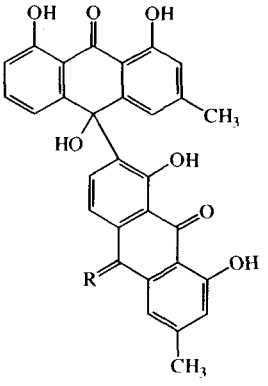
(**18**) R=$COOCH_3$ Aloesaponol I
(**19**) R=H Aloesaponol II

(**20**) R=R_1=H Aloesaponol III
(**21**) R=OCH_3, R_1=H Aloesaponol IV
(**22**) R=H, R_1=Glc Aloesaponol III-8-O-glc
(**23**) R=OCH_3, R_1=Glc Aloesaponol IV-8-O-glucoside

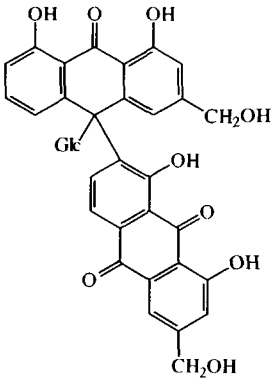
(**24**) R=$COOCH_3$ Aloesaponol I-6-O-glucoside
(**25**) R = H Aloesaponol II-6-O-glucoside



(**26**) R=O Asphodelin
(**27**) R=H_2 Bianthracene III



(**28**) R=O Bianthracene II
(**29**) R=H_2 Bianthracene IV

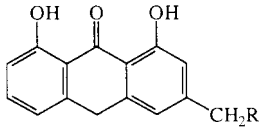


(**30**) Elgonicardine

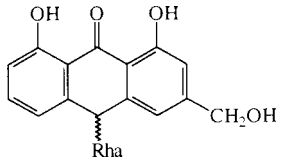
Several pre-anthraquinones, which could be considered as progenitors of the above two types of anthraquinones, have been isolated and characterized mainly from subterranean parts of *Aloe*. However, the pre-anthraquinone aloechrysone (**16**) was detected both in roots and leaves of four *Aloe* species from Ethiopia (Dagne and Alemu 1991). It is interesting to note that the related genus *Gasteria* (Aloaceae), elaborates *Aloe* type pre-anthraquinones both in the leaves and roots (Dagne *et al.* 1996). The pre-anthraquinones could be readily converted to the corresponding anthraquinones by treatment with base (Yenesew *et al.* 1993).

Anthrones

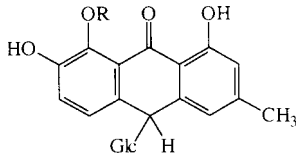
Anthrones are by far the most important of all the classes of compounds present in *Aloe* species. The most outstanding members of this class are aloin A and B (**42a, 42b**), which are collectively known as barbaloin because they were first isolated from Barbados aloe. Aloin A and B are two diastereomeric C-glucosides that differ in the configuration at C-10 of the aloe-emodin anthrone moiety. These compounds are believed to be mainly responsible for the bitter and purgative properties of the well known commercial aloe drug, which is principally made up of the leaf exudates of *A. ferox* and *A. vera*. The leaf exudate of *A. ferox* may contain up to 10% barbaloin (Groom and Reynolds 1987). However not all *Aloe* species are found to contain barbaloin. In a screening of 240 *Aloe* species, barbaloin was found to occur in exudates of 85 of the species examined (Reynolds 1985b) usually in 10-20% concentration. Although *A. littoralis* Baker is reported to be positive for presence of barbaloin by Reynolds(1985) and also reported to be present to the extent of 18.2 % by Groom and Reynolds (1987), our analysis by TLC and HPLC of the exudate of *A. littoralis* did not show the presence even of a trace of barbaloin (Dagne *et al.*, *Phytochemistry*, in press). Instead we isolated



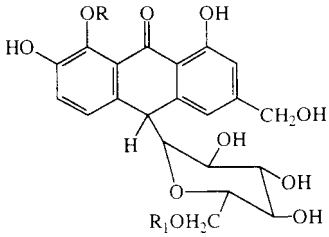
(**31**) R=OH Aloe-emodinanthrone
(**32**) R=H Chrysophanolanthrone



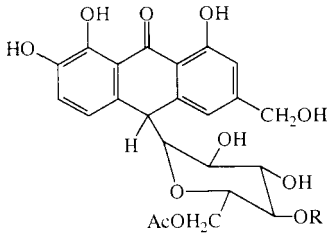
(**33**) Aloe-emodinanthrone-10-C-Rhamnoside



