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GENERALIA

Editorial note. The two survey articles here published complete each other most advantageously and are thus equally stimulating for the chemist and the biologist. A detailed exposition is given of the characteristics of those chemical substances in Arthropods which serve for both passive and active protection, and also for communication between individuals.

Arthropod Alkaloids

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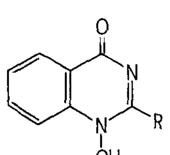
Arthropods constitute the most abundant and diversified group of animals. In this phylum, the use of chemicals for defense and communication purposes, amongst others, has reached a very high level of sophistication. During recent years the study of arthropod ecomones[1a] – the molecules acting as chemical messengers – has undergone a tremendous development[1], and unveiled an impressive array of structures, including a number of alkaloids, which constitute the subject of the present review. The term alkaloid is used here in a very broad sense and will encompass all secondary metabolites containing nitrogen. However, biogenic amines, pigments and their relatives, as well as the important group of cyanogenic compounds, already appropriately reviewed[1b,2], will not be covered here.

Diplopoda

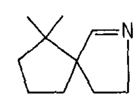
The European millipede *Glomeris marginata*, when disturbed, discharges from a row of dorsal glands a proteinaceous secretion containing *2* quinazolinones: glomerin (**1**) and homoglomerin (**2**)[3–5].



(**1**) $R=CH_3$
(**2**) $R=CH_2CH_3$

Both alkaloids have been synthesized[3,6]. It has been demonstrated[7] that they are biosynthesized by the millipede, using anthranilic acid as a precursor. The effectiveness of the defensive secretion of *G. marginata* as repellent against predators has been established[3]. Ingestion of *G. marginata* is reported to cause delayed general symptoms and even death in mice[3], as well as paralysis in spiders[8].

Quite recently the defensive secretion of the millipede *Polyzonium rosalbum* has been shown[9] to contain polyzonimine (**3**), a novel terpenoid alkaloid. The structure of this unusual, highly volatile imine has been deduced from an X-ray crystallographic analysis of a perchloric acid derivative and confirmed by synthesis[9]. It acts as a topical irritant to insects, a 10^{-4} *M* solution in ethylene glycol inducing scratching in cockroaches.



(**3**)

Polyzonimine is accompanied in this secretion by a smaller amount ($\simeq$ 15%) of a less volatile, crystalline component: nitropolyzonamine (**46**)[10], which, in addition to the same spirocyclic nucleus, has another

* We are grateful to Dr. J. M. Pasteels for stimulating discussions.

1 a See for example, M. Florkin, Bull. Acad. r. Belg. *51*, 239 (1965). J. M. Pasteels, Ann. Soc. r. zool. Belg. *103*, 103 (1973). – b T. Eisner, in *Chemical Ecology* (Eds. E. Sondheimer and J. B. Simeone, Academic Press, New York 1970), p. 157. – c M. Beroza, *Chemicals Controlling Insect Behavior* (Academic Press, New York 1970).

2 J. Weatherston and J. E. Percy, in *Chemicals Controlling Insect Behavior* (Ed. M. Beroza; Academic Press, New York 1970), p. 95.

3 H. Schildknecht, U. Maschwitz and W. F. Wenneis, Naturwissenschaften *54*, 196 (1967).

4 Y. C. Meinwald, J. Meinwald, and T. Eisner, Science *154*, 390 (1966).

5 H. Schildknecht and W. F. Wenneis, Z. Naturforsch. *21b*, 552 (1966).

6 D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta and H. K. Miller, Tetrahedron *16*, 224 (1961).

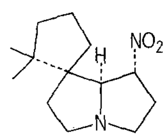
7 H. Schildknecht and W. F. Wenneis, Tetrahedron Lett., *1967*, 1815.

8 T. Eisner, in *Chemical Ecology* (Eds. E. Sondheimer and J. B. Simeone; Academic Press, New York 1970), p. 195.

9 J. Smolanoff, A. F. Kluge, J. Meinwald, A. McPhail, R. W. Miller, K. Hicks and T. Eisner, Science *188*, 734 (1975).

10 J. Meinwald, J. Smolanoff, A. T. McPhail, R. W. Miller, T. Eisner and K. Hicks, Tetrahedron Lett., *1975*, 2367.

unusual feature not often found among animal metabolites, an aliphatic nitro group. Treatment of



46

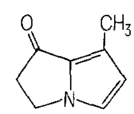
synthetic polyzonimine with β-nitroiodopropane gives a crystalline salt which is readily cyclized to ($\pm$)nitropolyzonamine[10].

Insecta

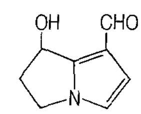
Isoptera. 1-nitro-*trans*-1-pentadecene[11], found in the frontal gland secretion of soldiers of *Prorhinotermes simplex,* is the only nitrogen compound so far isolated from a termite. The structure of this compound has been confirmed by synthesis[11]. Its biological role has not been reported.

