Alkamides: Structural Relationships, Distribution and Biological Activity¹

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Abstract: The alkamides comprise a group of about 70 biogenetically closely related fatty acid amides with characteristic olefinic and acetylenic patterns. Purely olefinic derivatives have been found, so far, only in the Piperaceae, Aristolochiaceae and Rutaceae, whereas the Asteraceae tribes Heliantheae and Anthemideae additionally contain a great number of different acetylenic amides. With regard to the restricted distribution of alkamides, their occurrence deserves systematic attention and may contribute to a more natural grouping of genera at least within the two latter tribes. Some olefinic isobutylamides have been shown to possess considerable insecticidal activity and to be effective as molluscicides and cercaricides and thus are of potential use against bilharzia. Furthermore, alkamides have been used medicinally since ancient times as sialogogues, antitussives and analgesics. More recently, some acetylenic derivatives have been shown to inhibit the RNA-synthesis in mice-ascites-tumour tests. This review highlights the present state of knowledge on the structural relationships, distribution and biological activities of the alkamides.

Introduction

The alkamides form a distinct class of natural products in which different amine parts are combined by an amide linkage with various unsaturated fatty acids. The latter may be derived from oleic acid and contain an unbranched alkyl chain of 9 to 18 carbon atoms with one or more double bonds frequently accompanied by one to three acetylenic linkages. With regard to the biogenetic origin, this class of compounds clearly deviates from other naturally occurring amides, whose acid moieties may either be derived from shikimic acid (e.g. piperine) or from the polyketide (acetate) pathway (e.g. capsaicin). The amine parts most probably arise from various amino acids by decarboxylation and, sometimes, by additional transformation processes.

Table I. Distribution of olefinic isobutylamides in the Aristolochiaceae, Piperaceae, and Rutaceae. (Numbers in brackets refer to the corresponding acid moieties only)

Plant species	C ₁₀		C ₁₂				C ₁₄		reference
	1 + 42	2 + 42	12	13	10	(10) + 43	11	(11) + 43	
PIPERACEAE									
Piper									
<i>longum</i> L.	•								(30)
<i>peepuloides</i> Roxb.	•								(30)
<i>sylvaticum</i> Roxb.		•							(32)
ARISTOLOCHIACEAE									
Asiasarum									
<i>heterotropoides</i> Maek.									
var. <i>mandshuricum</i> Maek.	•		•	•					(31)
RUTACEAE									
Zanthoxylum									
<i>clava-herculis</i> L.					•				(33)
<i>piperitum</i> (L.) DC.					•	•	•	•	(34, 29)
<i>planispinum</i> Sieb. & Zucc.					•	•			(29)
<i>beecheyanum</i> K. Koch					•		•		(29)
<i>ailanthoides</i> Sieb. & Zucc.							•	•	(28, 29)
<i>inerme</i> Koidz.							•		(29)
<i>senegalense</i> DC.	•								(11)

¹ Dedicated to Prof. Dr. R. Hegnauer on the occasion of his 65th birthday

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Up to now, about seventy different alkamides have been isolated and identified. Based on the available data the Asteraceae (Compositae) represents the main source of these compounds containing both purely olefinic as well as olefinic and acetylenic derivatives (Tab. II, III). In contrast, only olefinic

derivatives are known so far from the other alkamide producing families i.e. Piperaceae, Aristolochiaceae and Rutaceae (Tab. I).

Interest in this class of compounds has quickened since several olefinic isobutylamides have been shown to possess considerable insecticidal activity, particularly against house-flies (*Musca domestica* L.), sometimes surpassing that of the pyrethrins (1-6). Moreover, members of that series have a pungent taste and produce formication and local anaesthesia of the mucous membranes accompanied by profuse salivation. Consequently, plants which yield these compounds have been used medicinally since ancient times as sialogogues, antitussives or

anodynes, especially recommended for the alleviation of toothache and bronchitis (2, 7-11). Amongst the better known are *Anacyclus pyrethrum* (L.) Link ("pellitory", "bertram root"), *Spilanthes oleracea* L. ("para cress"), *Echinacea angustifolia* DC. ("American cone flower") and *Zanthoxylum clava-herculis* L. ("southern prickly ash"). In a more recent report on the molluscicidal activity of the olefinic isobutylamide affinin (9) isolated from the roots of *Heliopsis longipes* (A. Gray) Blake, attention was drawn to the potential use against bilharzia (12). Apart from this, some acetylenic amides have been isolated from *Achillea* species (13, 14) which inhibited the RNA-synthesis in mice-ascites-tumour tests (15).

