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CHEMISTRY OF SOME INSECT SECRETIONS

G.W.K. CAVILL

The Royal Society of New South Wales

George William Kenneth Cavill

GEORGE WILLIAM KENNETH CAVILL 1922-

George William Kenneth (Ken) **Cavill** was born on 23 April 1922 in Sydney. His secondary education was at Fort Street Boys' High School (1934-1938), and then with a Public Exhibition (1939-1942) and a Timbrol Scholarship for his Honours year, he graduated from the University of Sydney B.Sc. (1st. Class Hons.) in 1943. He was empolyed as Senior Chemist at W. Hermon Slade and Co. Pty Ltd, Rosebery, N.S.W. in 1943, and in the following year was appointed as Lecturer in Chemistry at Sydney Technical College, while working for his M.Sc. degree from the University of Sydney (conferred in 1946). In 1947, given three years leave from Sydney Technical College, and with the award of an ICI Research Fellowship, he proceeded to the University of Liverpool to work under Professor Alexander Robertson, FRS on the chemistry of the fungal metabolite, citromycetin. He graduated Ph.D. in 1949 and during 1950 continued working at the University of Liverpool on the chemistry of fungi. In the meantime the N.S.W. University of Technology, founded in 1949, had assumed responsibility for diploma courses of the Sydney Technical College and provided for their conversion to degree status. Late in 1950 Ken Cavill returned to the NSW University of Technology, and in the following year was promoted to Senior Lecturer in the School of Chemistry. In 1959 he was promoted to Associate Professor in the University of New South Wales (formerly the NSW University of Technology, 1949-1958). In 1964 he was awarded a Personal Chair, the first such appointment at the University of New South Wales, and for the period 1980-1982 he was Professor of Organic Chemistry. He was Head of the School of Chemistry in 1971, and Head Department of Organic Chemistry for the periods 1968-1970 and 1978-1982. Since his retirement at the end of 1982, he has been Emeritus Professor.

During periods of study leave he was Research Fellow at Harvard University Cambridge, USA (1958); Honorary Research Fellow at University College London (1963, 1970 and 1977); and Visiting Professor at Cornell University, Ithaca, USA in 1977. He was an invited lecturer at many national and international meetings, including the IUPAC Symposia on the Chemistry of Natural Products held since 1960.

Ken Cavill acted as a Member of Council for the University of New South Wales (1979-1981), for the Australian Academy of Science (1972-1975), and for Hawkesbury Agricultural College (1975-1981). He was a Member of the Australian Research Grants Committee for the period 1969-1974, and in 1975 he was President of the Chemistry Section of the Australian New Zealand Association for the Advancement of Science (ANZAAS).

Since retirement he has researched and documented the histories of notable silverware and jewellery manufacturers, especially those of the early 20th century; he has some 18 publications in this area.

Honours and Awards (Pre-2001)

1956 FRACI (Fellow of the Royal Australian Chemical Institute)

1957 D.Sc., University of Liverpool

1969 FAA

1970 Liversidge Research Lecture, Royal Society of New South Wales

Biographical Source

Personal communication

Scientific Publications by G.W.K. Cavill

Between 1945 and 1984 G.W.K. Cavill published 85 papers; most of these were on insect chemistry.

CHEMISTRY OF SOME INSECT SECRETIONS*

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Kensington, N.S.W., 2033

Introduction

A number of the secretions used by insects and other arthropods for defensive purposes, as venoms, and as chemical messengers in their patterns of social organization have been characterized.[1-3] These secretions are produced by exocrine, that is ducted glands, which commonly open to the exterior, and vary in number, complexity and location. For example, Figure 1 illustrates the exocrine gland system of the primitive Australian ant, *Myrmecia gulosa*.[4]

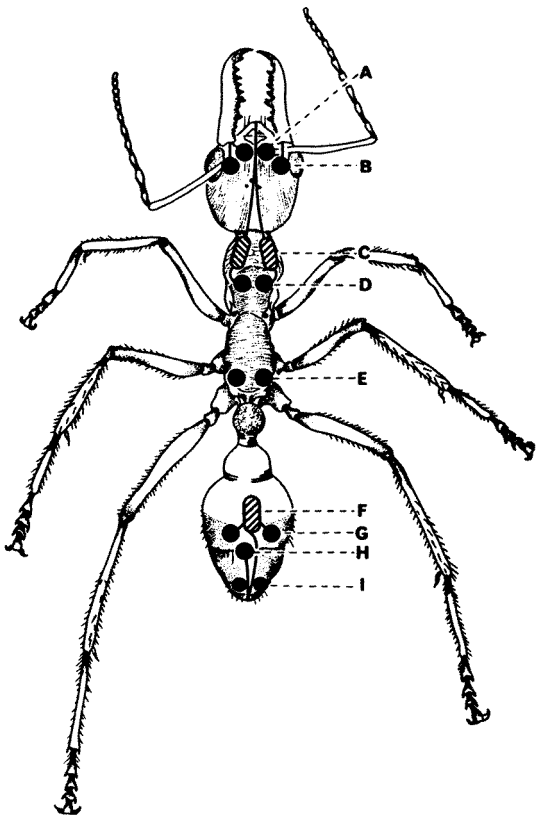

FIGURE 1. Exocrine gland system of the bull ant, *Myrmecia gulosa*. (A) Pharyngeal glands; (B) mandibular glands; (C) salivary reservoirs; (D) salivary glands; (E) metasternal glands; (F) venom reservoir; (G) venom glands; (H) accessory gland; (I) dorsal abdominal glands (Cavill and Robertson[4]).