Lepidoptera. Male Danainae butterflies (family Nymphalidae), possess a pair of extrusible hair-pencils which are used to disseminate pheromonal substances during courtship[12,13]. The pyrrolizidinone derivative **4** was identified in the hair-pencil secretion of *Lycorea ceres ceres*[14,15] and of *Danaus gilippus berenice*[16] where it was found to elicit strong olfactory receptor responses in the female antennae[17] and to act as the chemical messenger that induces the female to mate[18]. **4** is widely distributed among Danainae butterflies. The related pyrrolizidine derivatives **5**, **6** and **7** have also been detected in some other *Danaus*, as well as *Euploea* species (see Table I).

It has been pointed that: a) Danainae butterflies feed essentially on plants (mostly Boraginaceae, Compositae, Leguminosae and Apocynaceae) which are well known sources of pyrrolizidine alkaloids[22,24]; b) lycopsamine (**7**) is found in plant species on which these butterflies feed[23,25]; c) compounds **5** and **6** are closely related to the metabolites produced by mammals treated with pyrrolizidine alkaloids[21]. These and other confluent observations are regarded as confirming that the above pheromones derive from exogenous pyrrolizidine alkaloid precursors[22,23,25].



(4)



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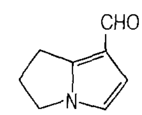
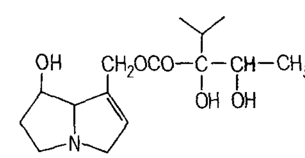


(6)



(7)

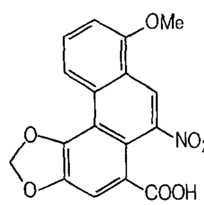
Some male butterflies of the family Arctiidae possess scent organs in form of brushes which are believed to be used for the dissemination of pheromones. These species are also known to utilize plants containing pyrrolizidine alkaloids as larval host plants. It has been found that the derivative **5** is present in the scent organ of *Utetheisa pulchelloides* and *U. lotrix*. Compound **6** is also present in *U. lotrix*[26]. It is supposed that these alkaloids play a role in the mating of these Lepidoptera, similar to that established for the related compounds of the Danainae.

Table I. Occurrence of pyrrolizidine alkaloids in Danainae butterflies

	References	4	5	6	7
Amauris alimaculata	20	+	−	−	−
A. echeria	20	+	−	−	−
A. niavius	20	+	−	−	−
A. ochlea	20	+	−	−	−
Danaus affinis affinis	21	+	−	+	−
D. affinis albistriga	22	+	−	+	−
D. chrysippus	19	+	−	−	−
D. chrysippus dorippus	20	+	−	−	−
D. gilippus berenice	16	+	−	−	−
D. gilippus strigosus	16	+	−	−	−
D. hamatus hamatus	21, 23	+	+	−	+
D. hamatus moderatus	22	+	+	−	−
D. limniace petiverana	20	+	−	−	−
D. pumilus hebridesius	22	−	+	−	−
Euploea lewinii lilybaea	22	−	+	−	−
E. nemertes	22	−	+	−	−
E. sylvester sylvester	21	−	+	−	−
E. treitschkei jessica	22	−	+	−	−
E. tulliola tulliola	21, 23	−	+	−	+
Lycorea ceres ceres	14	+	−	−	−

[11] J. VRKOC and K. UBIK, Tetrahedron Lett. *1974*, 1463.
[12] L. P. BROWER, J. V. Z. BROWER and F. P. CRANSTON, Zoologica *50*, 1 (1965).
[13] J. MYERS and L. P. BROWER, J. Insect Physiol. *15*, 2117 (1969).
[14] J. MEINWALD, Y. C. MEINWALD, J. W. WHEELER, T. EISNER and L. P. BROWER, Science *151*, 583 (1966).
[15] J. MEINWALD and Y. C. MEINWALD, J. Am. chem. Soc. *88*, 1305 (1966).
[16] J. MEINWALD, Y. C. MEINWALD and P. H. MAZZOCCHI, Science *164*, 1174 (1969).
[17] D. SCHNEIDER and U. SEIBT, Science *164*, 1173 (1969).
[18] T. E. PLISKE and T. EISNER, Science *164*, 1170 (1969).
[19] J. MEINWALD, W. R. THOMPSON, T. EISNER and D. F. OWEN, Tetrahedron Lett. *1971*, 3485.
[20] J. MEINWALD, C. J. BORIAK, D. SCHNEIDER, M. BOPPRE, W. F. WOOD and T. EISNER, Experientia *30*, 721 (1974).
[21] J. A. EDGAR, C. C. J. CULVENOR and L. W. SMITH, Experientia *27*, 761 (1971).
[22] J. A. EDGAR, C. C. J. CULVENOR and G. S. ROBINSON, J. Austr. ent. Soc. *12*, 144 (1973).
[23] J. A. EDGAR and C. C. J. CULVENOR, Nature, Lond. *248*, 614 (1974).
[24] J. A. EDGAR and C. C. J. CULVENOR, Experientia *31*, 393 (1975).
[25] D. SCHNEIDER, M. BOPPRE, H. SCHNEIDER, W. R. THOMPSON, C. J. BORIACK, R. L. PETTY and J. MEINWALD, J. comp. Physiol. *97*, 245 (1975).
[26] C. C. J. CULVENOR and J. A. EDGAR, Experientia *28*, 627 (1972).