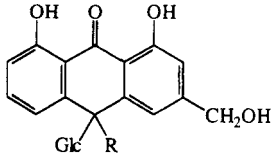
(**34**) R=CH_3 Homonataloin
(**35**) R=H Nataloin



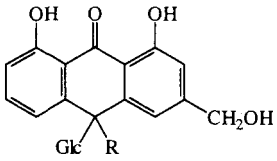
(**36**) R=R_1=H (7-Hydroxyaloin)
(**37**) R=H, R_1= *p*-coumaroyl (7-Hydroxyaloin-6'-O-*p*-coumaroyl)
(**38**) R=CH_3, R_1=H (8-O-Methyl-7-hydroxyaloin)
(**39**) R=CH_3, R_1= cinnamoyl (6'-O-Cinnamoyl-8-O-methyl-7-hydroxyaloin)



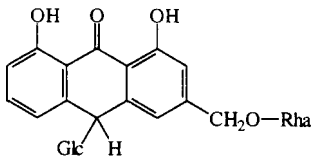
(**40**) R=H (7-Hydroxyaloin-6'-O-acetate)
(**41**) R=Ac (7-Hydroxyaloin-4',6'-diacetate)



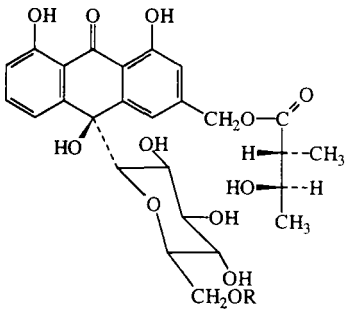
(**42a**) R=α-H Aloin A
(**42b**) R=β-H Aloin B



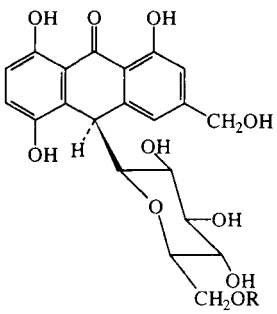
(**43a**) R=α-OH Hydroxyaloin A
(**43b**) R=β-OH Hydroxyaloin B



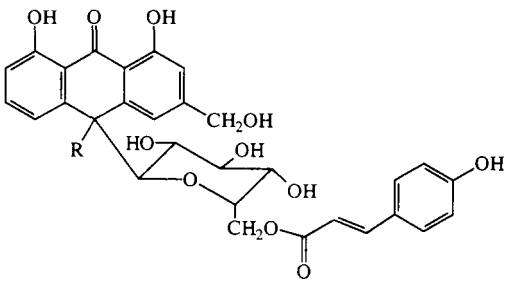
(**44**) Aloinoside



(**45**) R=H Deacetyllitoraloin
(**46**) R=Ac Littoraloin



(**47**) R=H 5-Hydroxyaloin
(**48**) R=caffeoyl Microstigmin A



(**49a**) R=α-H Microdontin A
(**49b**) R=β-H Microdontin B

10-hydroxyaloin B (**43b**) and its two novel nilate ester derivatives littoraloin (**46**) and deacetyllittoraloin (**45**). The chemotaxonomic significance of these compounds in *Aloe* has been recently published (Viljoen *et al.* 1996).

Interestingly barbaloin and homonataloin seem to be mutually exclusive, with the notable exception of *A. mutabilis* (Reynolds 1990). It should be pointed out that aloin should not be regarded to be confined only to *Aloe* species as it has also been found in the extracts of cascara bark (*Rhamnus purshiana* D.C.) (Manitto *et al.* 1990). Rauwald and Lohse (1992) have also reported occurrence of 10-hydroxy-aloin B (**43b**) in *Rhamnus* sp.

The determination of the absolute configuration of aloin A and B (**42a, 42b**) has engaged several workers (Rauwald *et al.* 1989; Manitto *et al.* 1990). In the true natural product, *i.e.* aloin B, the glucose moiety attached to C-10 has the α orientation (*i.e.*, 10*R*,1'*S*) and the β orientation (*i.e.*, 10*S*,1'*S*) follows for aloin A.

