The Chemistry of Arthropod Defensive Substances

By John Weatherston*
DEPARTMENT OF CHEMISTRY, BAKER LABORATORY, CORNELL UNIVERSITY, ITHACA, NEW YORK

The study of communication among animals by means of chemical stimuli is expanding rapidly, and co-operation between neurobiologists, entomologists, and organic chemists, together with advances in chemical techniques and methods of physical measurement have established and differentiated between various types of substances, *e.g.*, sex-attractants, trail marking, swarming, alarm, and defensive substances. Several reviews have recently been published dealing with various aspects of these compounds as applied to arthropods.[1–5]

This Review will be restricted to the defensive substances of the arthropods and will not include venoms which are administered by stinging or biting. Arthropods may be defined as being characterised by segmented bodies and jointed legs, and include crustaceans, arachnids, insects, and myriapodes.

Arthropods, of all the land-dwelling animals, have the most diverse and probably the best evolved chemical defences known to man. The chemical compounds used by these animals may be ejected in gaseous form or as a fine spray, simply ooze out as a liquid which quickly volatilises, or, as has been observed in some cases, they may be foams. No matter what the method of application, the predator attacking an arthropod possessing a defensive mechanism is left in no doubt as to the message which is being communicated to it. Although as a rule not fatal, the secretion is sufficiently unpleasant to cause the attacker acute discomfort for some time, usually sufficient for the attacked animal to make its escape. The secretion is usually effective against other predatory arthropods, small mammals, and birds. To illustrate method of delivery and effects on various predators, one case will be considered in detail; for further examples, see the excellent review by Roth and Eisner.[2]

The whipscorpion *Mastigoproctus giganteus* is an arachnid varying in length from 2—5 cm.; it has a short postabdominal knob that forms the base of its flagellum. This knob which contains the gland openings of the defensive secretion reservoir can turn so that a predator attacking almost any region of the whipscorpion is accessible to the spray.[6] One of the most impressive demonstrations which the Reviewer has seen took place when a whipscorpion was placed a few

* *Present Address:* The Institute of Insect Pathology, Sault Ste Marie, Ontario, Canada.
[1] E. O. Wilson and W. H. Bossert, *Rec. Progr. Hormone Res.*, 1963, **19**, 673.
[2] L. M. Roth and T. Eisner, *Ann. Rev. Entomol.*, 1962, **7**, 107.
[3] M. Jacobson, 'Insect Sex Attractants', John Wiley & Sons, Inc., New York, 1965.
[4] M. Jacobson, *Ann. Rev. Entomol.*, 1966, **11**, 403.
[5] G. W. K. Cavill and P. L. Robertson, *Science*, 1965, **149**, 1337.
[6] T Eisner, J. Meinwald, A. Monro, and R. Ghent, *J. Insect Physiol.*, 1961, **6**, 272.

millimetres above a large sheet of filter paper impregnated with a dark red solution of alkaline phenolphthalein. The arachnid was held by a small hook glued to its back, this hook being attached to a clamp in such a way that the animal was held in its normal stance. On subjection to mild traumatic stimuli, say applied to one rear leg, there was an immediate reaction and the filter paper around the area stimulated was decolorised by the acid spray emitted by the animal. The sprayed area was fairly broad but the spray was always aimed with sufficient accuracy to make certain that a predator in that area would receive enough secretion to deter it from further attack. By applying stimuli to various parts of the animal, it could be seen from the pattern of white spots on the filter paper that the discharge to a site of stimulus is brought about by direct contact at that site. When a varying stimulus was applied persistently at one site the animal discharged at intervals of several seconds and never in quick-fire sequence. The range of the discharge is about 20—40 cm. with a reported maximum of 80 cm.[6]

The secretion of the whipscorpion consists of acetic acid (84%), caprylic acid (5%), and water (11%). The presence of the caprylic acid adds considerably to the effectiveness of the defensive agent when it is used against other arthropods. By acting as a wetting agent this acid promotes the spread of the spray droplets over the cuticle of the predator, increasing the effective area of contact. Also, caprylic acid accelerates the penetration of the secretion through the cuticle, presumably by increasing the permeability of the epicuticular lipid barrier. In its natural habitat in the tropics and in the northern sub-tropics, the whipscorpion would have as natural enemies ants, amphibia, reptiles, and mammals. In laboratory experiments Eisner, Meinwald, Monro, and Ghent[6] tested the effectiveness of the arachnid's defences against ants, solpugids, birds, lizards, grasshopper mice, and an armadillo; in all categories the predators were successfully repelled.

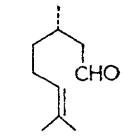
Arthropod Defensive Substances

Until the present, about fifty compounds have been isolated from arthropods, and claimed to be defensive substances. These compounds vary in complexity from hydrogen cyanide or formic acid to the furanoterpene, cantharidin; and pederin, the defensive compounds of *Paederus fuscipes*, the structure of which has been recently postulated by Quilico and his co-workers.[7] Although in many cases, such as that of the whipscorpion, there is no doubt that the compounds secreted are for defence, some authors claim that materials isolated by solvent extraction of whole animals are defensive secretions. For the purposes of this Review these claims are upheld.

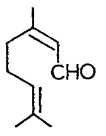
The diversity of the nature of the compounds isolated make classification arbitrary, and the following are the headings under which the defensive substances of arthropods are discussed: (*a*) terpenes, (*b*) quinones, and (*c*) miscellaneous compounds.

[7] C. Cardani, D. Ghiringhelli, R. Monelli, and A. Quilico, *Tetrahedron Letters*, 1965, 2537.

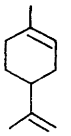
Terpenes.—The terpenes which have been isolated from arthropods and believed to be defensive agents are (1 — 13). Besides the true terpenes such as citral or limonene, also discussed in this section will be certain aliphatic ketones included because of their co-occurrence in terpene-secreting insects. Table 1 shows those arthropods from which terpenes have been obtained.

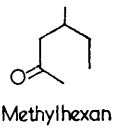


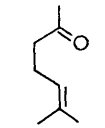
Citronellal (1)

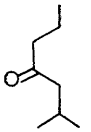


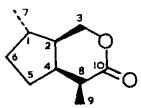
Citral (2)

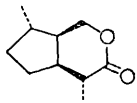

Limonene (3)

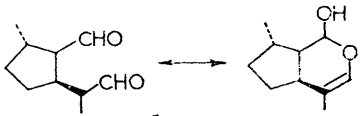

4-Methylhexan-2-one (4)


6-Methylhept 5-en-2-one (5)

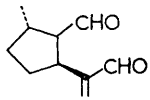

Isobutyl propyl ketone (6)


Iridomyrmecin (7)

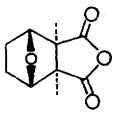

Isoiridomyrmecin (8)

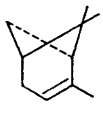


Iridodial (9)



Dolichodial (Anisomorphal) (10)


Cantharidin (11)


α-Pinene (12)

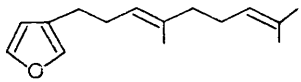

Dendrolasin (13)

Table 1

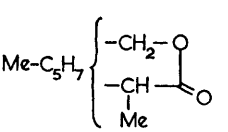
Arthropod	*Components of secretion*													
Formula number	1	2	3	4	5	6	7	8	9	10	11	12	13	*Ref.**
Acanthomyops claviger	×	×												*a*
Atta sexdens rubropilosa		×												*b, c*
Myrmicaria natalensis			×											*d*
Dolichoderus clarki				×						×				*e*
Iridomyrmex conifer					×				×					*f*
Iridomyrmex detectus					×				×					*e, f*
Iridomyrmex nitidiceps					×				×					*e*
Iridomyrmex rufoniger					×				×	×				*e*
Dolichoderus scabridus					×			×	×	×				*e*
Tapinoma nigerrimum					×	×			×					*g, h*

Table 1—*continued*

Arthropod	*Components of secretion*													
Formula number	1	2	3	4	5	6	7	8	9	10	11	12	13	*Ref.**
Iridomyrmex humilis							×							*f*
Iridomyrmex nitidus								×						*f*
Iridomyrmex myrmecodiae										×				*e*
Dolichoderus dentata										×				*e*
Dendrolasius fuliginosus													×	*i, j*
Anisomorpha buprestoides										×				*k*
Members of the family *Meloidae*											×			*l*
Three species of *Nasutitermes*												×		*m*

* The literature cited in this column refers to reports of the isolation of the compounds.
[a] M. S. Chadha, T. Eisner, A. Monro, and J. Meinwald, *J. Insect Physiol.*, 1962, **8**, 175; [b] A. Butenandt, *Naturwiss.*, 1959, **46**, 462; [c] A. Butenandt, B. Linzen, and M. Lindaur, *Arch. Anat. Microscop. Morphol. Exptl.*, 1959, **48**, 13; [d] P. Grünanger, A. Quilico, and M. Pavan, *Acad. Naz. Lincei, Rend. accad. sci. fis. mat.*, 1960, **28**, 293; [e] G. W. K. Cavill and H. Hinterberger, *Austral. J. Chem.*, 1960, **13**, 514; [f] G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Austral. J. Chem.*, 1956, **9**, 288; [g] R. Trave and M. Pavan, *Chim. e Ind.*, 1956, **38**, 1015; [h] M. Pavan and R. Trave, *Insectes sociaux*, 1958, **5**, 299; [i] A. Quilico, F. Piozzi, and M. Pavan, *Ricerca sci.*, 1956, **26**, 177; [j] A. Quilico, F. Piozzi, and M. Pavan, *Tetrahedron*, 1957, **1**, 177; [k] J. Meinwald, M. S. Chadha, J. J. Hurst, and T. Eisner, *Tetrahedron Letters*, 1962, 29; [l] W. Ude and E. F. Heeger, *Pharm. Zentralhalle*, 1941, **82**, 193; [m] B. P. Moore, *J. Insect Physiol.*, 1964, **10**, 371.