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Generally, defensive secretions are used by insects to prevent or discourage their enemies from interfering in their life patterns.[1] The venoms, communicated by biting or stinging, are used to kill or incapacitate the prey forming food for the insect or its young.[2] The exocrine secretions used as chemical messengers are termed pheromones.[3] They convey signals between individuals of the same or closely related species concerning, for example, food sources, mating or the presence of enemies. The broad categories - defensive secretions, venoms, pheromones - are not mutually exclusive, and a given secretion may have more than one function. The pheromones, as products of ducted exocrine glands, can be distinguished from hormones, which are products of ductless endocrine glands.

The chemistry of insect secretions has been studied, in detail, essentially in the last two decades. Whilst the work of pioneers such as Butenandt and his colleagues precedes this period, their structural studies on the sex pheromone, and the moulting hormone of *Bombyx mori* were not brought to fruition until the 1960s.[5] The earliest report of a chemical investigation on an insect secretion would appear to be one by the English botanist John Wray, who noted[6] in 1670 that Samuel Fisher had obtained an acid, formic, by dry distillation of wood ants. The chemical characterization of formic acid was undertaken by Berzelius[7] and Liebig[8] early in the nineteenth century. A number of biological observations on odoriferous insect secretions - some fragrant and others repugnant - have since been noted,[9] but these observations do not appear to have been followed up to any great extent by the chemist interested in natural products. Whilst the structure of cantharidin was investigated at the beginning of the twentieth century, this work does not appear to have been directed *per se* to an understanding of insect secretions.[10]

In the present lecture emphasis is placed on aspects of the chemistry of insect secretions that have interested us since 1952.*

Defensive Secretions, Venoms and Pheromones

In 1949, in the course of a search for antibiotics of animal origin, the Italian entomologist Pavan isolated iridomyrmecin (3) from anal glands of the Argentine ant, *Iridomyrmex humilis*.[11] In 1952 he reported to the Ninth International Congress of Entomology that iridomyrmecin was insecticidal.[12] This observation has prompted much of the interest since shown in defensive secretions.

A defensive secretion, often present in a relatively large amount, may be isolated as a major component by total extraction of the insects. The source of the material has then to be determined, odour and abundance enabling the rapid location of its glandular origin. Total extraction of the common Australian "meat" ant, *Iridomyrmex detectus*, with light petroleum gave 2-methylhept-2-en-6-one (1) and iridodial (2),[13,14] the then

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* Studies on insect chemistry in the University of New South Wales have received generous financial support from the Commonwealth Bank of Australia Rural Credits Development Fund, from the U.S. Public Health Service, and from the Australian Research Grants Committee.

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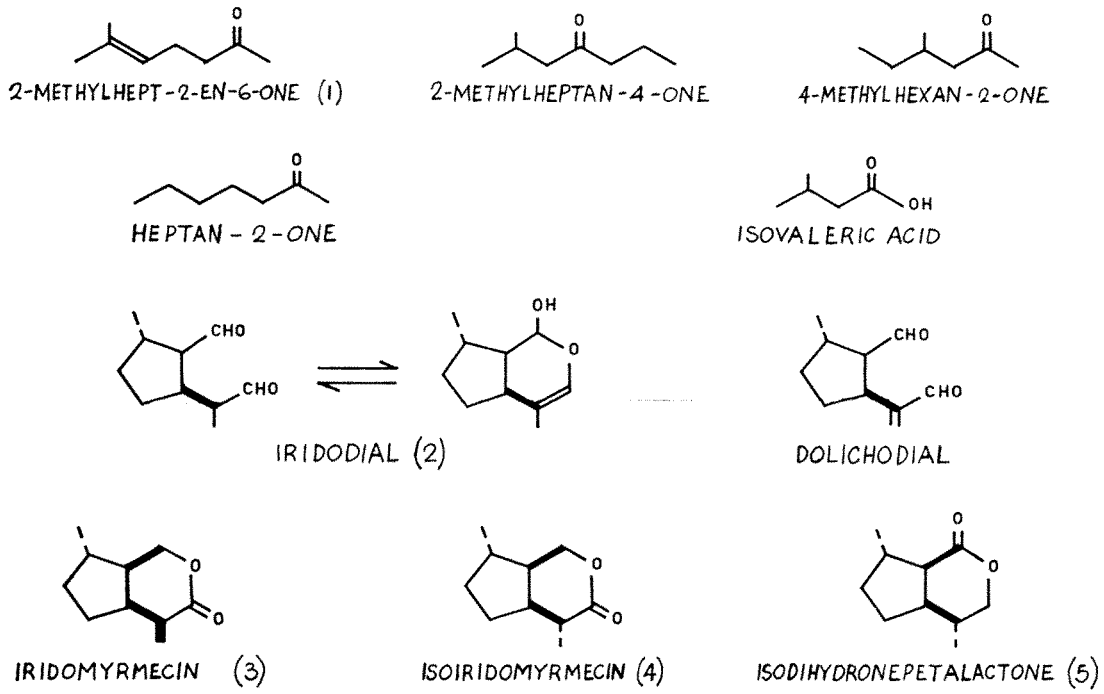

FIGURE 2. Dolichoderine ant extractives

novel 1,5-dialdehyde corresponding to iridomyrmecin. These anal gland constituents represented approximately 4% and 1% of body weight, respectively. Methylheptenone is now known to function as an alarm pheromone[15] as well as being a defensive secretion. A number of simple carbonyl compounds have been characterized from Dolichoderine ants and other insects (see Figure 2). These saturated and unsaturated ketones have "knockdown" insecticidal activity (see Table 1).[16] The activity of these ketones, on the basis of EC_{50} values, compares quite favourably with that of some well-known fumigants, but their volatility renders their contact toxicity slight when compared with, for example, that of the pyrethrins.