Accumulation of intact plant alkaloids by other Lepidoptera has also been documented: aristolochic acid (**8**) is found in *Pachlioptera aristolochiae*, a toxic butterfly which feeds on *Aristolochia clamatis* and *A. rotundo*, well known sources of **8**[27]. Similarly, the pupae and the imago of *Callimorpha jacobaeae*, reared on *Senecio jacobaea* or *S. vulgaris*, contain the same pyrrolizidine alkaloids as their host plants[28]. In both cases, it is assumed that these bases play some part in the defense mechanism of the insects[27,28].

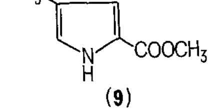


(**8**)

Hymenoptera. The use of pheromones and allomones is very widespread and prevalent in the order Hymenoptera[29]. Only a few of the ecomones so far identified are of alkaloid nature, all being found in ants.

Atta

Many species of ants are known to use trail pheromones. In particular the trail-following behaviour of the Texas leaf-cutting ant, *Atta texana*, has well been described[30]. MOSER and SILVERSTEIN[31] have found the trail pheromone to contain at least two components, one volatile and the other non-volatile. The major compound of the volatile fraction was identified as methyl 4-methylpyrrole-2-carboxylate (**9**)[32,33]. Synthetic **9**, obtained by esterification of the corresponding acid, showed the same level of activity as the natural compound in laboratory and field bio-assays[33]. Another synthesis starting from pyrrole has been described by SONNET[34]. Moreover several synthetic analogs of **9** have also been found to possess considerable trail pheromone activity[35].

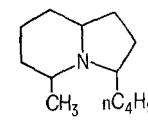


(**9**)

9 is also the major trail active compound of the volatile fraction from *Atta cephalotes*[36], and may well be a component of the trail pheromone of other ants of the Attini tribe. Indeed all but one of the 12 attine species tested by ROBINSON et al.[37] follow artificial trails of **9**, while non-attine ants do not.

Monomorium

The tropical ant, *Monomorium pharaonis*, is known to produce a persistent pheromone trail[38]. Recently RITTER et al.[39] showed that the biologically active fractions contain active nitrogen substances, one of which being an undetermined stereoisomer of **10**. Two other components, of formula $C_{13}H_{27}N$ and $C_{15}H_{29}N$, have also been isolated[39].



(**10**)

Stereochemically unambiguous synthesis of each of the 4 DL pairs of stereoisomers of **10** was made by SONNET and OLIVER[40,41]. Their individual activity has not been reported.

Solenopsis

The common name of the red form of the fire ant, *Solenopsis saevissima* derives from the potency of its venom which has pronounced haemolytic, insecticidal and antibiotic activities[42,43]. It is the only known non-proteinaceous venom delivered by bite or sting[38]. In 1966[44], the toxic effects of this venom were attributed to 2-methyl-3-hexadecyl-pyrrolidine and the corresponding Δ^3-pyrroline. SONNET[45] published a synthesis of this pyrrolidine and showed that neither the *cis* nor the *trans* form were present in the ant

[27] J. VON EUW, T. REICHSTEIN and M. ROTHSCHILD, Israel J. Chem. *6*, 659 (1968).

[28] R. T. APLIN, M. H. BENN and M. ROTHSCHILD, Nature, Lond. *219*, 747 (1968).

[29] For reviews, see for example: J. G. MACCONNELL and R. M. SILVERSTEIN, Angew. Chem. *B12*, 644 (1973). – M. S. BLUM and J. M. BRAND, Am. Zool. *12*, 553 (1972). – D. A. EVANS, C. L. GREEN, Chem. Soc. Rev. *2*, 75 (1973). – J. WEATHERSTON, Q. Rev. chem. Soc. *21*, 287 (1967). – M. S. BLUM, in *Chemicals Controlling Insect Behavior* (Ed. M. BEROZA; Academic Press, New York 1970), p. 61.

[30] J. C. MOSER and M. S. BLUM, Science *140*, 1228 (1963).

[31] J. C. MOSER and R. M. SILVERSTEIN, Nature, Lond. *215*, 206 (1967).

[32] J. H. TUMLINSON, R. M. SILVERSTEIN, J. C. MOSER, R. G. BROWNLEE and J. M. RUTH, Nature, Lond. *234*, 348 (1971).

[33] J. H. TUMLINSON, J. C. MOSER, R. M. SILVERSTEIN, R. G. BROWNLEE and J. M. RUTH, J. Insect Physiol. *18*, 809 (1972).

[34] P. E. SONNET, J. med. Chem. *15*, 97 (1972).

[35] P. E. SONNET and J. C. MOSER, J. agr. Food Chem. *20*, 1191 (1972).

[36] R. G. RILEY, R. M. SILVERSTEIN, B. CARROLL and R. CARROLL, J. Insect Physiol. *20*, 651 (1974).