Scheme 1.

With regard to the restricted distribution of alkamides in the plant kingdom, their formation in the Aristolochiaceae, Piperaceae, Rutaceae and Asteraceae (Tab. I–III) deserves special systematic attention. A survey of the present available chemical data of the Asteraceae suggests that the accumulation of amides provides a chemosystematic criterion, which might contribute to a better understanding of intergeneric relationships within the tribes Heliantheae (Tab. II) and Anthemideae (Tab. III). In the latter tribe, the genus *Achillea* especially represents a rich source of many different amides apparently replacing those polyacetylenes which are otherwise typical for the Anthemideae (16–17). During the last three years 25 different derivatives have been detected for the first time from that genus, indicating a strong tendency towards piperidine and pyrrolidine derived alkamides (13, 14, 18, 19).

The literature on the olefinic isobutylamide insecticides up to 1969 has been reviewed by Jacobson (20). Since then many new naturally occurring alkamides have been reported. However, up to now only scattered information on their distribution, structural relationships and their possible biological activities are available. In this paper an attempt has been made to gather this information and to present an up to date survey of the present knowledge.

Structural relationships

Although the biosynthesis of many alkamides is not yet sufficiently clarified, the available results, obtained by feeding experiments with ^{14}C - and ^3H -labelled precursors (16, 21), allow some general conclusions about the biogenetic connexions of the acid moieties to be made. Successive dehydrogenations and dehydrations frequently accompanied by isomerization lead to characteristic clusters of olefinic and acetylenic bonds. [In order to focus attention to the characteristic double and triple bonds, the symbols for the corresponding C and H atoms in the formulas were omitted.] Various oxidative degradations form carbon chains of different lengths (Schemes 1–4). Since most of the purely olefinic amides are supposed to be derived from common biogenetic steps, they are treated here as a separate group.

Apart from the derivatives demonstrated in Scheme 1 the olefinic isobutylamides **9–13** have been isolated from *Zanthoxylum* species (Tab. I) and some Heliantheae genera (Tab. II)

whose structures strongly suggest close biogenetic connexions. In *Achillea lycaonica* Boiss. & Heldr. a group of C_{18} -amides have been detected (14) which may be derived from linoleic acid via epoxidation followed by successive hydrogenation, oxidation and dehydration (Scheme 2).

Scheme 2.

Table II. Distribution of alkamides in the Asteraceae – Heliantheae

ASTERACEAE	olefinic			acetylenic amides													reference					
	C ₁₀		C ₁₂	C ₉				C ₁₀			C ₁₁	C ₁₂	C ₁₃	C ₁₄	C ₁₅	C ₁₈						
	9	10	12	30 + 50	30 + 52	30 + 53	31 + 53	29 + 50	29 + 52	29 + 53	28 + 42	27 + 42	37 + 42	37 + 44	38 + 42	21 + 42		36 + 42	36 + 43	40 + 42	39 + 42	41 + 42
Heliantheae																						
Spilanthes																						
<i>oleracea</i> L.	●																				(37–39)	
<i>alba</i> L'Herit.			●	●	●	●	●	●	●	●	●	●									(25)	
Wedelia																						
<i>parviceps</i> Blake	●																				(12)	
Echinacea																						
<i>angustifolia</i> DC.		●									●	●									(24, 40)	
<i>purpurea</i> (L.) Moench											●	●	●	●	●		●	●			(24, 41)	
<i>pallida</i> (Nutt.) Britton		●																			(40)	
Heliopsis																						
<i>longipes</i> (A. Gray) Blake	●																				(36, 38)	
<i>helianthoides</i> (L.) Sweet																			●		(26)	
<i>buphthalmoides</i> (Jacq.) Dunal.																●			●	●	●	(26)

Scheme 3.