Iridomyrmecin, isoiridomyrmecin and iridodial; structure. Reports by Pavan[8,9] that a constituent of the anal glands of the Argentinian ant *Iridomyrmex humilis* (sub-family Dolichoderinae) possessed both antibiotic and insecticidal activity aroused much interest in the chemistry of this sub-family. Continuing this work Pavan reported[10] that this compound was a terpenoid lactone which he named iridomyrmecin, and for which partial structure (14) was suggested.[11] The extrac-



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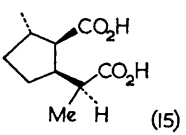

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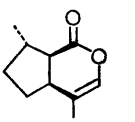


(16)

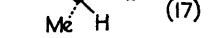
tion with light petroleum of four species of *Iridomyrmex* ants[12] indigenous to Australia led to the discovery of several terpenes related to iridomyrmecin. *I. humilis* yielded the lactone iridomyrmecin, confirming Pavan's original observation, while the compound isolated from *I. nitidus*, although a lactone

[8] M. Pavan, *Ricerca sci.*, 1949, **19**, 1011.
[9] M. Pavan, *Ricerca sci.*, 1950, **20**, 1853.
[10] M. Pavan, *Chim. Ind.*, 1955, **37**, 625.
[11] R. Fusco, R. Trave, and A. Vercellone, *Chim. Ind.*, 1955, **37**, 251.
[12] Table 1, ref. *f*.

of formula $C_{10}H_{16}O_2$, was not identical with iridomyrmecin and was subsequently named iridolactone. From *I. detectus* and *I. conifer* 6-methylhept-5-en-2-one (5) and a dicarbonyl compound $C_{10}H_{16}O_2$ (iridodial) were isolated. The structure of the naturally occurring methylheptenone was confirmed by direct comparison with authentic material obtained from citral (2) by the Verley's method.[13]

Iridomyrmecin, m.p. 60—61°, $[\alpha]_D$ + 210°, on oxidation with alkaline permanganate gave a dicarboxylic acid $C_{10}H_{16}O_4$, m.p. 117—118°, $[\alpha]_D$ + 14°.[11,14] This diacid has been shown to be identical with the known nepetalinic acid (15)[15] obtained in degradation studies of *cis/trans** nepetalactone (16), the major constituent of oil of catnip.[16,17,18]

Iridolactone, m.p. 58—59°, $[\alpha]_D^{17}$ − 62°, when oxidised for two days at room temperature with alkaline permanganate also afforded a dicarboxylic acid $C_{10}H_{16}O_4$ which had m.p. 81—82° and $[\alpha]_D^{25}$ + 24°. This acid is identical with the nepetalinic acid (17).[14] Fusco *et al.*[11] using sodium methoxide in methanol had previously epimerised iridomyrmecin to a compound of m.p. 56·5—57°, $[\alpha]_D^{20}$ − 52·5°. These authors had interpreted the conversion as taking place at the asymmetric centre adjacent to the lactone group. Iridolactone and isoiridomyrmecin have been shown to be identical,[14] hence both iridolactones† are represented by the structure (18).

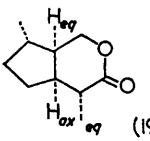


(17)

(18)

Since the difference in configuration of the iridolactones is at C(8), structures (19)—(22) represent the four possible isomers. (19) and (22) are preferred on grounds of conformational analysis since the *C*-methyl group at C(8) is in the equatorial position.[14,19]

X-Ray crystallographic analysis has shown the conformations of the iridolac-



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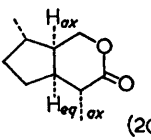

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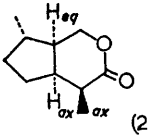

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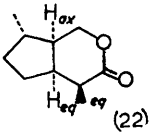


(22)

* Stereochemical relationships will be given always as C(4)/C(2) substituents, then C(2)/C(1).
† Structures (7) and (8) represent iridomyrmecin and isoiridomyrmecin; the term iridolactones is used to describe the stereoisomeric compounds represented by (18).

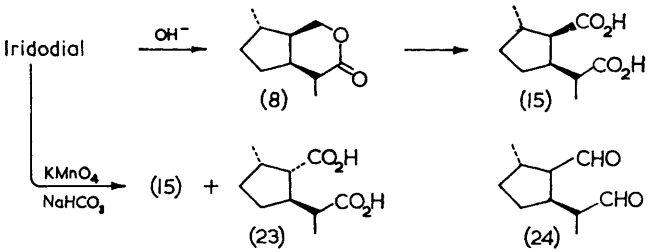
[13] A. Verley, *Bull. Soc. chim. France*, 1897, **17**, 175.
[14] G. W. K. Cavill and H. D. Locksley, *Austral. J. Chem.*, 1957, **10**, 352.
[15] R. Fusco, R. Trave, and A. Vercellone, *Chim. Ind.*, 1955, **37**, 958.
[16] S. M. McElvain and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, 1955, **77**, 1599.
[17] R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Amer. Chem. Soc.*, 1958, **80**, 3413.
[18] R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, *J. Amer. Chem. Soc.*, 1958, **80**, 3420.
[19] G. W. K. Cavill, *Rev. Pure Appl. Chem.*, 1960, **10**, 169.

tones[20,21] to be as in Figure 1.

Figure 1

Iridodial (9) has been isolated from *Tapinoma nigerrimum*[22,23] in addition to the already mentioned *Iridomyrmex* species.[12] It is a colourless liquid, b.p. 90—92°/1·0 mm., $C_{10}H_{16}O_2$, forms a bis-2,4-dinitrophenylhydrazone, m.p. 224—225°, and is converted into isoiridomyrmecin (8) by the action of hot aqueous sodium hydroxide, this reaction being typical of 1,5-dialdehydes.[24] Confirmation of the dialdehyde function was obtained when on oxidation iridodial yielded a mixture of stereoisomeric acids of formula $C_{10}H_{16}O_4$.[25] A Kuhn–Roth oxidation indicated two *C*-methyl groups, while the probability of a carbocyclic ring was postulated by inactivity towards hydrogen with Raney nickel and platinum oxide as catalysts.

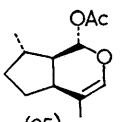
Iridodial on treatment with sodium hydroxide, as already stated, gives a complex mixture of δ-lactones including isoiridomyrmecin (8) which has already been correlated with the nepetalinic acid (15). Direct oxidation of the terpene dialdehyde itself with potassium permanganate and sodium hydrogen carbonate in acetone solution yields, besides the nepetalinic acid (15), the stereoisomer (23).[25] These inter-relationships establish structure (24) for iridodial in which there is a *trans*-1,3 relation between the methyl group at C(1) and the α-methylpropional group at C(4).



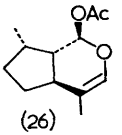
Structure (24) was established mainly on chemical grounds, and certain physical data indicated that the 1,5-dialdehyde is in equilibrium with cyclic tautomers.[25] The infrared spectrum of iridodial exhibits strong absorptions at 3610 cm.$^{-1}$ (—OH), 3050, 1675, and 852 cm.$^{-1}$ (—CH = C—). It was further

[20] J. F. McConnell, A. McL. Mathieson, and B. P. Schoenborn, *Tetrahedron*, 1962, 445.
[21] B. P. Schoenborn and J. F. McConnell, *Acta Cryst.*, 1962, **15**, 779.
[22] Table 1, ref. *g*.
[23] Table 1, ref. *h*.
[24] R. H. Hall, *J. Chem. Soc.*, 1954, 4303.
[25] G. W. K. Cavill and D. L. Ford, *Austral. J. Chem.*, 1960, **13**, 296.

observed[25] that in chloroform solution iridodial gave a yellow colour with tetranitromethane. Chemical confirmation of a lactol structure came with the isolation of a monoacetate when iridodial was treated with acetic anhydride. On conformational grounds, of the three possible structures (25), (26), and (27) put forward, this acetate was formulated as a mixture of (25) and (26). The infrared spectrum of the monoacetate measured in carbon disulphide solution, whilst showing the presence of bands at 3050, 1685, and 835 cm.$^{-1}$ (trisubstituted ethylene) and 1755 cm.$^{-1}$ (acetate carbonyl), failed to show an absorption at 1780 cm.$^{-1}$ which would have been indicative of a vinyl acetate. In this way structure (27) was excluded.[25] The main contributing structures in the tautomer distribution of iridodial are visualised as (9).



(25)



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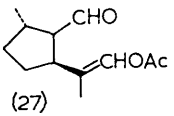
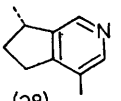


(27)



(28)

The action of hydrochloric acid in acetic acid solution converted iridodial bis-2,4-dinitrophenylhydrazone into actinidine (28). This new terpenoid alkaloid has recently been isolated from the Japanese plant *Actinidia polygama*,[26,27,28] from which isoiridomyrmecin (8) has also been obtained. The 1′,5-dimethyl-3,4-cyclopentenopyridine from iridodial has been shown to be identical with the alkaloid.[19,25] Iridodial has also been isolated from *Iridomyrmex rufoniger*, *I. nitidiceps*, and *Dolichoderus scabridus*.[29]

Dolichodial and anisomorphal; structure. Dolichodial, a pale yellow lachrymatory oil, $C_{10}H_{14}O_2$, characterised by the formation of two bis-2,4-dinitrophenylhydrazones, m.p.s 177° and 242°, has been isolated from the following species of Dolichoderine ants: *Iridomyrmex rufoniger*, *I. myrmecodiae*, *Dolichoderus scabridus*, *D. dentata*, and *D. clarki*. The spectral data of the lævorotatory compound $[\alpha]_D$ − 26° contributed greatly towards its structural determination.[30] The ultraviolet spectrum measured in water had a maximum at 223 mμ, suggesting the presence of an α- or β-monosubstituted $\alpha\beta$-unsaturated aldehyde group: a band at 223 mμ is also observed when the ultraviolet spectrum of crotonaldehyde is measured in water. Evidence supporting this suggestion was found in the infrared spectrum where the following bands were predominant: 1725 and 2720 cm.$^{-1}$ (carbonyl of an aliphatic aldehyde),[31] 1690—1700 cm.$^{-1}$, and 1633 cm.$^{-1}$ (carbonyl group and the double bond of an $\alpha\beta$-unsaturated