[37] S. W. ROBINSON, J. C. MOSER, M. S. BLUM and E. AMANTE, Insectes soc. *21*, 87 (1974).

[38] M. S. BLUM, Proc. R. ent. Soc. London (A) *41*, 155 (1966).

[39] F. J. RITTER, I. E. M. ROTGANS, E. TALMAN, P. E. J. VERWIEL and F. STEIN, Experientia *29*, 530 (1973).

[40] J. E. OLIVER and P. E. SONNET, J. org. Chem. *39*, 2662 (1974).

[41] P. E. SONNET and J. E. OLIVER, J. Hetero Chem. *12*, 289 (1975).

[42] G. A. ADROUNY, V. J. DERBES and R. C. JUNG, Science *130*, 449 (1959).

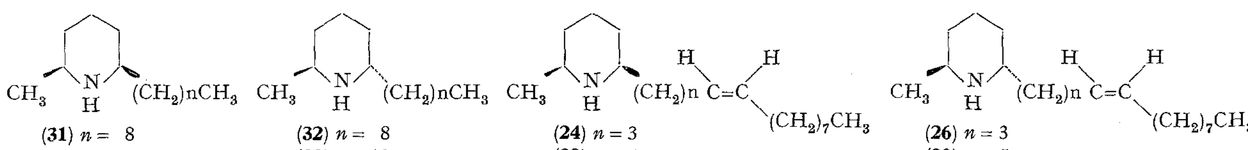
[43] M. S. BLUM, J. R. WALKER, P. S. CALLAHAN and A. F. NOVAK, Science *128*, 306 (1958).

[44] G. A. ADROUNY, Bull. Tulane med. Fac. *25*, 67 (1966).

[45] P. E. SONNET, Science *156*, 1759 (1967).

Table II. Occurrence of 2,6-dialkylpiperidines in *Solenopsis* ants

	21	22	23	24	25	26	27	28	29	30	31	32	References
S. saevissima (red form)	tr	+	tr	tr	++	++	tr	tr	++	++	—	—	47,48
S. saevissima (black form)	tr	++	tr	tr	+	++	—	—	—	—	—	—	48
S. xyloni	++	+	tr	tr	—	—	—	—	—	—	—	—	48
S. xyloni (worker)	++	+	tr	tr	—	—	—	—	—	—	—	—	49
S. xyloni (alate queen)	++	+	tr	tr	—	—	—	—	—	—	—	—	49
S. geminata	++	+	tr	tr	—	—	—	—	—	—	—	—	48
S. geminata (worker)	++	+	tr	tr	—	—	—	—	—	—	—	—	49
S. geminata (soldier)	++	+	tr	tr	—	—	—	—	—	—	—	—	49
S. geminata (alate queen)	++	+	tr	tr	—	—	—	—	—	—	tr	—	49,50
S. richteri (soldier)	tr	+	tr	tr	+	++	—	—	—	—	—	—	49
S. richteri (alate queen)	++	tr	—	—	—	—	—	—	—	—	tr	tr	49,50
S. invicta (soldier)	tr	+	tr	tr	++	++	tr	tr	++	++	—	—	49
S. invicta (alate queen)	++	tr	—	—	—	—	—	—	—	—	—	—	49
S. sp.	—	—	—	—	—	—	—	—	—	—	++	+	50
S. aurea	++	++	tr	—	—	—	—	—	—	—	—	—	53



(31) $n = 8$, **(21)** $n = 10$, **(23)** $n = 12$, **(27)** $n = 14$

(32) $n = 8$, **(22)** $n = 10$, **(25)** $n = 12$, **(29)** $n = 14$

(24) $n = 3$, **(28)** $n = 5$

(26) $n = 3$, **(30)** $n = 5$

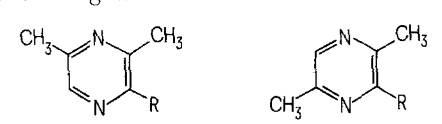
venom. Later, BLUM et al.[46,47] established that the 5 major constituents of the venom are 2,6-disubstituted piperidines. Comparison with authentic samples allowed the determination of structures **22**, **25**, **26**, **29** and **30** for these compounds[47].

Studies of the venoms of other *Solenopsis* species showed that these piperidinic alkaloids are characteristic of the genus[48–50]. Table II summarizes the distribution of the different 2,6-dialkylpiperidines in the species so far investigated. Despite quantitative individual variations within a nest[51], pooled venom samples of the same species, even from widely separated sites, are very similar. This might allow their use for chemotaxonomic purposes[50]. On this basis, BLUM et al.[49,50] proposed a hypothetical model for the evolution of the fire ants, but LOFGREN et al.[52] expressed reservation for further speculations on this hypothesis until much more data be acquired.

Finally, one should mention the detection of traces of 2-methyl-6-*n*-undecyl-$\Delta^{1,2}$-piperideine in *S. xyloni*[48] and of *cis*- and *trans*-2-methyl-6-*n*-nonylpiperidine (tentative structural attribution) in *S. richteri*[50].