TABLE 1
"Knockdown" Effect of the Vapour of Some Aliphatic Ketones and Other Fumigants[16]

Compound	EC_{50}*
2-Methylhept-2-en-6-one (1)	1.33
6-methylheptan-2-one	2.1
6-methylhept-3-en-2-one	1.17
4-methylpent-3-en-2-one	2.6
ethylene dichloride	5
ethyl formate	6
ethyl acetate	16

* EC_{50} is the vapour concentration in µl./l. required to give 50% knockdown of female houseflies in 2.5 hr.

The cyclopentanoid monoterpenes (see Figure 2) are also major constituents of the anal gland secretion of various species of Dolichoderine ants. The structure and

stereochemistry of the iridolactones, iridomyrmecin (3) and isoiridomyrmecin (4), and of iridodial (2), were established in the mid 1950's.[17] More recently a re-investigation of the anal gland secretion of *Iridomyrmex nitidus* gave isodihydronepetalactone (5) in addition to isoiridomyrmecin.[18] These defensive substances of insect origin are structurally related to nepetalactone (6), the physiologically active principle of the catmint plant, *Nepeta cataria*, through the nepetalinic acids.[19] For example, oxidation of iridomyrmecin with aqueous potassium permanganate solution gave the nepetalinic acid (7),[14,20] which is one of the two acids (7) and (8) originally isolated on hydrolysis and oxidation of nepetalactone (see Figure 3).

The suggested formation of iridodial in nature from citronellal by a terminal oxidation of the isopropylidene group, and then cyclization of the intermediate

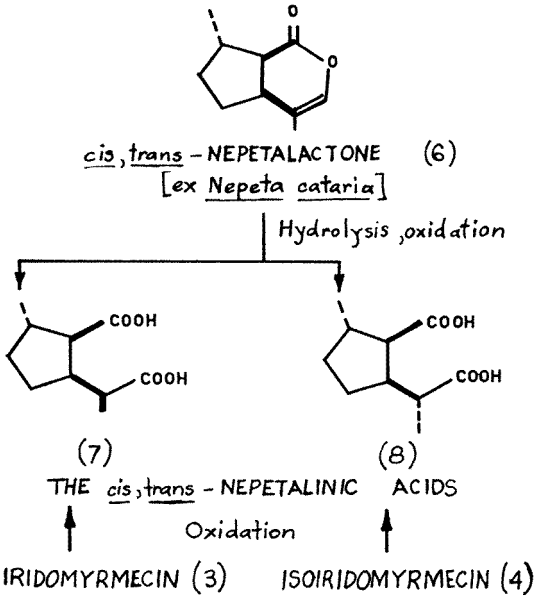

FIGURE 3. Interrelation of *cis,trans*-nepetalactone and the iridolactones

unsaturated dialdehyde (11) was simulated in the first synthesis of iridodial by Sir Robert Robinson and his co-workers (see Figure 4).[21] Citronellal (9), as its ethylene acetal (10) was oxidized with selenium dioxide in ethanol, and the product, on treatment with aqueous acetic acid, gave iridodial (12) together with the acyclic dialdehyde (11).

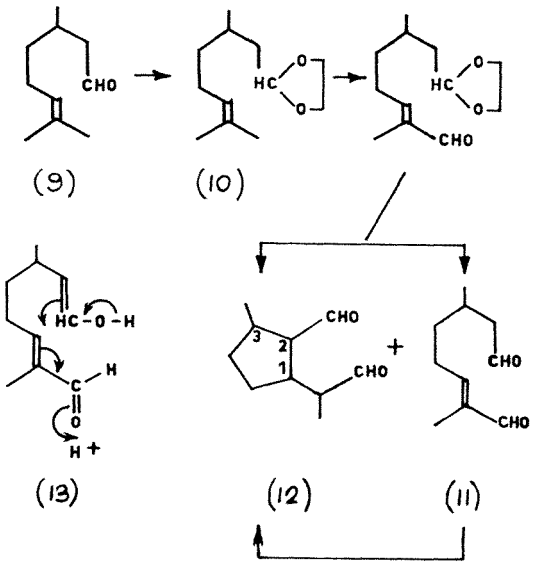

FIGURE 4. Synthesis of iridodial from citronellal (Sir Robert Robinson and co-workers[21]).

A likely mechanism for the cyclization involves an enolic intermediate of type (13), and hence a *trans*-relationship of the adjacent 1- and 2-substituents would be expected in the resultant iridodials. Additionally, equilibration of the centres α to the two formyl groups could occur, so that the iridodial should contain the *trans,trans-*, *trans,cis-* and *cis,trans*-isomers.*

Iridodial from the "meat" ant *I. detectus* was considered to be a mixture of the *cis,trans-* and *trans,cis*-isomers, with the former predominating.[22] However, the *trans,cis*-isomers may have resulted from a partial equilibration of the *cis,trans*-iridodial during isolation and purification. A stereospecific synthesis of the *cis,trans*-iridodial (20), that is, the enantiomer of the *cis,trans*-irododial related to iridomyrmecin, was undertaken[23] so that an iridodial of established configuration at each of the four optically active centres, would be available for comparative gas chromatography and, moreover, would provide a reference point for the determination of the stereochemistry of iridodials, and related enol-lactol tautomers, of insect and plant origin.