[26] T. Sakan, A. Fujino, F. Murai, Y. Butsugan, and A. Suzui, *Bull. Chem. Soc. Japan*, 1959, **32**, 315.
[27] T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Butsugan, *Bull. Chem. Soc. Japan*, 1959, **32**, 1156.
[28] T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Butsugan, *Bull. Chem. Soc. Japan*, 1959, **32**, 1157.
[29] Table 1, ref. *e*.
[30] G. W. K. Cavill and H. Hinterberger, *Austral. J. Chem.*, 1961, **14**, 143.
[31] L. J. Bellamy, 'Infrared Spectra of Complex Molecules', 2nd edn., Methuen, London, 1958, p. 132.

aldehyde). Dolichodial on hydrogenation over palladium–barium sulphate catalyst resulted in a compound which formed two bis-2,4-dinitrophenylhydrazones of m.p.s 217° and 228°. The latter yellow 2,4-dinitrophenylhydrazone was identical with the bis-2,4-dinitrophenylhydrazone of iridodial, thus establishing a cyclopentanoid monoterpene structure for dolichodial. This observation together with the spectral evidence led to the postulation of an α-(2-formyl-3-methylcyclopentyl)acraldehyde structure for dolichodial in which the configuration at C(1) and C(4) would be the same as in iridodial, *i.e.*, (10).[30] Both bis-2,4-dinitrophenylhydrazones of the dihydrodolichodial on treatment with hydrochloric acid in acetic acid formed 1′,5-dimethyl-3,4-cyclopentenopyridine (28).

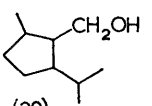
About the same time a report appeared[32] of the isolation and characterisation of a compound named anisomorphal. Both sexes and all nymphal stages of the large herbivorous insect *Anisomorpha buprestoides*, when disturbed, eject a defensive spray. After removal of water from the secretion, the remaining component was shown to be homogeneous. Infrared and nuclear magnetic resonance (n.m.r.) spectroscopic data for anisomorphal are in Table 2.

Table 2

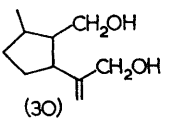
*Infrared absorption**	*N.m.r. (τ value)*	*Assignment*
3·71μ	0·45 and 0·23 (singlet) (doublet)	Protons of aldehyde groups
5·82μ, 5·93μ		Carbonyl group
6·20μ		Double bond in conjugation with a carbonyl group
1·67μ	4·03 and 3·70	Terminal methylene group

* Including near infrared region.

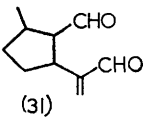
From the spectroscopic evidence both carbonyl groups were deduced to be aldehydic. The dial on borohydride reduction gave a diol which on catalytic hydrogenation gave a saturated alcohol which was shown to be 1-hydroxymethyl-2-isopropyl-5-methylcyclopentane (29) by direct comparison with an authentic sample.[32] It follows therefore that the diol has structure (30) and anisomorphal is (31).



(29)



(30)



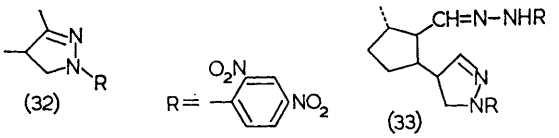
(31)

Hydrogenation of anisomorphal gave iridodial (9) characterised as its bis-2,4-dinitrophenylhydrazone by comparison with an authentic sample. Anisomorphal

[32] Table 1, ref. *k*.

($[\alpha]_D$ + 3·8°) and dolichodial ($[\alpha]_D$ −26°) have different specific rotations and the stereochemical relationships between the compounds is unclear.

As reported above, dolichodial forms two bis-2,4-dinitrophenylhydrazone derivatives; both derivatives absorb in the ultraviolet spectrum about 360 mμ, the region where saturated 2,4-dinitrophenylhydrazones absorb. There is a marked absence of a band in the region of 380 mμ, where the maximum of the 2,4-dinitrophenylhydrazones of $\alpha\beta$-unsaturated carbonyl compounds appears. On the basis of this and the acraldehyde structure of dolichodial (10), these unknown compounds can be assigned pyrazoline structures.[30] Kawahara[33] has reported the formation of the pyrazoline (32) from methyl isopropenyl ketone, so Cavill and Hinterberger[30] have assigned structure (33) to the lower melting of the two unknown compounds. Since the lower melting derivative can be transformed into the higher melting compound by the action of hydrochloric acid, and since both have similar spectroscopic properties, the higher melting compound is thought to be either a stereoisomer of (33) or a dimer, but this problem has as yet not been resolved.

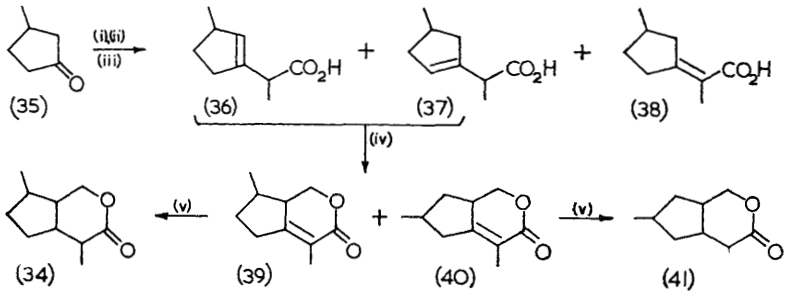


Iridomyrmecin, isoiridomyrmecin and iridodial; synthesis. The reports[8,9] of insecticidal and antibiotic properties of the ant extractives have initiated many synthetic studies.[34–40] The earlier attempts to synthesise the iridolactones and iridodial did not meet with success,[34,35] but recently several authors have reported successful syntheses.[36,38,39,40] DL-Iridomyrmecin (34) has been prepared by three different routes in the laboratory of Korte.[36,37] The route giving the best yield is outlined in Scheme 1.

The reaction of 3-methylcyclopentanone (35) with α-bromopropionate yielded α-(1-hydroxy-3-methylcyclopentyl)propionate which on dehydration with phosphorus oxychloride, followed by hydrolysis, gave a mixture of the unsaturated acids (36), (37), and (38). After removal of the exocyclic unsaturated acid (38) by distillation, the two remaining acids yielded the corresponding lactones (39) and (40) when treated with formaldehyde under the conditions of the Prins reaction. DL-Iridomyrmecin (34) was obtained from the reaction

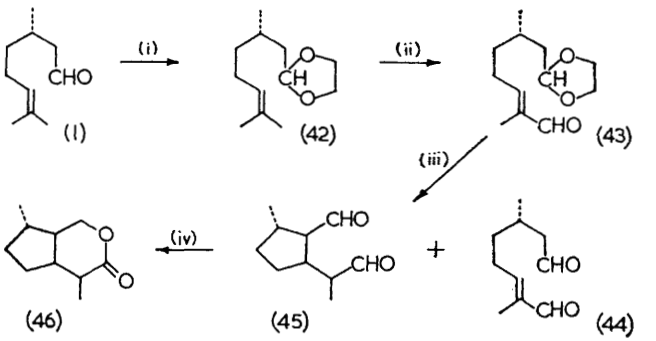
[33] F. K. Kawahara, *J. Amer. Chem. Soc.*, 1957, **79**, 1448.
[34] N. L. Wender and H. L. Slates, *J. Amer. Chem. Soc.*, 1958, **80**, 3937.
[35] J. Wolinsky and W. Baker, *J. Amer. Chem. Soc.*, 1960, **82**, 3937.
[36] F. Korte, J. Falbe, and A. Zschocke, *Tetrahedron*, 1959, **6**, 201.
[37] K. H. Buchel and F. Korte, Proc. 11th Internat. Congr. Entomol., Vienna, 1960, vol. 3, p. 60.
[38] K. J. Clark, G. I. Fray, R. H. Jager, and R. Robinson, *Tetrahedron*, 1959, **6**, 217.
[39] J. Wolinsky, T. Gibson, D. Chan, and H. Wolff, *Tetrahedron*, 1965, **21**, 1247.
[40] S. A. Achmad and G. W. K. Cavill, *Austral. J. Chem.*, 1965, **18**, 1989.

mixture after reduction of lactones (39) and (40) with Raney nickel as the catalyst.



Reagents: (i) CH_3·CHBr·CO_2Et–Zn (ii) $POCl_3$–C_6H_6 (iii) 50% KOH (iv) HCHO–AcOH–H_2SO_4 (v) H_2–Ni

Scheme 1

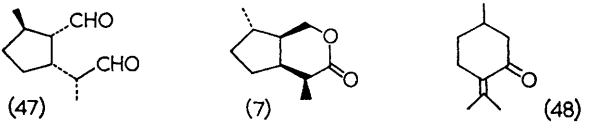


Reagents: (i) Ethylene glycol–toluene-*p*-sulphonic acid (ii) SeO_2 (iii) 50% AcOH (iv) 2N-KOH

Scheme 2

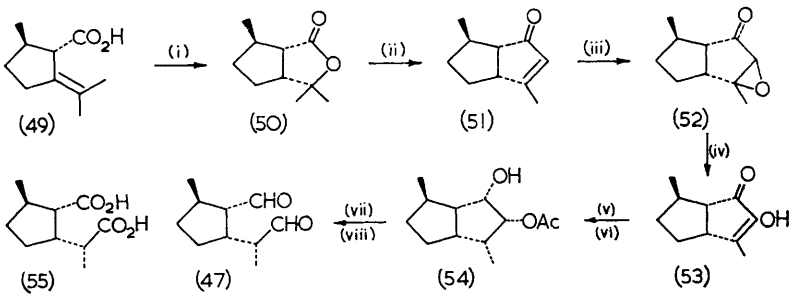
The route (Scheme 2) used by Robinson *et al.*[38] to synthesise iridodial realised in the laboratory their suggested biosynthetic scheme.[38] L-Citronellal (1) in the form of its ethylene acetal (42) was oxidised with selenium dioxide to give (43). Treatment of (43) with a 50% solution of acetic acid under nitrogen at reflux temperature yielded a mixture of L-iridodial (45) and the L-2,6-dimethyloct-2-en-1,8-dial (44). This aliphatic dialdehyde could be converted into L-iridodial (45) by refluxing with 10% hydrochloric acid in acetone. The synthetic iridodial (45), by the action of alkali, gave L-isoiridomyrmecin, (46) m.p. 57·5—58°, $[\alpha]_D^{28}$ −56°. Admixture with natural isoiridomyrmecin (8) did not depress the melting point, and the infrared spectrum of the synthetic material was identical with that of its natural enantiomer.