Odontomachus

Disturbed workers of the large neotropical ant *Odontomachus hastatus* discharge a secretion having the characteristic odour of chocolate, also present in the mandibular gland secretions of *O. brunneus* and *O. clarus*[54]. Analysis of dichloromethane extracts of the heads of different *Odontomachus* species by combined GC/MS and comparison with authentic samples show the presence of various chocolate-smelling alkylpyrazines[54]. *O. brunneus* was found to contain compounds **11**, **12**, **13** and **14** in a 91:7:1.4:0.6 ratio. Compound **15** is the major product in *O. hastatus* and *O. clarus*. *O. clarus* also contains a small amount of **16**. An unidentified *Odontomachus* from Costa Rica contains 2,6-dimethyl-3-*n*-pentylpyrazine as the major component along with small amounts of $n-C_3$, $-C_4$



R

(11) $(CH_2)_4CH_3$
(12) $(CH_2)_3CH_3$
(13) $(CH_2)_2CH_3$
(14) CH_2CH_3

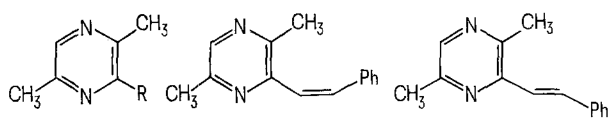
(15) $CH_2CH_2CH(CH_3)_2$
(16) CH_2CH_3

and $-C_6$ side chain derivatives[54]. These pyrazines are powerful releasers of alarm behaviour for *Odontomachus* workers and might also be used as defensive substances[54].

[46] J. G. MACCONNELL, M. S. BLUM and H. M. FALES, Science *168*, 840 (1970).
[47] J. G. MACCONNELL, M. S. BLUM and H. M. FALES, Tetrahedron *26*, 1129 (1971).
[48] J. M. BRAND, M. S. BLUM, H. M. FALES and J. G. MACCONNELL, Toxicon *10*, 259 (1972).
[49] J. M. BRAND, M. S. BLUM and H. H. ROSS, Insect Biochem. *3*, 45 (1973).
[50] J. G. MACCONNELL, R. N. WILLIAMS, J. M. BRAND and M. S. BLUM, Ann. ent. Soc. Am. *67*, 134 (1974).
[51] J. M. BRAND, M. S. BLUM and M. R. BARLIN, Toxicon *11*, 325 (1973).
[52] C. S. LOFGREN, W. A. BANKS and B. M. GLANCEY, A. Rev. Ent. *20*, 1 (1975).
[53] M. S. BLUM, J. M. BRAND, R. M. DUFFIELD and R. R. SNELLING, Ann. ent. Soc. Am. *66*, 702 (1973).
[54] J. W. WHEELER and M. S. BLUM, Science *182*, 501 (1973).

Iridomyrmex

Pyrazine derivatives have also been characterized as minor constituents of the volatile fraction of the Argentine ant *Iridomyrmex humilis*[55,56]: 2,5-dimethyl-3-isopentylpyrazine (**17**), the (Z)- and (E)-2,5-dimethyl-3-styrylpyrazine (**18**) and (**19**) were identified by comparison with synthetic samples. **17** and **18** amount respectively to 70 and 200 ppm of the body weight of the insect. Mass spectrometric data suggest that a fourth pyrazine (**20**) is present at approximately 5 ppm[56]. These pyrazines are essentially located in the head of the insect.



R (**18**) (**19**)

(**17**) $CH_2CH_2CH(CH_3)_2$

(**20**) $CH_2CH_2CH_3$

Since it is known that on exposure to sunlight the (E)-isomer **19** is transformed into the (Z)-isomer **18**, an extraction of the insect was carried out in the dark and the extract immediately analyzed by GC, showing a small peak for the (Z)-isomer and a major peak for the (E)-isomer. After exposure to light for a few hours, the extract was found to contain only the (Z)-isomer. The (E)-isomer is thus considered to be the predominant if not the sole 3-styrylpyrazine present in the insect[55].

It is not established whether these compounds act as alarm pheromones in *I. humilis*. No traces of pyrazine derivatives were found in the Australian ant *I. detectus*[55]. However a series of pyrazines have been identified in the mandibular gland secretion of a formicine ant, *Calomyrmex sp.*[57].

Coleoptera. Amongst the many defensive compounds already described from this order of insects[1b,2], about 15 are alkaloids which are distributed in four families: Coccinellidae, Dytiscidae, Staphylinidae and Curculionidae.

Coccinellidae

Coccinellidae (ladybugs), when molested, emit haemolymph droplets at their joints. This well-described mechanism, known as reflex bleeding[58,59], has been shown to constitute an efficient protection against predators[60]. The bitter taste of the secretion was already reported in the 18th century and has since been frequently alluded to in literature[59]. The chemical deterrent present in the haemolymph of the common European ladybug *Coccinella septempunctata*, was shown recently[61] to be a novel alkaloid N-oxide, coccinelline (**33**). The corresponding free base, precoccinelline (**34**) is also present in the beetle, although generally in smaller quantity. The structure of coccinelline (**33**), first proposed without stereochemistry on the basis of spectral and chemical properties[62], was definitely established by single-crystal X-ray diffraction analysis on coccinelline hemi-hydrochloride[63].