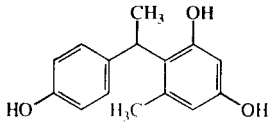
Biosynthetic study of Grün and Franz (1980) has shown that aloin B is the true natural product but is gradually converted to aloin A. That study also established that aloin B is formed by attachment of glucose to aloe-emodinanthrone (**31**), a compound detected so far in flowers but not in leaves of *Aloe* (Sigler and Rauwald 1994). In 10-hydroxyaloin B (**43b**) and its two novel nilate ester derivatives **45** and **46** obtained from *A. littoralis*, the glucose also has the α configuration indicating that hydroxylation at C-10 occurs prior to epimerization of the natural aloin B (Dagne *et al.*, *Phytochemistry*, in press). On the other hand, 5-hydroxyaloin A (**47**) is known only in the A form (Rauwald and Beil 1993) *i.e.* with the β orientation for the glucose moiety at C-10, an observation which is also the case for its natural derivative microstigmin A (**48**) a novel compound that we recently found in *A. microstigma* (Dagne *et al.*, submitted to *Phytochemistry*).

Roots of *Aloe* spp. elaborate in the main anthraquinones and pre-anthraquinones. It has recently been shown that inflorescence of *Aloe* also produce anthrones (Sigler and Rauwald).

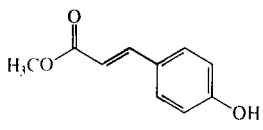
Benzene/naphthalene derivatives

Several naphthalene and benzene based secondary metabolites have been reported from *Aloe* species. One of the first such compounds to be reported is the naphthalene derivative of isoeleutherol-5-O-glucoside (**58**) isolated by Yagi *et al.* (Yagi *et al.* 1977b) from the subterranean stems of *Aloe saponaria*. It is interesting to note that such a glycoside is present in the subterranean part of *Aloe*. The aglycone isoeleutherol (**57**) was reported for the first time as a natural product by our group (Dagne *et al.* 1994) from roots of more than a dozen *Aloe* species belonging to the series Saponariae. Isoeleutherol was conspicuously absent from other series investigated, indicating its chemotaxonomic significance in delineating members of the Saponariae series from other series. The insecticidal compound pluridone (**52**) isolated from roots of the South African *A. pluridens* is the only example of a sulfur containing compound ever isolated from *Aloe*. The

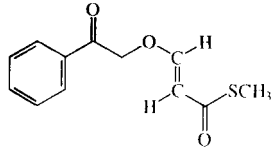
recently reported 1,1-diphenylethane (**50**) from Cape aloe (Speranza *et al.* 1994) and plicataloside (**62**) from *A. plicatilis* (Wessels *et al.* 1996) have added more variety to benzene- and naphthalene-derived compounds found in *Aloe* species. Furthermore the discovery of the tetrahydronaphthalenes feroxidin (**54**), feroxin A (**55**) and B (**56**) in Cape aloe by Speranza *et al.* (1990, 1992) is a further testimony of the diversity of the constituents of this aloes of commerce.



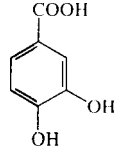
(**50**) 1,1-Diphenylethane



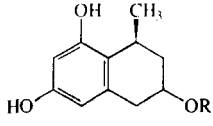
(**51**) Methyl-*p*-coumarate



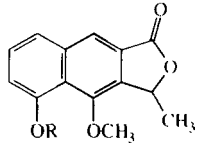
(**52**) Pluridone



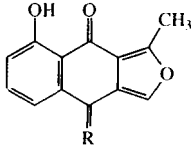
(**53**) Protocatechuic acid



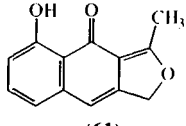
(**54**) R=H Feroxidin
(**55**) R=Glc Feroxin A
(**56**) R=4,6-Dicoumaroyl-Glc
= Feroxin B



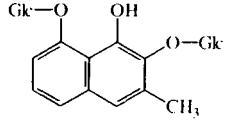
(**57**) R=H Isoeleutherol
(**58**) R=Glc Isoelutherol-5-O-glucoside



(**59**) R=H_2
(**60**) R=O



(**61**)

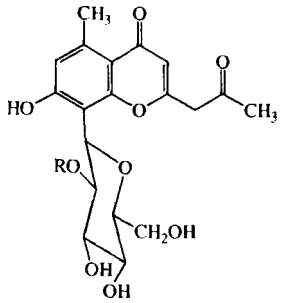


(**62**) Plicataloside

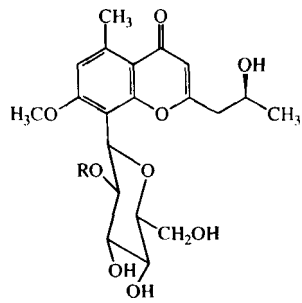
Chromones

Aloesin (**63**) formerly called aloeresin B, is one of the three most significant constituents of aloe drug, the other two being barbaloin and aloeresin A. Random screening of *Aloe* species indicated its presence in leaves of at least 30% of the species examined (Reynolds 1985a). Its structure was established as **63** in by Haynes *et al.* (1970) and subsequently in 1972 its aglycone named as aloesone (**77**) was recognized as an *Aloe* leaf constituent by Holdsworth (1972). The structure of aloeresin A, first proposed incorrectly as a *p*-coumarate ester of aloesin esterified on C_6 of the sugar moiety, was later on revised to structure **64** in