Iridodial obtained from *Iridomyrmex detectus* is considered to be a mixture of *cis/trans* and *trans/cis* isomers with the former predominating.[40] With this in mind, Achmad and Cavill have synthesised stereospecifically an enantiomer (47) of iridodial which they related to iridomyrmecin (7).[40,41]



(47) (7) (48)

D-(+)-Pulegone (48) was converted into the dibromide which when subjected to a Favorskii rearrangement with sodium ethoxide in ethanol yielded (+)-*trans*-pulegenic acid (49).[42] From this as the starting material, (47) was synthesised as shown in Scheme 3.



Reagents: (i) HCl–MeOH (ii) Polyphosphoric acid (iii) H_2O_2–OH^- (iv) H_2SO_4–AcOH (v) Ac_2O–pyridine (vi) H_2–PtO_2 (vii) 10% KOH (viii) $NaIO_4$

Scheme 3

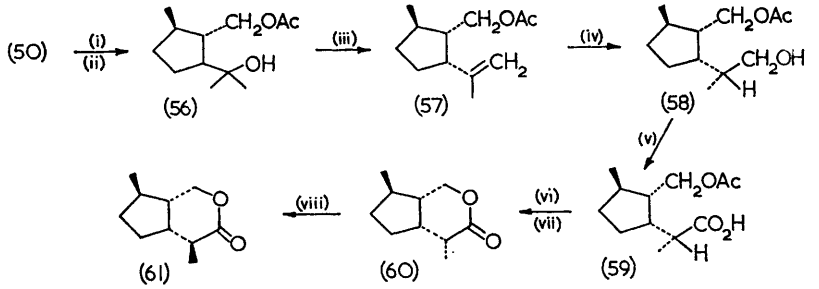
The stereospecificity of the synthesis was confirmed when the enantiomer (47) was oxidised with zinc permanganate to give the nepetalinic acid (55), shown to be enantiomeric with the acid derived from iridomyrmecin.[40]

Finally a report in which Wolinsky *et al.*[39] claim the successful syntheses of six enantiomers of the iridolactones. The most satisfactory of the syntheses is the one which yields the enantiomers of natural iridomyrmecin (7) and isoiridomyrmecin (8).

Starting with the same acid (49) which Cavill has used in his synthesis of iridodial and forming the same lactone (50), the Purdue group[39] reduced the lactone and acetylated the product to give 2-acetoxymethyl-3-(α-hydroxyisopropyl)-1-methylcyclopentane (56). Dehydration of this material yielded 78% of the desired unsaturated isomer (57) which on hydroboration with bis-2-butyl-3-methylborane gave the alcohol (58). The final two stages were effected by oxidation of the unprotected alcohol group to give (59) followed by hydrolysis,

[41] S. A. Achmad and G. W. K. Cavill, *Proc. Chem. Soc.*, 1963, 166.
[42] S. A. Achmad and G. W. K. Cavill, *Austral. J. Chem.*, 1963, **16**, 466.

then lactonisation of the hydroxy acid to give *cis/trans* iridomyrmecin (60) (Scheme 4).

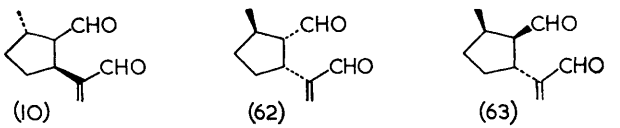


Reagents: (i) $LiAlH_4$ (ii) Ac_2O–pyridine (iii) Ac_2O–△H (iv) Bis-2-butyl-3-methylborane (v) CrO_3–H_2SO_4–H_2O (vi) aq. NaOH (vii) H_3O^+ (viii) NaOMe–MeOH

Scheme 4

On treatment with sodium methoxide, (−)-iridomyrmecin (60) yielded (+)-*cis/trans* isoiridomyrmecin (61). Both iridolactones are identical with their naturally occurring counterparts except in the sign of their optical rotations.

Synthesis of dolichodial. Degradative studies have shown dolichodial to possess the α-(2-formyl-3-methylcyclopentyl)acraldehyde structure (10).[30] This natural material on vapour-phase chromatography at a slow flow rate exhibits two peaks indicating the resolution of the 2-formyl epimers in the C(1)/C(4) *trans* system.[43] The synthesis of the two enantiomeric dolichodials (62) and (63) has been reported.[43]

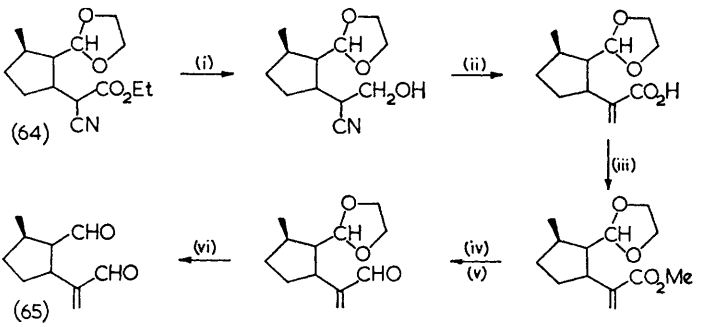


The key compound in the synthesis is ethyl 2-cyano-8,8-ethylenedioxy-methyloct-2-enoate (64).[44] This cyanoacetate acetal was converted in six stages into a mixture of the enantiomeric dolichodials (62) and (63) as briefly outlined in Scheme 5.

The key compound (64) was a mixture of C(1)/C(4)-*cis* and C(1)/C(4)-*trans*, so (65) is also a mixture. Preparative vapour-phase chromatography was used to separate the isomers. The minor isomer (40%) on re-chromatography at a slow flow rate yielded the *cis/trans* and the *trans/cis* isomers (62) and (63), these being enantiomeric with the natural material.

Dendrolasin and cantharidin. Apart from iridolactones, iridodial, and dolichodial, other insect terpenoids worthy of discussion are dendrolasin (13) and cantharidin

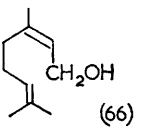
[43] G. W. K. Cavill and F. B. Whitfield, *Austral. J. Chem.*, 1964, **17**, 1260.
[44] G. W. K. Cavill and F. B. Whitfield, *Austral. J. Chem.*, 1964, **17**, 1245.



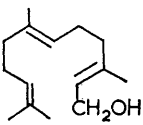
Reagents: (i) $NaBH_4^-$ (ii) aq. NaOH (iii) CH_2N_2 (iv) $LiAlH_4$ (v) MnO_2 (vi) $AcOH-H_2O$

Scheme 5

(11). An oil (60—70 ml.) containing 75% of dendrolasin was obtained from the petroleum extract of 8—10 kg. of the formicine ant *Dendrolasius fuliginosus*.[45,46] The pure compound is a neutral, colourless, optically inactive oil with a molecular formula of $C_{15}H_{22}O$ and b.p. 148—150°/16 mm. It was inactive towards carbonyl reagents and phenyl isocyanate indicating the absence of an aldehyde, ketone, or alcohol group. Colour reactions[46] pointed to the presence of a furan derivative, this being substantiated by the infrared spectrum which Pavan interpreted as that of a β-substituted furan. The ultraviolet spectrum showed a marked similarity to the spectra of the terpene alcohols geraniol (66) and farnesol (67).

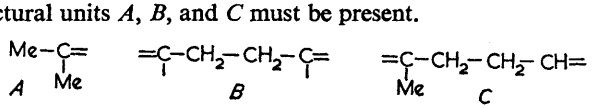


(66)



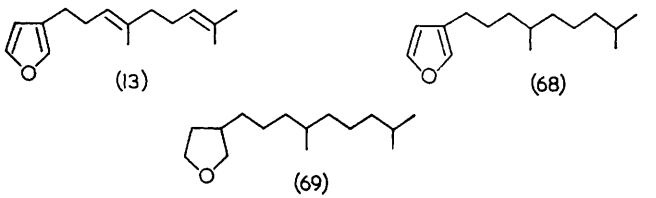
(67)

Depending on the conditions employed, dendrolasin on hydrogenation formed either a tetrahydro-derivative or an octahydro-derivative. Spectral data for the former indicated the presence of the furan system and an isopropyl group, the bands for which were absent from the spectrum of the parent compound. The infrared spectrum of the perhydro-derivative was consistent with a tetrahydrofuran structure. It appears therefore that dendrolasin is a furan with a β-substituted terpenoid side chain. Ozonolysis of dendrolasin in ethyl acetate yielded acetone, succinic acid, and lævulinaldehyde showing that the three structural units *A*, *B*, and *C* must be present.

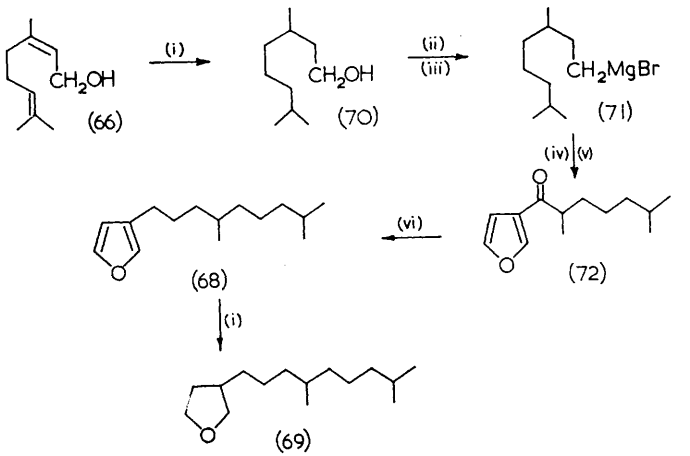


[45] Table 1, ref. *i*.
[46] Table 1, ref. *j*.