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* In the designation of configuration, the relationship of the substituents at Cl and C2 is given first, and that at C2 and C3 second. For example, formula (20) is a *cis,trans*-iridodial

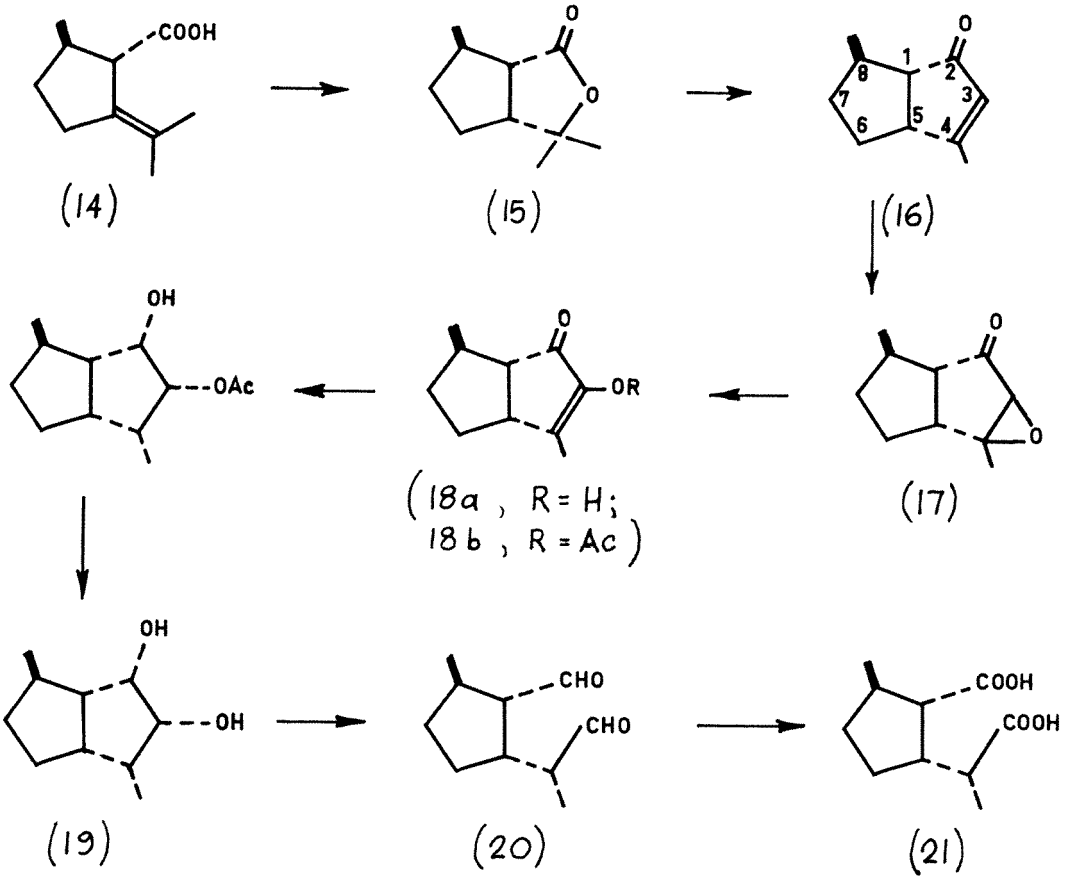


FIGURE 5. A stereospecific synthesis of iridodial (Achmad and Cavill [23]).

This synthesis depended on the availability of (+)-*trans*-pulegenic acid (14) which was obtained from D-(+)-pulegone by a Favorskii rearrangement of the freshly prepared dibromide with sodium ethoxide in ethanol.

Treatment of the (+)-pulegenic acid (14) with hydrochloric acid in methanol gave the γ-lactone (15) in good yield. The more stable *cis*-fused structure was assigned to this lactone, whilst the *cis,trans*-configuration at the cyclopentane ring is that required in the final product. The key step in the synthesis was the conversion of this γ-lactone into the corresponding bicyclooctenone (16) by the action of polyphosphoric acid. A likely mechanism for this conversion is given in Figure 6 (cf. [23]).

Epoxidation of the conjugated double bond with alkaline hydrogen peroxide solution, thence fission of the epoxide (17), and loss of a molecule of water in the presence of mineral acid, gave the hydroxybicyclo-octenone (18a) as a crystalline solid. Hydrogenation of the acetoxybicyclo-octenone, thence hydrolysis of the acetoxy group with alkali, yielded the intermediate glycol. On the basis that hydrogen had been added from the least hindered side of (18b), the glycol was assigned structure (19). The final step was fission of this bicyclic diol with sodium metaperiodate, yielding the *cis,trans*-iridodial (20). The stereochemical assignments were confirmed by oxidation of the synthetic iridodial (20) with zinc permanganate. The expected nepetalinic acid (21), that is the enantiomer of (7), was isolated, and identified by a gas chromatographic comparison of its methyl ester with that of the dimethyl nepetalinate obtained *via* the oxidation of iridomyrmecin.[23]

Further gas chromatographic studies using the freshly prepared synthetic iridodial (20), and natural iridodial from *I. detectus,* showed that the natural product is a mixture consisting predominantly of the *cis,trans*-isomers corresponding to isoiridomyrmecin and iridomyrmecin.