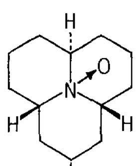
This compound was the first of a novel structural group of alkaloids belonging to the 2-methyl-perhydro-9b-azaphenalene ring system. One could predict for this ring system the existence of only 3 ring junctions stereoisomers, 2 of them the *cis,trans,cis*- and the *trans,trans,trans*-possessing a plane of symmetry, the 3rd one (*cis,cis,trans*-) being a DL-pair. Compounds corresponding to each of these 3 ring stereoisomers have been found in different species of ladybugs. Thus, coccinelline (**33**) and precoccinelline (**34**) (vide supra) correspond to the *cis, trans, cis*-isomer, the N-oxide convergine (**35**)[64] and its free base hippodamine (**36**)[64] from *Hippodamia convergens* to one of the *cis,cis, trans*-isomers, while myrrhine (**37**)[65] from *Myrrha octodecimguttata* represents the *trans,trans,trans*-isomer.

Moreover *Propylea quatuordecimpunctata* afforded yet another alkaloid, propyleine (**38**)[66], which was shown to be a dehydroprecoccinelline, whereas *Adalia bipunctata* yielded the homotropane alkaloid adaline (**39**)[67].

The structure and absolute configuration of convergine (**35**)[64] [and thus hippodamine (**36**)] and of adaline (**39**)[67] was established by single-crystal X-ray diffraction analysis on their respective hydrochlorides, while the structures of propyleine (**38**)[66] and myrrhine (**37**)[65] derive from spectral data and from chemical correlations with coccinelline. The total synthesis of coccinelline[68], myrrhine[68], DL-convergine[68] and DL-adaline[69] have been reported. Moreover, a stereocontrolled synthesis of the two possible stereoisomers of the parent ring system from the coccinellid alkaloids: perhydropyrido[2,1,6-de]-quinolizine, has also been published[70].

[55] G. W. K. Cavill and E. Houghton, Austr. J. Chem. *27*, 879 (1974).
[56] G. W. K. Cavill and E. Houghton, J. Insect Physiol. *20*, 2049 (1974).
[57] B. P. Moore, personal communication to G. W. K. Cavill (cited in ref.[56]).
[58] C. Hollande, Archs Anat. microsc. *13*, 171 (1911).
[59] C. Hollande, Archs Anat. microsc. *22*, 392 (1926). – McIndoo, Ann. ent. Soc. Am. *9*, 201 (1916).
[60] G. M. Happ and T. Eisner, Science *134*, 329 (1961).
[61] B. Tursch, D. Daloze, M. Dupont, J. M. Pasteels and M. C. Tricot, Experientia *27*, 1380 (1971).
[62] B. Tursch, D. Daloze, M. Dupont, C. Hootele, M. Kaisin, J. M. Pasteels and D. Zimmermann, Chimia *25*, 307 (1971).
[63] R. Karlsson and D. Losman, Chem. Commun. *1972*, 626.
[64] B. Tursch, D. Daloze, J. C. Braekman, C. Hootele, A. Cravador, D. Losman and R. Karlsson, Tetrahedron Lett. *1974*, 409.
[65] B. Tursch, D. Daloze, J. C. Braekman, C. Hootele and J. M. Pasteels, Tetrahedron *31*, 1541 (1975).
[66] B. Tursch, D. Daloze and C. Hootele, Chimia *26*, 74 (1972).
[67] B. Tursch, J. C. Braekman, D. Daloze, C. Hootele, D. Losman, R. Karlsson and J. M. Pasteels, Tetrahedron Lett. *1973*, 201.
[68] W. A. Ayer and R. Dawe, private communication.
[69] B. Tursch, C. Chome, J. C. Braekman and D. Daloze, Bull. Soc. chim. Belg. *82*, 699 (1973).
[70] R. H. Mueller and R. M. Dipardo, Chem. Commun. *1975*, 565.

It is worth mentioning that the three stereoisomers **34**, **36** and **37** exhibit nearly identical NMR- and mass spectra, which precludes the use of these methods for identification purposes. However, discrimination can easily be achieved by IR-spectroscopy. In this context, the reported presence of precoccinelline (**34**) as the defensive alkaloid of the coccinellid[71] *Coleomegilla maculata* by HENSON et al.[72], may be questioned since identification rested essentially on mass spectral data. Comparison of the IR-spectra of **34**, **36** and **37** with the values reported by HENSON et al.[72] for the alkaloid[73] of *Coleomegilla maculata* clearly suggests that the latter is most probably myrrhine (**37**).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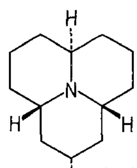
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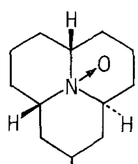
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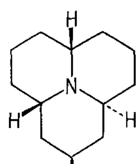
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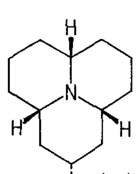
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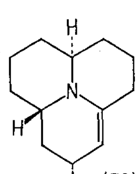
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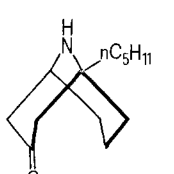