Anacyclin (**16** + **42**), from the underground parts of *Anacyclus pyrethrum*, was the first alkamide to be shown to possess acetylenic linkages (**22**). Based on the extensive investigations of Bohlmann and his collaborators, the main lines of the biosynthetic sequence of many acetylenic amides are already known (**21**, **23**). However, there are still some biogenetic pathways that as yet have not been verified (Scheme 3).

In some Anthemideae genera, especially in *Achillea*, additional dehydration and/or dehydrogenation steps form highly unsaturated C₁₄-chains, sometimes leading to fully conjugated

systems (**23**–**26**). From *Echinacea angustifolia* DC., *E. purpurea* (L.) Moench and *Spilanthes alba* L'Hérit., the acetylenic amides **27**–**30** have been isolated which deviate from structurally related derivatives by a Z-oriented double bond conjugated with the carbonyl (amide) group (**24**, **25**). Apart from the

C₁₄

biogenetic information obtained from feeding experiments, additional conclusions about structural relationships can be drawn from comparative phytochemical analyses within related genera. For example, from *Achillea ageratifolia* (Sibth. & Smith) Boiss. and *A. tomentosa* L., amides with similar structures and stereochemistries lead one to expect a biogenetic sequence demonstrated in Scheme 4 and suggest direct connections with oleic acid (18).

More recently, a group of C₁₈-amides has been isolated from *Heliopsis* species (Tab. II) whose olefinic and acetylenic patterns resemble those of some derivatives shown in Scheme 4 (26). In contrast to the C₁₈-compounds found in *Achillea lycanica*, they are characterized by a high degree of unsaturation (39–41).

C₁₈

The amine parts of all alkamides reported so far may be regarded as amino acid derivatives, formed by decarboxylation and some subsequent modifications. This hypothesis is also supported by the naturally occurring alkamide **54** from *Poria si-*

nuosa Fr. (Basidiomycetes) in which valine is attached to a tri-ynenoic acid by an amide linkage (27). Whereas valine, phenylalanine and tyrosine, for example, might represent the precursor of the amines **42**, **43** and **50**, **51**, lysine has been suggested to be the precursor of piperidine (2,3-dehydropiperidine) (**46**) (**48**) (Scheme 5).

Distribution

In the Piperaceae, Aristolochiaceae and Rutaceae, all amides are characterized by purely olefinic acid moieties with C₁₀ to C₁₄ chains uniformly linked to isobutylamine (**42**) or the corresponding hydroxy-derivative **43** (Table I). Comparative investigations on the bark and the fruits of different *Zanthoxylum* species have shown that the hydroxylation of the isobutylamine is restricted to the pericarp (28, 29). Additional divergence results from the formation of C₁₂ or C₁₄ acids and the number of *E*-oriented double bonds conjugated with the amide group (**10**, **11**). From the root-bark of *Z. senegalense* DC., the decadien-isobutylamide (**1** + **42**) was isolated (11) and has also been reported for the Piperaceae (30) and the Aristolochiaceae (31). The corresponding 4,5-dihydroxy-decen-isobutylamide (**2** + **42**) has been shown to occur in the seeds of *Piper sylvaticum* Roxb. (32).

Scheme 4.

From the Asteraceae-Heliantheae, 21 different alkamides have been isolated and identified so far, consisting of both purely olefinic as well as acetylenic derivatives (Table II). From the purely olefinic derivatives, affinin (= spilanthalol) (9) has been found to occur in *Spilanthes oleracea* L. [recently recogni-

zed as a member of the genus *Acmella* Rich. ex Pers. (35)] (37–39), *Wedelia parviceps* Blake (12) and in *Heliopsis longipes* (A. Gray) Blake (36, 38). Neoherculin (= α -sanshoöl, = echinacein) (10) was isolated from the roots of *Echinacea angustifolia* DC. and *E. pallida* (Nutt.) Britton (40).

Scheme 5.