Considering the colour tests and the infrared spectra indicating a furan, the ultraviolet spectrum showing similarity to the terpenes (66) and (67), and the degradation evidence, one could represent dendrolasin by the β-(4,8-dimethylnona-3,7-dienyl)furan structure (13) which is derived from the head-to-tail linking of three isoprene units.[46] It follows that tetrahydrodendrolasin and the perhydro-compound would have structure (68) and (69) respectively.



That structure (13) was correct has been unambiguously proved by Quilico and his co-workers[47] who have synthesised, as outlined in Scheme 6, the tetra- and per-hydro-derivatives (68) and (69) and shown them to be identical with the compounds from natural sources.



Reagents: (i) H_2–Ni (ii) HBr (iii) Mg–Et_2O (iv) $CdCl_2$ (v) β-Furoylchloride (vi) N_2H_4–OH^-

Scheme 6

Tetrahydrogeraniol (70) is converted into the magnesium bromide (71) which on reaction with cadmium chloride gives the corresponding tetrahydrogeranylcadmium. Subsequent condensation with β-furoyl chloride to give the keto-furan (72), followed by a Wolff–Kishner reduction, gave synthetic tetrahydro-

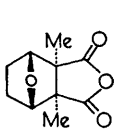
[47] A. Quilico, P. Grünanger, and F. Piozzi, *Tetrahedron*, 1957, **1**, 186.

dendrolasin (68). The easy conversion of the synthetic tetrahydro- to the perhydro-compound was achieved by hydrogenation over Raney nickel.

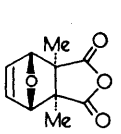
Dendrolasin has also recently been obtained from plant sources; Japanese workers having isolated it from sweet-potato fusel oil[48] and from the wood oil of *Torreya nucifera*;[49] in both these cases it co-occurs with other sesquiterpenes.

Cantharidin, $C_{10}H_{12}O_4$, m.p. 218°, is a colourless, crystalline, optically inactive compound which has been long known as a powerful skin irritant or blistering agent; in fact the members of the family of beetles (Meloidae) from which it is obtained are often called 'Blister Beetles'. Besides its vesicant properties, cantharidin may also cause gastroenteritis, renal damage, hæmaturia, and even death; as little as 10 mg. has been known to be fatal.

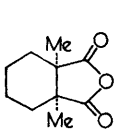
Since the isolation of cantharidin in 1810 by Robiquet[50] the substance has been widely investigated, no doubt owing to the notoriety it has received as an aphrodisiac commonly callled 'Spanish Fly'. Work by Gadamer[51] and Rudolph[52] led, in 1914, to the suggestion of structure (11). Pyrolyses carried out by von Bruchhausen and Bersch,[53] and yielding furan and dimethylmaleic anhydride, interpreted as a reverse Diels–Alder reaction, on the dehydro-compound (73) formed *in situ*, have helped substantiate structure (11). Proof that this structure was correct came with the synthesis of *cis*-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride (74)[54] which proved to be identical with deoxycantharidin.



(11)



(73)

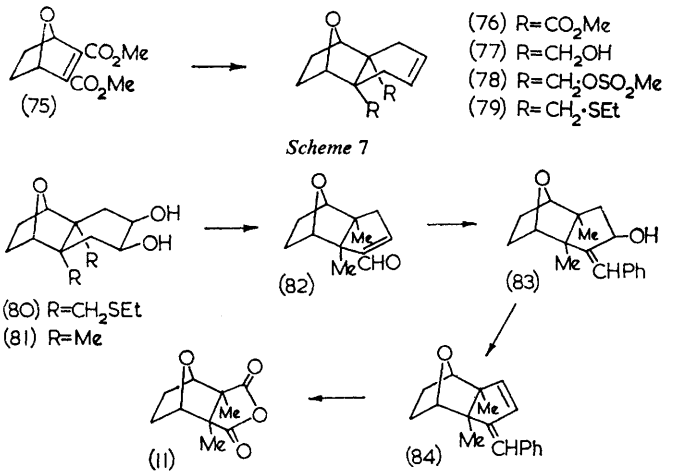


(74)

The Diels–Alder reaction involving furan and dimethylmalaic anhydride cannot be effected and so the obvious synthetic route must be by-passed. Cantharidin was first synthesised by Schenck and Ziegler[55,56] but their extremely low yields prompted Stork and his co-workers[57,58] to evolve a more rewarding synthesis (Scheme 7).

The condensation of 3,6-epoxy-3,4,5,6-tetrahydrophthalic acid dimethyl ester (75) with butadiene gave the adduct (76). Reduction of the ester groups with

[48] M. Ogawa and Y. Hirose, *Nippon Kagaku Zasshi*, 1962, **83**, 747.
[49] T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Japan*, 1965, **38**, 381.
[50] M. Robiquet, *Ann. chim.*, 1810, **76**, 302.
[51] J. Gadamer, *Arch. Pharm.*, 1914, **252**, 609.
[52] W. Rudolph, *Arch. Pharm.*, 1916, **254**, 423.
[53] F. von Bruchhausen and H. W. Bersch, *Arch. Pharm.*, 1928, **266**, 697.
[54] R. B. Woodward and R. D. Loftfield, *J. Amer. Chem. Soc.*, 1941, **63**, 3167.
[55] G. O. Schenck and K. Ziegler, 'Festschrift A. Stoll', Birkhauser, Basel, 1957, p. 620.
[56] K. Ziegler, G. O. Schenck, E. W. Krockow, A. Siebert, A. Wenz, and H. Weber, *Annalen*, 1942, **551**, 1.
[57] G. Stork, E. E. van Tamelen, L. J. Friedman, and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 4501.
[58] G. Stork, E. E. van Tamelen, L. J. Friedman, and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 1953, **75**, 384.



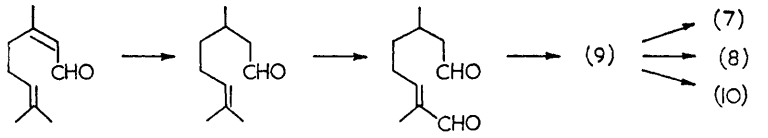
Scheme 7

lithium aluminium hydride yielded the diol (77). The dithioethyl derivative (79) was obtained from the diol *via* the intermediate di-mesylate (78) by the action of potassium–ethanethiol in t-butyl alcohol. Hydroxylation with osmium tetroxide followed by desulphurisation with Raney nickel in boiling ethanol gave the glycol (81). After periodic acid oxidation and cyclisation of the dialdehyde produced, the Harvard group obtained (82). Phenyl-lithium gave the alcohol (83) which was easily dehydrated to the diene (84). The final stage was accomplished by ozonolysis of the diene in ethyl acetate followed by oxidation of the ozonide with hydrogen peroxide to give cantharidin.

Biosynthesis of Arthropod Terpenes.—As yet, experimental verification of plausible biosynthetic schemes relating to the terpenoid defensive substances has not been forthcoming. Clark, Fray, Jager and Robinson's route[38] for the synthesis of the cyclopentanoid monoterpenes was that of the suggested biosynthetic pathway. This scheme envisaged citronellal (1) as being an earlier intermediate. Methylheptenone (5) can be obtained from citral by a reverse Aldol reaction,[13] and the other aliphatic ketones which co-occur with the cyclopentanoid terpenes in the *Iridomyrmex* and *Dolichoderus* species could also arise from citral by simple chemical transformations. Cavill *et al.*[5,19,59] prefer a scheme where citral (2) is enzymatically reduced to citronellal (1), terminal oxidation of which would yield 2,6-dimethyloct-2-ene-1,8-dial (75), which on cyclisation would yield iridodial (9). This compound occupies a key position in Cavill's scheme as easy transformations yield the iridolactones (7 and 8) and dolichodial (10).

Citral occurs in the mandibular gland of the ant *Atta sexdens rubropilosa*[60,61]

[59] G. W. K. Cavill and H. Hinterberger, Proc. 11th Internat. Congr. Entomol., Vienna, 1963, vol. 3, p. 53.
[60] Table 1, ref. *b*.
[61] Table 1, ref. *c*.



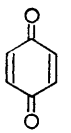
(2) (1) (75)

and both citral and citronellal have been isolated from *Acanthomyops claviger*.[62] Tracer studies[63] with the latter ant species have shown that both compounds of the secretion (1 and 2) incorporated [1-^{14}C]acetate [2-^{14}C]acetate, and [2-^{14}C]-mevalonate, suggesting that the normal pathway to terpene formation is being followed.[64] [1-^{14}C]mevalonate was not incorporated, the activity being lost by decarboxylation during the formation of Δ^3-isopentylpyrophosphate before terpene formation.

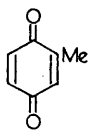
Tracer incorporation studies using the 'walking stick' insect *Anisomorpha buprestoides* have also been reported.[65] The results provide qualitative evidence that this insect synthesises the cyclopentanoid monoterpene anisomorphal (dolichodial) from normal terpene precursors, acetate, malonate, and mevalonic lactone.

Dendrolasin (13), a sesquiterpenoid derivative, is most probably derived from farnesol (67) or farnesal which has arisen biogenetically by the normal terpenoid pathway.[64]

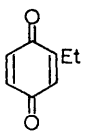
Quinones.—Benzoquinones have been the most widely found components of arthropod defensive substances, having been isolated from at least six orders belonging to the classes Arachnida, Diplopoda, and Insecta. So far, the benzoquinones which have been identified as defensive agents are (86—93).