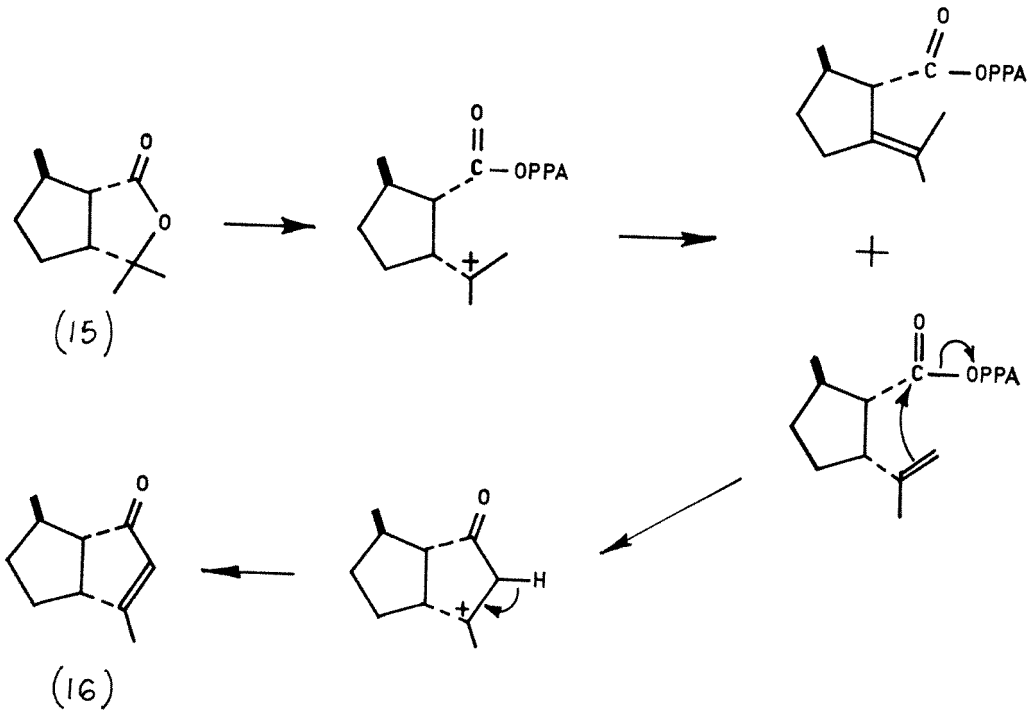


FIGURE 6. Conversion of the γ-lactone (15) into the bicyclo-octenone (16). (PPA = polyphosphoric acid.)

Iridodial does not show a "knockdown" insecticidal effect comparable with that established for the iridolactones. It was suggested[24] that iridodial may function as a fixative for the more volatile carbonyl compounds with which it is usually associated; in this case it is the ketones that have the "knockdown" action. More recently, in a study of the anal gland secretion of *Iridomyrmex nitidiceps*, which comprises iridodial and isovaleric acid, it was noted that iridodial could be contributing to the alarm pheromonal pattern for this insect.[25]

The venoms of the stinging Hymenoptera, especially of the bees and wasps, have been studied in detail in recent years.[26] However, until the recent work in Australia on the venom of the "bull-dog" ants, knowledge of proteinaceous ant venoms was sparse. In particular, the venom of the primitive red "bull-dog" ant, *Myrmecia gulosa,* well known for its aggressive behaviour and painful sting, has been characterized.[27] The venom is synthesized in the free gland filaments, stored in the venom sac or reservoir, then delivered by the duct to the sting barb. The Dufour's (accessory venom) gland secretion would also be delivered *via* the sting barb. The venom was isolated after individual collection of these ants, and dissection of the reservoirs, the yield on a dry weight basis being 0.5 mg./ant.

The venom is a proteinaceous one, and acid hydrolysis showed the presence of at least 19 aminoacids.[28] The crude venom was resolved into eight fractions by paper electrophoresis (see Figure 7). Fraction I was identified as histamine; it comprises 2% of the venom.[27] A histamine-releaser was also identified in the whole venom of bull-dog ants.[29] Fractions II to VIII were stained by the protein dyes bromophenol blue and Amidoschwarz 10B. Of these proteinaceous fractions, IV and V showed a

sustained kinin-like activity,[30] whilst fraction VII contained a direct, heat labile haemolytic factor,[27] this activity being used in bioassay. Further, the venom contains a small protein molecule not associated with a single electrophoretic fraction, which is an inhibitor of insect mitochondrial respiration.[28,31] Fractions IV and V also showed hyaluronidase activity,[27,28] while phospholipase C activity was associated with fraction VI.[28] Thus the venom of *M. gulosa*, and also that of related "bull-dog" ants, is typical of the hymenopterous proteinaceous venoms: it contains a low molecular weight physiologically active amine, biogenic peptides, proteins and toxins, and enzymes

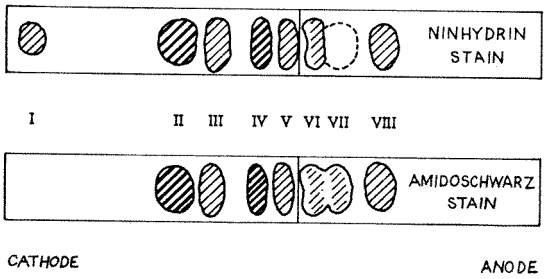


FIGURE 7. Electrophoretic separation of *M. gulosa* venom. (*After* Cavill, Robertson and Whitfield.[27])

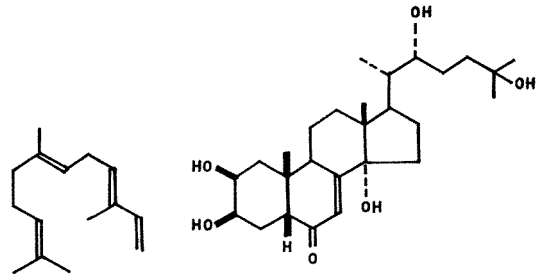
(cf.[32]). The "bull-dog" ant venoms are effective in killing their insect and other prey, also they are capable of inflicting pain on predators, including man, and hence are highly efficient in defence. Injection of saline extracts of the crude venom of *Myrmecia pyriformis* into mice shows that this venom is quite toxic; the LD_{50} was estimated to be 2-10 mg./kg. body weight.[30] The LD_{50} for *M. gulosa* venom injected into the house fly, *Musca domestica,* was ~10 μg./g.[33]

Recently, a study of the glandular origin and pattern of pheromonal activity involved in aggression in the "bull-dog" ant, *M. gulosa,* was undertaken.[34] The presence of at least three pheromones, a minor alarm pheromone in the rectal secretion which alerts the ant, a major alarm pheromone in Dufour's gland which activates the ant, and an attack pheromone in the mandibular glands, are involved in the pattern which results in stinging by these insects. No pheromonal activity was noted for the venom.