(39)

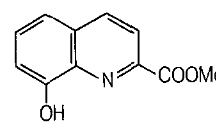
Coccinelline and precoccinelline have been found in the eggs and larvae of *C. septempunctata*, whereas neither of these compounds could be detected in the aphids that constitute the prey of the ladybug[61], thus indicating that these alkaloids are most probably synthetized by the insect itself. Indeed, by feeding *Coccinella septempunctata* with [1-^{14}C]- and [2-^{14}C]-acetate[65], the biosynthesis of coccinelline has been shown to be endogenous and to proceed through a polyacetate pathway.

Coccinelline, which has a very bitter taste, amounts to 1.5% of the dry weight of *C. septempunctata* and its effectiveness for the chemical protection of the insect has been demonstrated[75] using laboratory tests on quails and ants. Coccinelline dissolved in water efficiently repels ants at a concentration of 1×10^{-3} *M*, and exerts complete repulsion at 1×10^{-2} *M*. Similar results were obtained with convergine[75].

Preliminary results[75] seem to indicate a good agreement between the distribution of the alkaloids in the Coccinellidae and the modern taxonomy of this family[76]. From a survey of 35 species and varieties of ladybugs, the presence of alkaloids seems to be correlated with the existence of aposematic colours and not with a carnivorous or phytophagous alimentation[75]. Tables of distribution of alkaloids in Coccinellidae have been published[65,75].

Dytiscidae

The defensive chemistry of the Dytiscidae or water beetles has been studied by SCHILDKNECHT et al.[77]. From the prothoracic defensive gland of *Ilybius fenestratus*, they have isolated, in addition to testosterone, estrone and estradiol, methyl 8-hydroxyquinoline-2-carboxylate (**40**)[78], whose structure was deduced from spectral data and confirmed by synthesis.


(40)

Compound **40**, which is powerful antiseptic[77], could be used by the insect to prevent penetration of microorganisms. It is not toxic for amphibians and fishes, but produces clonic spasms in mice[79].

Staphylinidae

In 1952, PAVAN and BO[80] reported the isolation of a toxic principle, pederin, from the haemolymph of *Paederus fuscipes*. The structure determination of this complex molecule met with many difficulties. The first structure, proposed on the basis of extensive degradation work by CARDANI et al.[81], was slightly modified to **41** by MATSUMOTO et al.[82] relying on

[71] Curiously ascribed to Curculionidae by HENSON et al.[72].

[72] R. D. HENSON, A. C. THOMPSON, P. A. HEDIN, P. R. NICHOLS and W. W. NEEL, Experientia *31*, 145 (1975).

[73] Apparently the same compound (erroneously reported to be propyleine (**38**)) has also been detected in the boll-weevil *Anthonomus grandis* by HEDIN et al.[74].

[74] P. A. HEDIN, R. C. GUELDNER, R. D. HENSON and A. C. THOMPSON, J. Insect. Physiol. *20*, 2135 (1974).

[75] J. M. PASTEELS, C. DEROE, B. TURSCH, J. C. BRAEKMAN, D. DALOZE and C. HOOTELE, J. Insect Physiol. *19*, 1771 (1973).

[76] H. SASAJI, Etizenia *35*, 1 (1967).

[77] H. SCHILDKNECHT, Angew. Chem. *B9*, 1 (1970).

[78] H. SCHILDKNECHT, H. BIRRINGER and D. KRAUSS, Z. Naturforsch. *24b*, 38 (1969).

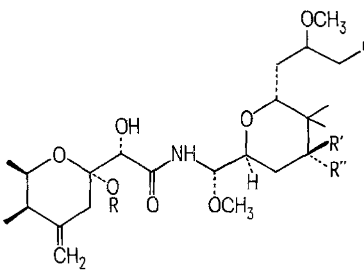
[79] H. SCHILDKNECHT, Endeavour 30, 136 (1971).

[80] M. PAVAN and G. BO, Memorie Soc. ent. Ital. *31*, 67 (1952).

[81] C. CARDANI, D. GHIRINGHELLI, R. MONDELLI and A. QUILICO, Tetrahedron Lett. *1965*, 2537. – Gazz. chim. ital. *96*, 3 (1966).

[82] T. MATSUMOTO, M. YANAGIYA, S. MAENO and Y. YASUDA, Tetrahedron Lett. *1968*, 6297.

careful NMR-spectrum analysis. Finally, the structure and stereochemistry of pederin as depicted in **41** was confirmed by single-crystal X-ray diffraction analysis on pederin di-*p*-bromobenzoate[83,84]. The intriguing chemical properties of pederin have been further studied by CARDANI et al.[85]. Two other closely related compounds, pseudopederin[86] and pederone[87], were also isolated from *P. fuscipes*. Structures **42** and **43** were established for these products by chemical correlation with pederin[81,85,87].