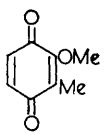
(86) Benzoquinone



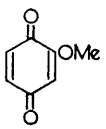
(87) Toluquinone



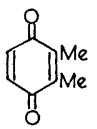
(88) 2-Ethylbenzoquinone



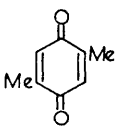
(89) 2-Methoxy-3-methylbenzoquinone



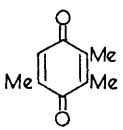
(90) 2-Methoxybenzoquinone



(91) 2,3-Dimethylbenzoquinone



(92) 2,5-Dimethylbenzoquinone



(93) 2,3,5-Trimethylbenzoquinone

[62] Table 1, ref. *a*.
[63] G. M. Happ and J. Meinwald, *J. Amer. Chem. Soc.*, 1965, **87**, 2059.
[64] J. B. Hendrickson, 'The Molecules of Nature', W. A. Benjamin Inc., New York, 1965, p. 33.
[65] J. Meinwald, G. M. Happ, J. N. Labows, and T. Eisner, *Science*, 1966, **151**, 79.

The occurrence of these compounds has been reported in the arthropods listed in Table 3.

Table 3

Arthropod	*Components of Secretion*								*Ref.*
	86	87	88	89	90	91	92	93	
Arachnida									
Heteropachyloidellus robustus						×	×	×	*a, b*
Diplopoda									
Archiulus sabulosus		×		×					*c*
Chicobolus spinigerus		×		×					*d*
*Floridobolus penneri**		×		×					*d*
Julus terrestris	×								*e*
*Narceus annularis**		×		×					*d*
Narceus gordanus		×		×					*d*
Pachybolus laminatus		×							*f*
Spirostreptus castaneus	×								*f*
*Spirostreptus virgator**		×							*f*
Trigoniulus lumbricinus		×		×					*d, f*
Brachyiulus unilineatus		×		×					*g*
Cylindroiulus teutonicus		×		×					*g*
*Rhinocricus insulatus**		×							*h*
Cambala hubrichti		×		×					*i*
Orthoporus flavior		×		×					*i*
Orthoporus punctilliger		×		×					*i*
Orthoporus conifer		×		×					*i*
Doratogonus annulipes		×		×					*i*
Unidentified diplopods		×		×					*j*
Insecta									
*Diploptera punctata**	×	×	×						*k*
Forficula auricularia		×	×						*l*
Brachinus crepitans	×	×							*m*
Brachinus explodens	×	×							*n*
Brachinus sclopeta	×	×							*n*
Pheropsophus catoirei†	×	×							*n*
Blaps lethifera	×	×	×						*o*
Blaps mortisaga		×	×						*o*
Blaps mucronata		×	×						*o*
Blaps requienii		×	×						*o*
Diaperis maculata		×	×						*k*
Diaperis boleti		×	×						*j*
Helops quisquilius		×	×						*j*
Helops aenus		×	×						*j*
Opatrum sabulosum		×	×						*j*
Opatrum punctulatus		×	×						*j*

Table 3—*continued*

Arthropod	*Components of Secretion*								*Ref.*
	86	87	88	89	90	91	92	93	
*Eleodes longicollis**	×	×	×						*p*
*Eleodes hispilabris**	×	×	×						*q*
Gnaptor spinimanus†		×	×						*o*
Morica planta tingitana†		×							*o*
Pimelia confusa†		×							*o*
Tenebrio molitar		×							*j, r*
Tenebrio obscurus†	×								*o*
Tribolium castaneum		×	×		×				*k, s, t*
Tribolium confusum		×	×						*s, u, v*

* Contains other components

† Museum specimens

[a] C. Estable, M. I. Ardao, N. P. Brasil, and L. F. Fieser, *J. Amer. Chem. Soc.*, 1955, **77**, 4942; [b] L. F. Fieser and M. I. Ardao, *J. Amer. Chem. Soc.*, 1956, **78**, 774; [c] R. Trave, L. Garanti, and M. Pavan, *Chim. e Ind.*, 1959, **41**, 19; [d] A. Monro, M. S. Chadha, J. Meinwald, and T. Eisner, *Ann. Entomol. Soc. Amer.*, 1962, **55**, 261; [e] A. Behal and M. Phisalix, *Bull. Museum Natl. Hist. nat. (Paris)*, 1900, **6**, 338; [f] M. Barbier and E. Lederer, *Biokhimiya*, 1957, **22**, 236; [g] H. Schildknecht and K. H. Weiss, *Z. Naturforsch.*, 1961, **16b**, 810; [h] J. W. Wheeler, J. J. Hurst, J. Meinwald, and T. Eisner, *Science*, 1964, **144**, 540; [i] T. Eisner, J. J. Hurst, W. T. Keeton, and Y. Meinwald, *Ann. Entomol. Soc. Amer.*, 1965, **58**, 247; [j] H. Schildknecht, *Angew. Chem.*, 1964, **3**, 73; [k] L. M. Roth and B. Stay, *J. Insect Physiol.*, 1958, **1**, 305; [l] H. Schildknecht and K. H. Weiss, *Z. Naturforsch.*, 1960, **15b**, 755; [m] H. Schildknecht, *Angew. Chem.*, 1957, **69**, 62; [n] H. Schildknecht and K. Holoubeck, *Angew. Chem.*, 1961, **73**, 1; [o] H. Schildknecht and K. H. Weiss, *Z. Naturforsch.*, 1960, **15b**, 757; [p] M. S. Chadha, T. Eisner, and J. Meinwald, *J. Insect Physiol.*, 1961, **7**, 46; [q] M. S. Blum and R. D. Crain, *Ann. Entomol. Soc. Amer.*, 1961, **54**, 474; [r] H. Schildknecht, *Angew. Chem.*, 1959, **71**, 524; [s] P. Alexander and D. H. R. Barton, *Biochem. J.*, 1943, **37**, 463; [t] J. D. Loconti and L. M. Roth, *Ann. Entomol. Soc. Amer.*, 1953, **46**, 281; [u] R. H. Hackman, M. G. M. Pryer, and A. R. Todd, *Biochem. J.*, 1948, **43**, 474; [v] M. Engelhardt, H. Rapoport, and A. Sokoloff, *Science*, 1965, **150**, 632.

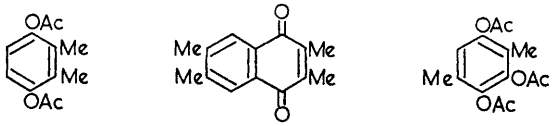
Besides being the most widely found arthropod defensive agents, quinones must rank amongst the most effective, owing in part to their high volatility. The Reviewer has experienced severe headaches after handling *Eleodes longicollis* in a badly ventilated hood. In several of the animals the quinones are part of a mixture which also contains long-chain hydrocarbons or a long-chain aliphatic aldehyde. The quinones are dissolved in these secondary compounds whose rôle is thought to be one of increasing the effectiveness of the quinonoid secretion by rendering cuticle permeable to it.[66]

In 1943 Alexander and Barton[67] reported the isolation of ethylquinone from the secretion of two species of flour beetle. The quinone imparted to the flour a pink colour, and such flour was unpalatable. These authors, although not certain of the function of the quinone, thought it to be a spermicide since they had observed remarkable population control on culturing these insects. A

[66] Table 3, ref. *q*.
[67] Table 3, ref. *s*.

previous report[68] had shown that this secretion from *Tribolium* is capable of producing abnormalities often found in *Tribolium* cultures.

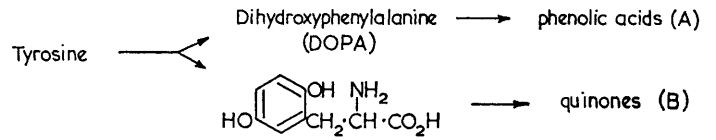
It will be noticed from Table 3 that all the arthropods listed, with one exception, give various mixtures involving benzoquinone (86), toluquinone (87), ethylbenzoquinone (88), and 2-methoxy-3-methylbenzoquinone (89). The exception, an arachnid, secretes a mixture of 2,3- and 2,5-dimethylbenzoquinones and 2,3,5-trimethylbenzoquinone, which is known as gonyleptidine. This volatile antibiotic substance was isolated from the cepthalothoracic glands of a South American arachnid of the *Gonyleptidae* family.[69,70] Gonyleptidine was found effective against 18 genera of bacteria and protozoa; it is a low-melting (12°) yellow compound which gave colour reactions characteristic of quinones. The extract on reaction with 2,3-dimethylbutadiene yielded an adduct which on oxidation gave the tetramethylnaphthaquinone (95). The presence of 2,3-dimethylbenzoquinone (91) was further demonstrated by dithionite reduction of the antibiotic mixture followed by acetylation to yield 2,3-dimethylquinol diacetate (94).



(94) (95) (96)

The unchanged quinones which remained after the isolation of the naphthaquinone (95) were reoxidised and subjected to a Thiele acetoxylation to yield a steam-volatile and a non-steam-volatile fraction; the former was shown to be 2,3,5-trimethylbenzoquinone (93) while the latter was 1,3,4-triacetoxy-2,5-dimethylbenzene (96) derived from 2,5-dimethylbenzoquinone (92). The proportions of the constituent quinones in gonyleptidine have been shown to be: 2,3-dimethylbenzoquinone, 71 parts; 2,5-dimethylbenzoquinone, 11 parts; and 2,3,5-trimethylbenzoquinone, 15 parts.