The acetylenic amides contain acid chains of 9 to 18 carbon atoms attached to many different amine parts (42, 43, 44, 50, 52, 53). *Spilanthes alba* L'Hérit was the first species found to possess styrylamides (30 + 52, 30 + 53, 31 + 53, 29 + 52, 29 + 53) (25). Moreover, from that species two diyne-diene-isobutylamides (28 + 42, 27 + 42) were isolated, which have also been found in *Echinacea* species (24). Since all acetylenic compounds mentioned above are distinguished from other naturally occurring amides by α -Z-oriented double bonds, the common occurrence of the two latter derivatives in *Spilanthes* and *Echinacea* suggests close connexions between those genera. On the other hand, compound 38 + 42 isolated from *E. purpurea* (41) shows a close structural and stereochemical affinity with the C₁₈-amides 40 + 42, 39 + 42 and 41 + 42 detected in *Heliopsis buphthalmoides* (Jacq.) Dunal. and *H. helianthoides* (L.) Sweet. Further investigations will reveal whether these amides are identical with scabrin (5) and heliopsin (42) from *H. helianthoides* (L.) Sweet ssp. *scabra* (Dunal) T. R. Fisher, whose structures and stereochemistries as yet are not sufficiently clarified. Finally, it should be pointed out that the occurrence of alkamides in *Spilanthes* (*Acmella*), *Wedelia*, *Echinacea* and in *Heliopsis* agrees with a recent taxonomic treatment of the Heliantheae, in which these genera are grouped together in the subtribe Ecliptinae (35).

The greatest number of different olefinic and acetylenic alkamides were found in the Asteraceae-Anthemideae containing C₁₀ to C₁₈ acid moieties linked to various amine parts (42, 45–51) (Table III). In contrast to the Heliantheae, the amide pattern is characterized particularly by the formation of piperidides, piperideides, pyrrolidides and pyrrolideides. Furthermore, with the exception of the acids 1 (reported for the Piperaceae, Aristolochiaceae and Rutaceae) and 21 (reported for *Heliopsis helianthoides*), the occurrence of all other acid moieties have been shown to be restricted to the Anthemideae.

Decadien-isobutylamide (1 + 42) is one of the most common olefinic derivatives found in the Anthemideae, frequently accompanied by the dehydro-derivative 5 + 42. The former compound was shown to be the major component of pellitorine, a

crystalline mixture consisting of at least three substances (22). Pellitorine was isolated from pellitory roots (*Anacyclus pyrethrum* (L.) Link) and was formerly accepted as a pure compound (43, 44). Apart from that, the homologues 1 + 45, 1 + 46, 1 + 47 and 1 + 51 have also been found, especially in *Achillea* species (13, 14, 18, 19). Some systematic importance may be attached to the occurrence of the decatrien-piperideide (3 + 46) in *Achillea millefolium* L., *A. setacea* Waldst. & Kit. and in the probably closely related *A. crithmifolia* Waldst. & Kit. and *A. biebersteinii* Afan. (13, 45). Sometimes, decadien-amides were found to form mixtures with dodeca-, trideca- and tetradecadienamides, which are very difficult to separate by thin layer chromatography. Whereas decadien (1 + 51)-, dodecadien- and tetradecadien-tyramide (6 + 51) were detected in *Anacyclus pyrethrum* (46), a corresponding series of isobutylamides together with a tridecadien-derivative was found in *Leucocyclus formosus* Boiss. ssp. *formosus* (13). In addition, the latter species contains tetradecatrien (7 + 42)- and tetradecatetraen-isobutylamides (8 + 42), which have also been reported for *Achillea nana* L. (19). Piperidides and pyrrolidides with completely saturated C₁₈ acid chains (14 + 45, 14 + 48) together with the corresponding dehydro-derivatives (15 + 45, 15 + 48) were shown to occur in *A. lycaonica* Boiss. & Heldr. (Scheme 2) (14).