Some twelve hydrocarbons were reported[35] from the Dufour's gland, these components comprising 0.06% of the body weight of the insect. The major constituents were pentadecane (17%), *cis*-heptadec-8-ene (62%), and heptadecane (4%). In passing, it is noted that these hydrocarbons correspond in structure and proportion to the major free fatty acids isolated from *M. gulosa,* that is, palmitic, oleic and stearic.[36] The Dufour's gland hydrocarbons, whilst having a minor alarm effect, do not represent the alarm pheromone.[34] Thus a complex pattern of pheromonal activity has been established, but the chemical problem has yet to be solved.

The characterization of Dufour's gland constituents has also been achieved in more highly evolved ant species. Thus α-farnesene (22) was isolated from this gland in the Myrmicine ant *Aphaenogaster longiceps*.[37] This single constituent represents some 4% of the body weight of the insect. Current work on the Dufour's gland secretion of the Formicine ant, *Camponotus intrepidus*, again shows the presence of aliphatic hydrocarbons, within the range C_{10} to C_{17}. The normal alkanes are the major

constituents (81%), together with a series of 3-methyl (16%) and 5-methylalkanes (2.3%). Alk-l-enes are minor constituents (~0.2%).[38]



α-FARNESENE (22) ECDYSONE (23)

There has been, and still is, conjecture as to the function of the above hydrocarbons. Their presence in the sting-bearing Myrmeciinae is not inconsistent with one of the earlier proposals that Dufour's gland secretion may function in the Hymenoptera, in general, as a sting lubricant. However, a remarkably wide range of feeding, foraging and nesting habits is displayed within the Formicidae and it is considered likely that the function of Dufour's gland secretion in relation to these habits could have undergone considerable change from the more primitive Myrmeciinae to the more advanced Myrmicinae and Formicinae (cf. [4]).

Hormones

Whereas pheromones are products of the exocrine system and convey chemical signals between members of the same or closely related species, hormones are products of the endocrine system and convey signals between tissues within an individual of the species.

Present knowledge of the hormonal control of insect development stems largely from the pioneering studies of Sir Vincent Wigglesworth.[39] At least three hormones, one originating in the brain, the juvenile hormone, and the moulting hormone, are involved in the regulation of post-embryonic development in insects which is characterized by moulting and metamorphosis. The structure of the brain hormone is unknown. The moulting hormone, ecdysone (23), isolated from the pupae of the silkworm, *Bombyx mori*, is steroidal.[5]

In 1967 the juvenile hormone from the giant silkworm moth, *Hyalophora cecropia*, was shown to have a modified sesquiterpenoid structure (24).[40] Currently this hormone is attracting much attention as its action in preventing maturation to the adult form renders it of potential value in insect control.[41] Not unexpectedly, a number of juvenile hormone syntheses have now been reported.[42] The synthesis, presently described,[43] follows our earlier work on α-farnesene (cf. [37]).