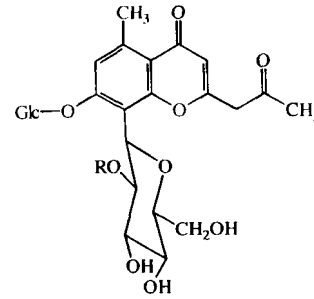
which the ester was placed on C_2 of the sugar (Gramatica *et al.*1982). Mebe (1987) reported the aloeresin derivative (**68**) from *A. excelsa* but incorrectly named it as 2'-*p*-methoxycoumaroylaloeresin when it should have been called either 2'-*p*-O-methylcoumaroylaloesin or 2'-*p*-methoxycinnamoylaloesin.



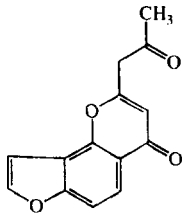
(**63**) R=H	Aloesin or Aloeresin B
(**64**) R=*p*-coumaroyl	Aloeresin A
(**65**) R=cinnamoyl	Aloeresin F
(**66**) R=feruloyl	2'-O-Feruloylaloesin
(**67**) R=*cis*-*p*-coumaroyl	Iso-aloeresin A
(**68**) R=*p*-O-methylcoumaroyl	2'-O-Methylcoumaroylaloesin
(**69**) R=tigloyl	2'-O-Tigloylaloesin



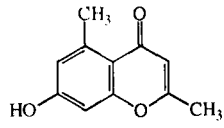
(**70**) R=*p*-coumaroyl Aloeresin D
(**71**) R=caffeoyl Rabaichromone



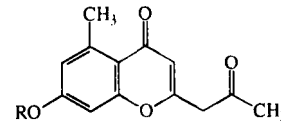
(**72**) R=*p*-coumaroyl Aloeresin C
(**73**) R=cinnamoyl Aloeresin E



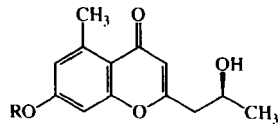
(**74**) Furoalesone



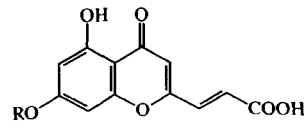
(**75**)



(**76**) Aloesol



(**77**) Aloesone

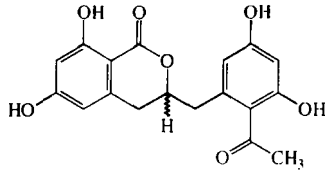


(**78**)

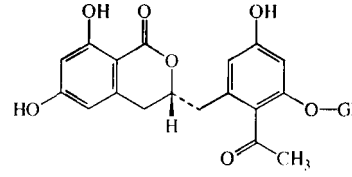
TLC and HPLC examination of *Aloe rupestris* Bak. leaf exudate showed the total absence of aloin and homonataloin as well as aloeresin A, C and D but instead revealed the presence of two major and several other minor constituents. Isolation of the major components resulted in their characterization as aloesin (**63**) and the new natural product 7-O-methylaloesin (Dagne *et al.*, submitted to *Biochemical Systematics and Ecology*). The latter compound is of considerable chemotaxonomic value since it is present in most species of *Aloe* series Asperifoliae Berger.

Pyrones

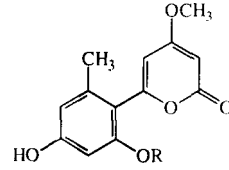
Aloenin (**81**), a phenylpyrone derivative, is a relatively infrequently encountered bitter component of *Aloe* leaf exudate, whose revised structure was reported in 1974 (Suga *et al.*1974). Aloenin aglycone (**82**) and the coumaroyl ester **85** were



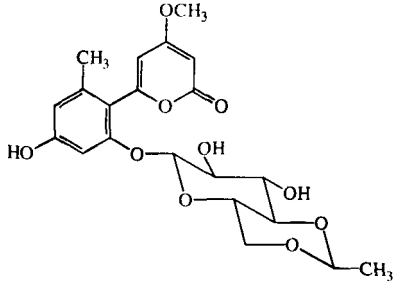
(**79**)