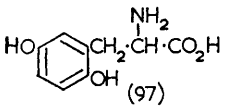
Most interest in the arthropod quinones is centred on their modes of biosynthesis. Hackman and his co-workers,[71] investigating the occurrence of phenolic acids in various species of insects, acids which they believed to be used

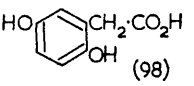


Scheme 8

[68] L. M. Roth and R. B. Howland, *Ann. Entomol. Soc. Amer.*, 1941, **34**, 151.
[69] Table 3, ref. *a*.
[70] L. F. Fieser and M. I. Ardao, *J. Amer. Chem. Soc.*, 1956, **78**, 774.
[71] Table 3, ref. *u*.

in the tanning processes by which insect cuticle is hardened, also noted that *Tribolium* species possessed methyl- and ethyl-benzoquinones. These authors believed the phenolic acids and the quinones to come from a common precursor, namely tyrosine, as indicated in Scheme 8. Route (*B*) is analogous to the route whereby toluquinone is prepared from *p*-cresol by oxidation with potassium persulphate.[72] Although 2,5-dihydroxyphenylalanine (97) is unknown in Nature, it is reasonable to think of it as an oxidation product of tyrosine on the route to quinones since it is thought to be an intermediate in the production of homogentisic acid (98) in human alcoptonurea.


(97)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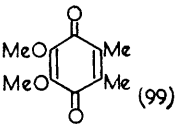
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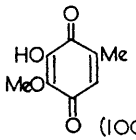
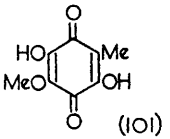
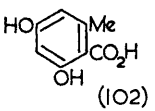

(100)


(101)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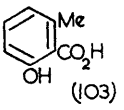

(103)

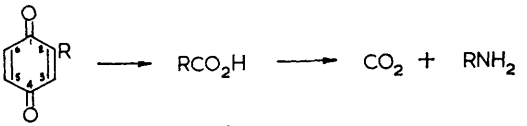
The biosynthesis of the simple quinones, which occur as metabolites in fungi, has been widely studied,[73–77] and it has been shown that aurantioglíocladin (99), fumigatin (100), and spinulosin (101) are derived from acetate and malonate which first combine to give an orsellinic acid (102) or 6-methylsalicylic acid (103) type of intermediate which is then modified to the quinone. The methyl groups of phenolic ethers are derived from methionine.[74,75]

The related case of the ubiquinones has lately also been a field of much activity.[78] The quinone ring of the ubiquinone is not derived from acetate irrespective of whether the substrate is rat kidney, baker's yeast, or the bacterium *Azobacter vinelandii*.[79] In these cases the quinonoid moiety is derived from a pre-formed aromatic ring of the *p*-hydroxybenzoic acid type which in the case of the rat seems to have tyrosine or phenylalanine as precursors but which in the case of the bacteria could arise *via* the shikimic acid pathway. Ubiquinone produced by the ciliated protozoon *Tetrahymena pyriformis* has been shown to arise from glucose *via* shikimic acid and *p*-hydroxybenzoic acid.[80]

Work on the biosynthesis of the arthropod quinones is still in its infancy although results of a study involving the tenebrionid beetle *Eleodes longicollis*

[72] T. Kumagai, *Ber.*, 1908, **41**, 297.
[73] A. J. Birch, R. I. Fryer, and H. Smith, *Proc. Chem. Soc.*, 1958, 343.
[74] G. Pettersson, *Acta Chem. Scand.*, 1963, **17**, 1323.
[75] G. Pettersson, *Acta Chem. Scand.*, 1964, **18**, 335, 1202.
[76] G. Pettersson, *Acta Chem. Scand.*, 1965, **19**, 1016, 1827.
[77] N. M. Packter, *Biochem. J.*, 1965, **97**, 321.
[78] W. W. Parson and H. Rudney, *J. Biol. Chem.*, 1965, **240**, 1855 and refs. therein.
[79] W. W. Parson and H. Rudney, *Proc. Nat. Acad. Sci.*, 1964, **51**, 444.
[80] J. E. Miller, *Biochem. Biophys. Res. Comm.*, 1965, **19**, 335.

have been reported.[81] The secretion of this insect contains benzoquinone (86), toluquinone (87), and ethylbenzoquinone (88), which have been shown to arise *via* two independent pathways. From exploratory studies it is apparent that while the main pathway to benzoquinone (86) involves the utilisation of a preformed aromatic ring from tyrosine or phenylalanine, the alkylated quinones (87) and (88) arise from other precursors. High incorporation in (87) and (88) was obtained when radioactive acetate, propionate, and malonate were used as substrates. These results are indicative of the building of the quinonoid rings in these compounds from the condensation of malonate units with an acyl coenzyme A.[82] Further experiments have been reported[81] which have defined



Scheme 9

the incorporation patterns when sodium [1-^{14}C]acetate and sodium[1-^{14}C]propionate were injected into the insects. By use of Scheme 9, the quinones (87) and (88) were separately oxidised with potassium permanganate to give their respective aliphatic acids which were then subjected to the Schmidt reaction. With (87), 30% of the activity, using acetate as substrate appears at C(2). Less than 0·1% occurs in the methyl group, hence the remaining 70% must be distributed among the other five ring carbon atoms. The significant result from the sodium [1-^{14}C]propionate experiment is that 95% of the activity of 2-ethylbenzoquinone is localised at C(2) in the ring. The latter findings thus substantiate the conclusions drawn from the exploratory incorporation studies. Indications are strong that in the case of the alkylbenzoquinones the aromatic ring formed from the condensation of the acyl coenzyme A and the malonate units is modified to a quinol, the oxidation to the quinone being the last step in the synthesis. Quinols have been identified in three of the quinone-secreting insects.[83] In the secretion of *Eleodes longicollis*, Hurst *et al.*[84] identified glucose; it is probable that this compound came from the cleavage of quinol glucosides which it is reasonable to assume are intermediates in the latter stages of the quinone biosynthesis. The significance to the beetle of maintaining two separate biosynthetic pathways is not known but it is hoped that continuing studies with other arthropods may clarify this problem.

Miscellaneous.—Terpenoid and quinonoid arthropod defensive agents were well defined, but in the third class the remaining types of compounds are presented in Table 4.

The highly toxic substance hydrogen cyanide is a component of one of the

[81] J. Meinwald, K. F. Koch, J. E. Rogers, and T. Eisner *J. Amer. Chem. Soc.*, 1966, **88**, 1590.
[82] A. J. Birch, C.I.B.A. Foundation Symposium Quinones in Electron Transport, Little, Brown and Co. Boston, 1962, p. 233.
[83] H. Schildknecht and H. Krämer, *Z. Naturforsch*, 1962, **17b**, 701.
[84] J. J. Hurst, J. Meinwald, and T. Eisner, *Ann. Entomol. Soc. Amer.*, 1964, **57**, 44.

Table 4 *Chemicals found in the defensive secretions of arthropods*

Compound	*Arthropod from which the substance has been isolated**
Aliphatic acids	
A Formic acid	1, 2, 3, 4
B Acetic acid	52
C Caprylic acid	5, 52
D Methacrylic acid	6
E Tiglic acid	6
F Isobutyric acid	7
G α-Methylbutyric acid	7
Aliphatic aldehydes	
H n-Hexanal	8—16
I *trans*-2-Hexenal	17—28
J *trans*-4-Oxohex-2-enal	21, 29
K *trans*-2-Heptenal	21, 28
L *trans*-2-Octenal	22, 23, 27, 28
M *trans*-2-Decenal	21, 27
N *trans*-2-Dodecenal	43
Aromatic compounds	
O *m*-Cresol	32
P *p*-Cresol	44
Q Benzoic acid	38, 39
R Benzaldehyde	45—50
S Cuminaldehyde	51
T Salicylaldehyde	33—37
U *p*-Hydroxybenzaldehyde	38—41
V *p*-Hydroxybenzoic acid methyl ester	38—40
Other compounds	
W Hydrogen cyanide	45—51
X Pederin	42
Y n-Tridecane	5, 21

* Numbers refer to the arthropods listed in Table 5.

most interesting defensive secretions so far elucidated. In 1963 Eisner and his co-workers[85] reported that five species of millipedes discharged hydrogen cyanide when disturbed. In one of the species, *Apheloria corrugata*, benzaldehyde was also identified in the secretion. It was obvious that both compounds might arise from a hydrolytic breakdown of the cyanohydrin, mandelonitrile (104). Since the isolation of the glucoside of cuminaldehyde cyanohydrin (105) from the millipede *Polydesmus* (*Fontaria*) *vicinus* L., had been previously reported[86] the Cornell group searched for free sugars in the secretions, but with no success.

[85] Table 5, ref. *ii*.
[86] Table 5, ref. *kk*.

Table 5 *Arthropods whose defensive secretions have components classified as miscellaneous*

Arthropods	*Compounds*	*Ref.*
Insecta		
1. Many species of ants	A	*a, b, c, d*
2. *Pseudophonus pubescens*	A	*e, f*
3. *Pseudophonus griseus*	A	*e, f*
4. Carabid beetles of the genera *Acinopus* and *Calathus*	A	*e, f*
5. *Eleodes longicollis*	C, Y	*g, h*
6. Carabid beetles of the sub-family Carabinae	D, E	*e*
7. Larva of *Papillo machaon*	F, G	*i*
8. *Mictus profana*	H	*j*
9. *Mictus caja*	H	*j*
10. *Amorbus rubiginosus*	H	*k*
11. *Amorbus rhombifer*	H	*k*
12. *Amorbus alternatus*	H	*k*
13. *Aulacosternum nigrorubrum*	H	*k*
14. *Pachycolpura manca*	H	*k*
15. *Agriopocoris froggatti*	H	*k*
16. *Hyocephalus species*	H	*k*
17. *Cutilia soror*	I	*l*
18. *Eurycotes floridana*	I	*m*
19. *Platyzosteria novae seelandiae*	I	*n*
20. *Brochymena quadripustulata*	I	*o*
21. *Nezara viridula*	I, J, K, M, Y	*j, p, q*
22. *Poecilometis strigatus*	I, L	*j*
23. *Rhoecocoris sulciventris*	I, L	*j*
24. *Crematogaster africana*	I	*r*
25. *Pelmatosilpha coriacea*	I	*s*
26. *Acanthocephala femorata*	I	*t*
27. *Dolychoris baccarum*	I, L, M	*u*
28. *Scaptocoris divergens*	I, K, L	*v*
29. *Sigara falleni*	J	*w, x*
30. *Cerura vinula*	A	*y*
31. *Schizura leptinoides*	A	*z*
32. *Chlaenius cordicollis*	O	*aa*
33. *Calosoma prominens*	T	*bb*
34. *Phyllodecta vitellinae*	T	*cc*
35. *Aromia moschata*	T	*dd*
36. *Melasoma populi*	T	*dd*
37. *Plagiodera species*	T	*dd*
38. *Dytiscus marginalis*	Q, U, V	*e*
39. *Dytiscus lattissimus*	Q, U, V	*e*
40. *Cybister laterimarginalis*	U, V	*e*