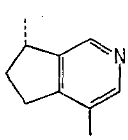


	R	R′	R″
(41)	CH_3	H	OH
(42)	H	H	OH
(43)	CH_3	=O	

Incorporation of (1-^{14}C)- and (2-^{14}C)-acetate into pederin, followed by selective degradation, suggests that pederin is most probably biosynthesized through a polyketide pathway[88].

Pederin is a powerful cytotoxin, capable of inhibiting growth of cultured cells at concentrations of about 1.5 ng/ml[89]. Moreover, it has strong vesicating properties when applied to human skin and can induce severe systemic effects when ingested[90]. A review of the biological and medicinal properties of pederin has been published by PAVAN[90].

Another alkaloid reported[91] from staphylinid beetles is the well-known monoterpene alkaloid, actinidine[92] (**44**), which was shown to be present in the pygidial defensive secretion of *Hesperus semirufus* and *Philonthus politus*, together with citronellal, iso-valeraldehyde and iridodial. The presence of iridodial in the defensive secretion of these beetles suggests a terpenoid biosynthetic pathway for actinidine, as already demonstrated in plants[93]. Moreover, stenusine (**45**)[94] has been isolated from the pygidial defense glands of *Stenus comma* together with 6-methyl-5-hepten-2-one and eucalyptol. Stenusine possesses a high spreading power providing the beetle with an elegant escape mechanism.



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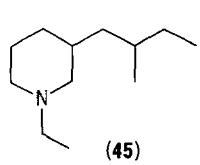

(45)

Curculionidae

HEDIN et al.[74] reported the occurrence in the bollweevil *Anthonomus grandis* of the alkaloid already isolated from *Coleomegilla maculata*[72] (vide supra, Coccinellidae). A second nitrogen-containing compound was also detected in *A. grandis*. It has the empirical formula C_2H_3NBrCl and was tentatively identified by its mass spectral fragmentation to 2-bromo-2-chloroaziridine, but alternative structures cannot be ruled out[74].

Arthropod alkaloids, despite their relative paucity, are quite diversified, chemically as well as biologically. They can be of exogenous or endogenous origin. They are either found in specialized glands or present in the haemolymph. It is noteworthy that in most cases the ecological role of these substances has been clearly established.

Together with the possession of elaborate chemical communications, the great evolutionary and ecological success of arthropods (especially insects) seems to be linked with the great development of chemical defenses. Chemical deterrents seem to have played a similar role in regard to the success of plants (especially Angiosperms). Alkaloids in particular constitute a classical plant defense mechanism, to the extent that they were once considered to be exclusively vegetal metabolites. While it is estimated that alkaloids are produced by 1/6[95] to 1/15[96] of the Angiosperms, only a small number of alkaloids are encountered among the multitude of described arthropod ecomones. Indeed, their biosynthesis by arthropods has been demonstrated only in a few cases, and their distribution seems restricted to a few families. Moreover, most of the great classical groups of plant alkaloids are until now conspicuously absent in these animals.

[83] A. FURUSAKI, I. WATANABE, T. MATSUMOTO and M. YANAGIYA, Tetrahedron Lett. *1968*, 6301.
[84] A. BONAMARTINI CORRADI, A. MANGIA, M. NARDELLI and G. PELIZZI, Gazz. chim. ital. *101*, 591 (1971).
[85] C. CARDANI, D. GHIRINGHELLI, R. MONDELLI and A. SELVA, Gazz. chim. ital. *103*, 247 (1973).
[86] A. QUILICO, C. CARDANI, D. GHIRINGHELLI and M. PAVAN, Chimica Ind. Milano *43*, 1434 (1961).
[87] C. CARDANI, D. GHIRINGHELLI, A. QUILICO and A. SELVA, Tetrahedron Lett. *1967*, 4023 .
[88] C. CARDANI, C. FUGANTI, D. GHIRINGHELLI, P. GRASSELLI, M. PAVAN and M. D. VALCURONE, Tetrahedron Lett. *1973*, 2815.
[89] A. BREGA, A. FALASCHI, L. DE CARLI and M. PAVAN, J. Cell Biol. *36*, 484 (1968).
[90] M. PAVAN, *Industrie Lito-Tipografiche* (M. Ponzio, Pavia 1963).
[91] T. E. BELLAS, W. V. BROWN and B. P. MOORE, J. Insect Physiol. *20*, 277 (1974).
[92] T. SAKAN, A. FUJINO, F. MURAI, Y. BUTSUGAN and A. SUZUI, Bull. chem. Soc. Jap. *32*, 315 (1959).
[93] H. AUDA, G. R. WALLER and E. J. EISENBRAUN, J. biol. Chem. *242*, 4157 (1967).
[94] H. SCHILDKNECHT, D. KRAUSS, J. CONNERT, H. ESSENBREIS and N. ORFANIDES, Angew. Chem. *B 14*, 427 (1975).
[95] R. HEGNAUER, *Chemataxonomie der Pflanzen* (Birkhäuser Verlag, Basel 1962), vol. 1 and 2.
[96] C. C. J. CULVENOR, Search. *1*, 103 (1970).