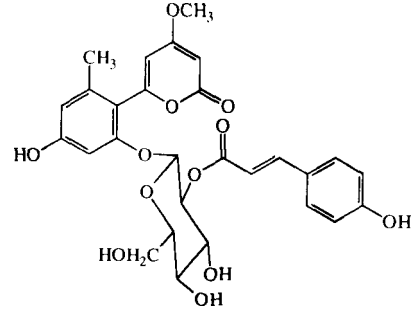
(**80**) Feralolide



(81) R=Glc Aloenin
(82) R=H Aloenin aglycone



(**83**) Aloenin acetal



(**84**) R=Glc Aloenin B
(**85**) R=H Aloenin-2'-*p*-coumaroyl ester

reported recently (Conner *et al.* 1987). Aloenin B (**84**) is one of the major (13.5%) constituents of commercial Kenya aloe (Speranza *et al.* 1986).

Contribution to the study of the chemistry of aloes of Ethiopia

There are nearly 36 species of *Aloe* in Ethiopia with 18 endemics. The ethanol extract of the leaves of the endemic Ethiopian species *A. berhana* now renamed as *A. debrana* (Demissew and Gilbert, in *Flora of Ethiopia and Erythrea*, Addis Ababa, in press). yielded the interesting pre-anthraquinone, aloechrysone (**16**) (Dagne and Alemu 1991) in addition to chrysophanol, aloe-emodin, barbaloin and β-sitosterol. Aloechrysone fluoresces strongly under 366 nm UV light, a property that helps to identify it during separation using silica gel columns and plates. Aloechrysone was first detected in the roots of *A. berhana* (Dagne *et al.* 1992) and was later found also in roots of other *Aloe* species (Dagne *et al.* 1994). It is the most likely precursor of chrysophanol-8-methyl ether (**6**), an anthraquinone that also occurs in roots of *A. berhana* and other *Aloe* species. The isolation of the simple, biologically important, aromatic acid, 3,4-dihydroxybenzoic acid, also known as protocatechuic acid, from *A. berhana* leaves is noteworthy (Dagne and Alemu 1991). Although this acid is known to occur in other plants such as in coffee pulp (Dagne and Alemu 1991), this was the first report of its occurrence in *Aloe* species. Other constituents of roots of *A. berhana* include: aloesaponol I, laccaic acid D methyl ester, aloesaponol III, aloesaponarin I, chrysophanol-8-methyl ether and chrysophanol (Dagne *et al.* 1994).

Likewise study of the leaves of *A. megalacantha* yielded, barbaloin, chrysophanol, aloinoside and β-sitosterol (Dagne and Alemu 1991), while its roots (Dagne *et al.* 1994) afforded aloechrysone, aloesaponarin I, aloesaponol I, aloesaponarin II, aloesaponol II, aloesaponol III, asphodelin, chrysophanol, chrysophanol-8-methyl ether, helminthosporin and laccaic acid D methyl ester.

A recent study (Yenesew *et al.* 1993) of the subterranean stem of this species, *i.e.*, *A. lateritia* Engl. var. *graminicola* (formerly *A. graminicola*) resulted in the isolation and characterization of prechrysophanol (**25**), which can be considered as the direct progenitor of chrysophanol. This plant has also been shown (Dagne *et al.* 1994) to be among the few species of *Aloe* that elaborate in their roots the chemotaxonomicaly important 2-naphtoic acid derivative, isoeleutherol (**57**), which has been indicated as a chemotaxonomic marker for a group of *Aloe* lumped in the series Saponariae. The presence of isoeleutherol in the roots of *A. kefaensis* Gilbert & Sebsebe and *A. macrocarpa* Tod. also confirms their placement in the above mentioned series Saponariae.

A. pulcherrima is one of the most beautiful of the *Aloe* taxa found in Ethiopia. It is known as "Sete-Eret" and is mainly used to accelerate wound healing. Chemical analysis of its leaves revealed the conspicuous absence of barbaloin but showed instead nataloin and 7-hydroxy-barbaloin as its major constituents (Dagne and Alemu 1991).

The root chemistry of *A. calidophila, A. camperi, A. gilbertii, A. pulcherrima, A. rivae, A. schelpei, A. sinana* is similar to that of *A. megalacantha*. However, *A. secundiflora* differs because it does not contain aloechrysone, a compound also absent from all members of the Saponariae series (Dagne *et al.* 1994).

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