Table 5—*continued*

Arthropods	*Compounds*	*Ref.*
Insecta		
41. *Hydroporus palustis*	U	*e*
42. *Paederus fuscipes*	X	*ee, ff, gg*
Diplopoda		
43. *Rhinocricus insulatus*	N	*hh*
44. *Abacion magnum*	P	*aa*
45. *Apheloria corrugata*	R, W	*ii*
46. *Cherokia georgiana*	R, W	*ii*
47. *Nannaria species*	R, W	*ii*
48. *Oxidus gracilis*	R, W	*ii*
49. *Pseudopolydesmus serratus*	R, W	*ii*
50. *Polydesmus collaris*	R, W	*jj*
51. *Polydesmus vicinus*	S, W	*kk*
Arachnida		
52. *Mastigoproctus giganteus*	B, C	*ll*

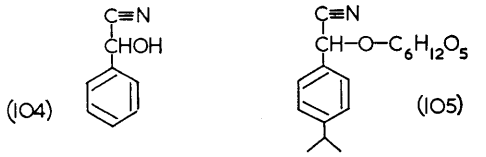
[a] R. Stumper, *Compt. rend.*, 1952, **234,** 149; [b] R. Stumper, *Compt. rend.*, 1951, **233,** 1144; [c] R. Stumper, *Compt. rend.*, 1959, **249,** 1154; [d] M. F. H. Osman and J. Brander, *Z. Naturforsch.*, 1961, **16b,** 749; [e] H. Schildknecht, *Angew. Chem.*, 1964, **3,** 73; [f] H. Schildknecht and K. Weiss, *Z. Naturforsch.*, 1961, **16b,** 361; [g] Y. C. Meinwald and T. Eisner, *Ann. Entomol. Soc. Amer.*, 1964, **57,** 513; [h] J. J. Hurst, J. Meinwald, and T. Eisner, *Ann. Entomol. Soc. Amer.*, 1964, **57,** 44; [i] T. Eisner and Y. C. Meinwald, *Science*, 1965, **150,** 1733; [j] D. F. Waterhouse, D. A. Forss, and R. A. Hackman, *J. Insect. Physiol.*, 1961, **6,** 113; [k] D. F. Waterhouse and A. R. Gilby, *J. Insect Physiol.*, 1964, **10,** 977; [l] M. S. Chadha, T. Eisner, and J. Meinwald, *Ann. Entomol. Soc. Amer.*, 1961, **54,** 642; [m] L. M. Roth, W. D. Niegisch, and W. H. Stahl, *Science*, 1956, **123,** 60; [n] L. M. Roth and E. R. Willis, *Smithsonian Inst. Misc. Collections*, 1960, **141,** 1; [o] M. S. Blum, *Ann. Entomol. Soc. Amer.*, 1961, **54,** 410; [p] A. R. Gilby and D. F. Waterhouse, *Austral. J. Chem.*, 1964, **17,** 311; [q] A. R. Gilby and D. F. Waterhouse, *Proc. Roy. Soc.*, 1965, *B*, **162,** 105; [r] C. W. L. Bevan, A. R. Birch and H. Caswell, *J. Chem. Soc.*, 1961, 488; [s] M. S. Blum, *Ann. Entomol. Soc. Amer.*, 1964, **57,** 600; [t] M. S. Blum, R. D. Crain, and J. B. Chidester, *Nature*, 1961, **189,** 245; [u] H. Schildknecht, K. H. Weiss, and H. Vetter, *Z. Naturforsch.*, 1962, **17b,** 350; [v] L. M. Roth, *Ann. Entomol. Soc. Amer.*, 1961, **54,** 900; [w] A. R. Pinder and B. W. Staddon, *Nature*, 1965, **205,** 106; [x] A. R. Pinder and B. W. Staddon, *J. Chem. Soc.*, 1965, 2955; [y] F. B. Poulton, *British Assoc. Adv. Sci.*, 57th meeting, Manchester, 1888, 765; [z] A. Monro, J. Meinwald, and T. Eisner, unpublished observations; [aa] T. Eisner, J. J. Hurst, and J. Meinwald, *Psyche*, 1963, **70,** 94; [bb] T. Eisner, C. Swithenbank, and J. Meinwald, *Ann. Entomol. Soc. Amer.*, 1963, **56,** 37; [cc] R. L. Wain, *Ann. Report Agric. Hort. Research Sta., Long Ashton, Bristol*, 1943, 108; [dd] M. A-Ch. Hollande, *Ann. Univ. Grenoble, Sect. Sci-Med.*, 1909, **21,** 459; [ee] M. Pavan and G. Bo, *Mem. Soc. Entom. It.*, 1952, **31,** 67; [ff] M. Pavan and G. Bo, *Phys. Comp. et Oecol.*, 1953, **3,** 307; [gg] C. Cardani, D. Ghiringhelli, R. Monelli, and A. Quilico, *Tetrahedron Letters*, 1965, **29,** 2537; [hh] J. W. Wheeler, J. Meinwald, J. J. Hurst, and T. Eisner, *Science*, 1964, **144,** 540; [ii] H. E. Eisner, T. Eisner, and J. J. Hurst, *Chem. and Ind.*, 1963, 124; [jj] G. Casnati, G. Nencini, A. Quilico, M. Pavan, A. Ricca, and T. Salvatori, *Experientia*, 1963, **19,** 409; [kk] E. S. Pallares, *Arch. Biochem.*, 1946, **9,** 105.

Continuing this work[87,88] they showed that the species *Apheloria corrugata* produced hydrogen cyanide from mandelonitrile by an elegant mechanism.

Apheloria (see Figure 2) has a pair of glands, in each of its body segments, for the specific purpose of storing and using its defensive substances. Control of the

[87] T. Eisner, H. E. Eisner, J. J. Hurst, F. C. Kafatos, and J. Meinwald, *Science*, 1963, **139,** 1218.

[88] T. Eisner and H. E. Eisner, *Natural History*, 1964, **74,** 30.



operation of these glands is highly developed, so that a localised stimulus to the animal elicits a response only from the segments closest to the area stimulated.

Apheloria

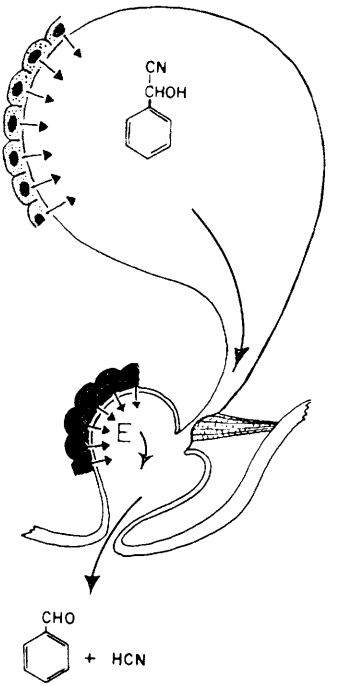


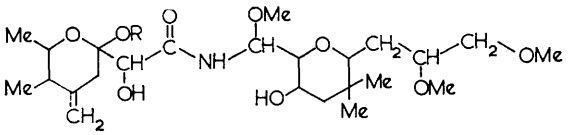
Figure 2

When such a stimulus is applied to the millipede, it is thought that the reservoir is compressed, the valve connecting the two chambers is opened and the mandelonitrile passes through the outer chamber containing emulsin-like enzymes which cause cyanogenesis to begin, giving the very effective defensive agent hydrogen cyanide.

In 1952 Pavan and Bo[89] reported the isolation of a toxic principle from the

[89] Table 5, ref. *ee*.

insect *Paederus fuscipes*; to this compound they give the name pederin. Recently a preliminary report[7] has been published giving the barest details of the structural elucidation of pederin and a second related component of the toxin, pseudopederin. The structures put forward for these compounds are (106) and (107) respectively.



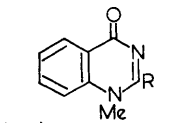
(106) R=Me
(107) R=H

This Review has dealt with only a minute section of the field of insect chemistry. There is still much work to be done and so by way of encouragement to prospective workers, the following quotation from Proverbs chapter 6, seems especially applicable,

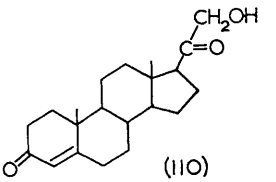
'Go to the ant thou sluggard
Consider her ways and be wise. . . .'

Note added in proof:

Since this Review was written several papers have been published pertaining to arthropod defensive substances and mention should be made to the isolation and characterisation of substances until now never before found in defensive secretions. Work by Schildknecht *et al.*[90] and Meinwald, Meinwald, and Eisner[91] has shown that the secretion of the millepede *Glomeris marginata* contains two 1,2-dialkyl-4(3)-quinazolinones, namely (108) and (109). The vertibrate hormone cortexone (110) has been isolated from glands in the head of the water beetle *Dytiscus marginalis*.[92]



(108) R=Me
(109) R=Et



(110)

I acknowledge receipt of a stipend from the U.S. Public Health Service, also the helpful discussions of Professors J. Meinwald and T. Eisner.

[90] H. Schildknecht, W. F. Wenneis, K. H. Weiss, and U. Maschwitz, *Z. Naturforsch* 1966, **21b**, 121.
[91] Y. C. Meinwald, J. Meinwald, and T. Eisner, *Science*, 1966, **154**, 390.
[92] H. Schildknecht, R. Siewerdt, and U. Maschwitz, *Angew. Chem. Internat. Edn.*, 1966, **5**, 421.