The acetylenic amide 22 + 42 was isolated from *Achillea ptarmica* L. (47) and was the first alkamide reported for that genus. Later, it was also detected in *A. spinulifolia* Fenzl ex Boiss. (14), *Anacyclus pyrethrum* (49) and *Cladanthus arabicus* (L.) Cass. (23). The formation of thiophene amides has proved to be a characteristic biogenetic trend of the Anthemideae. As shown in Scheme 3, they might be regarded as derivatives from acetylenic precursors (23). The amides of the thienyl-heptatrienoic acid (otanthic acid) (19) have been shown to co-occur with the presumable precursors (18 + 42, 18 + 45, 18 + 46) in *Otanthus maritimus* (L.) Hoffm. & Link (23). The isobutyl derivative 19 + 42 was also found in *Anacyclus clavatus* (Desf.) Pers. (as *A. tomentosus*) (23). Another thiophene amide (20 + 42) was shown to be responsible for the pungent taste of some *Argyranthemum* species (52, 45) and of the N-African annual *Matricaria pubescens* (Desf.) Schultz-Bip. (53). Based on the avai-

lable data, the accumulation of C_{14} acetylenic amides represents a common trend within the Anthemideae. Apart from anacyclin (**16** + **42**), its dehydrogenation product dehydroanacyclin (**23** + **42**) was also isolated from *Anacyclus pyrethrum* (49, 54), *Achillea millefolium* (48), *A. nana* (19), and as a main component from *Chamaemelum* species (45). Whereas related C_{14} amides with different patterns of unsaturation (e.g. **24** + **45**, **21** + **42**, **25** + **45**, **26** + **45**) appear to be widespread in the genus *Achillea*, the C_{16} derivatives have been reported so far only for *A. tomentosa* L. (13) and *A. ageratifolia* (Sibth. & Smith) Boiss. (18). With the exception of the amide **21** + **42**, which was isolated in small amounts from the Heliantheae genus *Heliopsis* (26), all other derivatives mentioned above appear to be typical for the Anthemideae. Moreover, with regard to fruit morphological characters, the accumulation of amides suggests close relationships between *Achillea*, *Leucocyclus* and *Anacyclus* (55) as well as between *Chamaemelum* and *Cladanthus*.

Comparative and preliminary analyses within the alkamide containing Anthemideae genera have shown that in addition to the derivatives listed in Table III, a great number of further amides are to be expected which have not been identified so far. The isolation and structure elucidation of these compounds is currently under investigation in our laboratory.

Biological activity

No attempt will be made here to cite all the numerous papers on the application of alkamides in medicine or on their use as insecticides, except to call attention to those articles which give reviews of the literature on these subjects.

The underground parts [in *Anacyclus pyrethrum* the stems are fused with roots to form a submerged, woody caudex (55)] of *Anacyclus pyrethrum* (known in the older literature as *Anthemis pyrethrum*, Spanish chamomile, or pellitory of Spain) produces, when chewed, a persistent tingling and partial insensibility of the tongue and neighbouring mucous membranes, causing a remarkable flow of saliva. In 1876, Buchheim (56) separated a crystalline material from that plant, which he regarded as its active constituent and named "pyrethrine". Later, that product was called "pellitorine" (43) and was shown to contain at least three substances (22). The major component was identified as decadien-isobutylamide (**1** + **42**) (22). Crude pellitorine was found to be toxic to house-flies (*Musca domestica* L.) and also highly lethal to adult yellow meal-worms (*Tenebrio molitor* L.) (20). The medicinal use of *A. pyrethrum* and the probably closely related, but now extinct, annual *A. officinarum* Hayne is summarized by Humphries (55).

The flower heads of *Spilanthes oleracea* L. [for nomenclatural changes see refs. (35, 57)] also contain a pungent principle which has been used medicinally (7, 58). It was first obtained in the crude state by Gerber (7), who designated it "spilanthol". The same material has been reported to be effective against the larvae of *Anopheles* and *Culex* mosquitoes [for further literature see (58)]. During extensive investigations on natural insecticidally active amides Jacobson (37) has shown that spilanthol (for which various structures have been proposed) is identical with affinin (**9**), whose structure and stereochemistry was established by Crombie and his collaborators (38), later also supported by ^{13}C -NMR analysis (39). Affinin was originally obtained from the roots of *Heliopsis longipes* (36), an insecticidally active plant from Mexico [in earlier literature erroneously identified as *Erigeron affinis* (59)]. It was reported that the roots are chewed to relieve toothache and that an extract of the roots is also used for colds and pneumonia (1). More recently, affinin was shown to be effective against the freshwater snail

Physa occidentalis Tryon and the cercariae released by the mollusc. Thus, this amide may be of potential use against bilharzia (12).