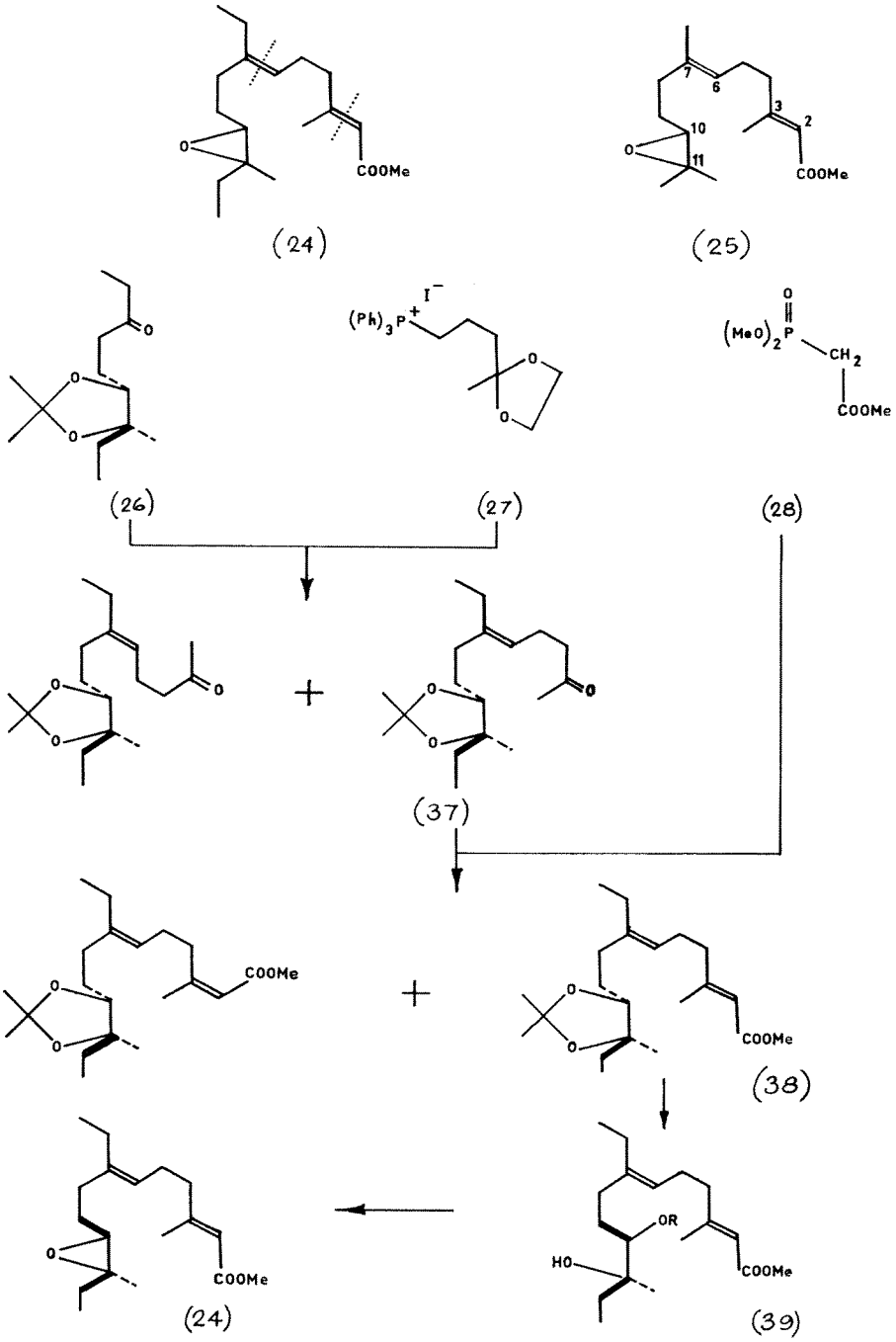


FIGURE 8. Synthesis of the juvenile hormone (Cavill, Laing and Williams[43]).

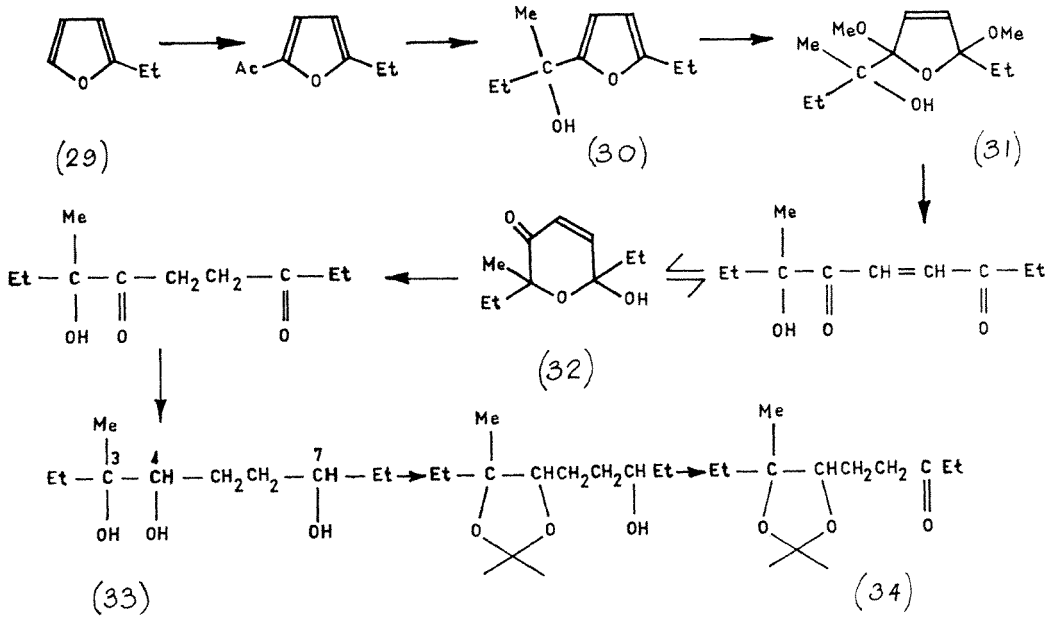


FIGURE 9. Synthesis of the acetonide of 7-oxo-3-methylnonane-3,4-diol (34).

Structurally, the hormone may be considered as a bishomologue of the known sesquiterpenoid, methyl 10,11-epoxy-3,7,11-trimethyl-dodeca-2,6-dienoate (25) which shows high juvenile hormone activity.[44] That is, in the hormone (24) two ethyl substituents replace the methyl groups at C7 and C11 in (25). The method of synthesis is a general one, being applicable to the synthesis of homologues and analogues.

The structure was built up from three units, of which the key C_{10} unit was the *trans*-acetonide of 7-oxo-3-methylnonane-3,4-diol (26). Sequential Wittig reactions were used to add the C_5 unit (27) and the C_3 unit (28). These steps were modelled on a synthesis of the bisnor-hormone (25).[45] The chain-extending steps introduced the two olefinic bonds of (24), and at each step the required *trans*-isomer was separated by preparative gas chromatography. Finally, the intermediate ester (38) was converted into the *cis*-10,11-epoxide structure of (24) *via* the 10,11-diol monomesylate (39).

The C_{10} unit was synthesized from 2-ethylfuran (29). The appropriate substituents were introduced into the furanoid intermediates, and importantly the furan (30), provides the genesis of the oxygen functions for the ketoacetonide (26). The furan (30), on treatment with bromine in methanol, gave the dihydrofuran derivative (31). Hydrolysis of this cyclic acetal with dilute hydrochloric acid yielded the dihydropyranone (32). Hydrogenation of (32) and reduction of the intermediate hydroxydiketone with sodium borohydride gave the triol (33). From the mode of synthesis of this acyclic triol (33), the centres at C3 and C4 are racemic, and the derived ketoacetonide (34) would be a mixture of enantiomeric pairs of *cis*- and *trans*-isomers about the 1,3-dioxolan ring. The *threo*-form of the triol (35) would give the *trans*-ketoacetonide (26), and thence the *cis*-expoide (24) (see Figure 10). Separation of the *threo*- and *erythro*-forms of the triol was achieved using an alumina column impregnated with boric acid for elution chromatography. At this stage configuration was assigned to the *trans*-ketoacetonide (26) on the basis of comparative n.m.r. data (see reference 43). The chemical shift value (δ) of the singlet for the protons (3H) of the

methyl group situated *trans* to the hydrogen atom on the dioxolan ring in (26), was compared with that for the equivalent methyl group in the known[46] *cis*-tetramethyl dioxolan (36). The methyl and hydrogen substituents at C4 and C5 in this model

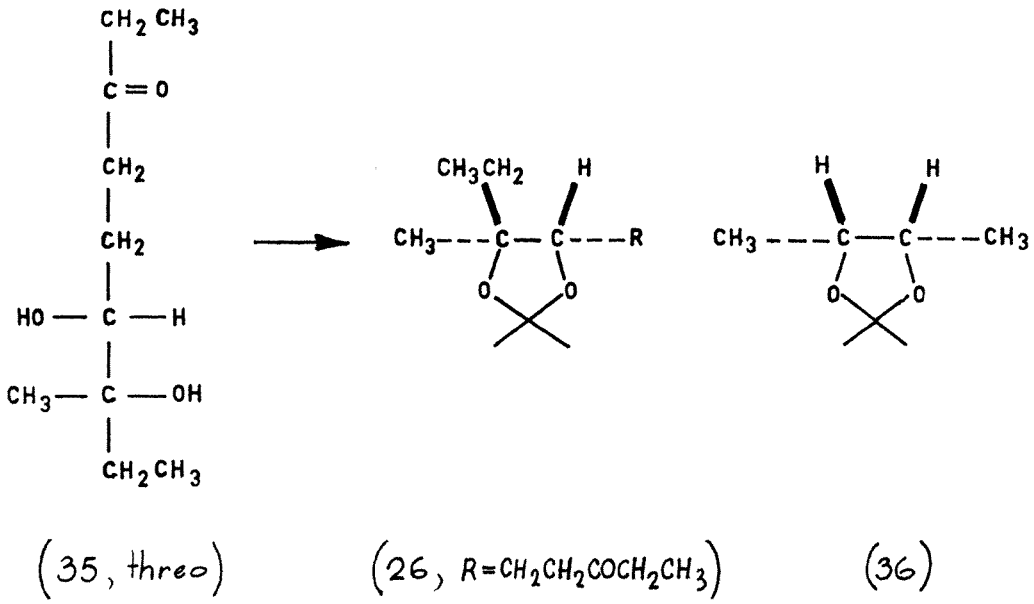


FIGURE E10. Stereochemistry of the acetonide (26). (*After* Cavill, Laing and Williams.[43])

dioxolan (36) are, of course, *trans*. The signal for the protons of the tertiary methyl group appears at approximately 0.1 p.p.m. upfield from the *trans*-ketoacetonide and related compounds, compared with the equivalent *cis*-isomers.

Reaction of the *trans*-ketoacetonide (26) with the Wittig reagent prepared from (27) gave a mixture of the *cis*- and *trans*-isomers of the bisacetal. Selective hydrolysis of the ethylene acetal was achieved using toluene-*p*-sulphonic acid in the presence of a large excess of acetone (cf. [45]). The required *trans,trans*-dodecenone (37) having the longer retention time was separated from the *trans,cis*-isomer by preparative gas chromatography, and subjected to the second Wittig reaction with the sodium salt of trimethylphosphonoacetate (28). The required *trans,trans,trans*-product (38)* of longer retention time was separated from the *trans,cis,trans*-isomer. Finally, an acid hydrolysis of the isopropylidene group, and conversion of the diol into its monomesylate (39, R=Ms), then treatment with sodium methoxide in methanol, gave the required *cis*-epoxide (24).[43]

Whether the natural product is one of the optical antipodes, or the racemate, has yet to be determined, also resolution of the racemic hormone, as synthesized, has yet to be reported.

Conclusion

In summary, I would refer to more general aspects of the chemistry and biology of insect secretions.

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* In the *trans,trans,trans*-isomer the first *trans* refers to the isopropylidenedioxy group, the second to the 2,3 double bond, and the third to the 6,7 double bond.

The defensive secretions that have been characterized are broadly grouped as (*a*) terpenoids and steroids, (*b*) aliphatics, primarily simple oxygenated alcohols, carbonyl compounds, acids and their derivatives, and (*c*) aromatics, including 1,4-benzoquinones, mandelonitrile derivatives and phenolics (cf.[1]). Many of these secretions, whilst fulfilling the defensive needs of the insects which produce them, are not necessarily adaptable for other insecticidal purposes. Studies on insect venoms, and especially on the proteinaceous venoms of the Hymenoptera, have a more biochemical and pharmacological bias. Apart from formic acid, little is known of the non-proteinaceous insect venoms. Work on insect pheromones and hormones is likely to be pursued with increasing vigour, and it is in this area that the major problems of isolation, prior to structure elucidation, have been noted. The need for satisfactory bioassay procedures is clear.

In studies on chemical communication in insects, the overall problem is very much an interdisciplinary one. The chemist is contributing to the solution of a problem in insect behaviour in which, say, the use of a given pheromone is but part of a complex behaviour pattern. The close collaboration of chemists and biologists is essential. The recent and intense synthetic studies[42] in relation to the juvenile hormone are prompted by potential applications of the ensuing compounds for insect control.

The advances of the last two decades have been considerable, and in turn they have relied on major advances in spectroscopic and chromatographic techniques. Yet, our total knowledge of insect secretions is meagre.

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