Various species of the genus *Zanthoxylum* have been reported to possess insecticidal activity (2). The active material is accumulated in the bark of the stems and roots as well as in the fruits. The bark of *Z. clava-herculis* (commonly called southern prickly ash, Hercules' club, or toothache tree) has been used medicinally as an irritant, stomachic and analgesic, particularly in cases of toothache. Similar effects have also been reported for other *Zanthoxylum* species (2). The fruits of the E-Asiatic *Z. piperitum* are used as an anthelmintic [for further literature see (60)]. Neoherculin (**10**) was isolated from the bark of *Z. clava-herculis* and its structure and stereochemistry was determined by Crombie (33). It is a highly insecticidal compound and strong sialogogue which probably represents the pure form of herculin reported in the earlier literature (2). Later, it was shown that neoherculin is identical with α -sanshoöl isolated from *Z. piperitum* (34). This compound has also been detected in some other Japanese *Zanthoxylum* species together with related derivatives (Table I) (28, 29).

The roots of the American cone-flower *Echinacea angustifolia* are highly pungent and are reported to contain a mosquito larvicide (61). Moreover, the roots are also used medicinally in healing of wounds and inflammations (62) and are considered as a mild counter-irritant, stimulant and antiseptic (8). Jacobson (63) separated the insecticidal isobutylamide echinacein from the roots, which was later also found in *E. pallida* and was shown to be identical with neoherculin (40). From *E. angustifolia* and *E. purpurea* a further series of acetylenic amides has been isolated (24, 41). None of these compounds has as yet been tested for its biological activity.

Two C_{18} -isobutylamides (scabrin, heliopsin) were isolated from *Heliopsis helianthoides* ssp. *scabra* which possess considerable insecticidal activity (5, 42). It was reported that a trace of scabrin, when placed on the tongue, produced in intense burning, paralytic effect on the tongue and lips, lasting for about two hours. It was proved to be appreciably more toxic than the pyrethrins to house-flies (5). The structures and stereochemistries of both compounds have as yet not been sufficiently clarified. However, they may be expected to be closely related to, or even identical, with those amides recently isolated from *H. helianthoides* (26).

"Asiasari radix" from *Asiasarum heterotropoides* var. *mandshuricum* (Aristolochiaceae) is an important crude drug in Chinese medicine, and has been used since ancient times as an antitussive, expectorant or analgesic (31). The roots have been shown to contain the olefinic isobutylamides **11**–**13** which are thought to contribute to the antitussive property (31).

All the biologically active compounds mentioned above have been shown to consist of purely olefinic isobutylamides. More recently, however, attention was drawn to the antibiotic property of some acetylenic amides (15) isolated from *Achillea* species (13, 14), which exhibited a strong inhibition of RNA-synthesis in mice-ascites-tumour tests (64).

Existing evidence suggests that the position of double bonds as well as *E-Z*-isomerism plays an important role in the physiological and insecticidal activities of the alkamides. Significant insecticidal activity against house-flies had been found only in those isobutylamides in which double bonds conjugated with the carbonyl of the amide group, were separated from unsaturation further along the chain by a dimethylene bridge (65). In that case, at least one of the bonds near the centre of the chain should be *Z*-oriented. Further, the established structures

suggest that the unsaturation conjugated with the isobutylamide linkage is all-*E*-oriented. This was also supported by synthetic studies which show that, for the system decadienisobutylamide the *2E,4E*-configuration is ten times more active than the *2E,4Z*-compound against *Musca domestica* (22).

Finally, attention should be drawn to the frequent co-occurrence of amides and lignans (46) which has also been established in more recent investigations on Anthemideae genera (45). As already pointed out in a previous report (66), sesamin and closely related lignans increase the insecticidal potency of pyrethrins. Hence, it is tempting to suppose that the lignans and alkamides have a similar synergistic activity (67).

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