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SOME METABOLITES FROM AUSTRALIAN MARINE ORGANISMS

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Abstract—Natural product research on Australian marine organisms is reviewed for the period 1959–1975. Results from both Australian and international groups are considered and the established structures of secondary metabolites reported.

Involvement of Australian organic chemists in the study of substances from marine organisms may be considered an expected logical extension of their established reputation in traditional natural product chemistry. In this way it can be fairly said that the development of interest by Australian organic chemists in marine natural products has followed closely on the pattern established for the interest of their forebears in essential oils and alkaloids from Australian flora. Price, in his special lecture to the I.U.P.A.C. Symposium in Australia in 1961 when he discussed Australian natural product research,[1] indicated that the initial stimulus may well have come from Ferdinand von Mueller, a German, who was appointed Government Botanist of Victoria in 1853 and who subsequently made an outstanding contribution to the scientific description of Australian flora.

Ferdinand von Mueller and Joseph Bosisto, the latter initially interested in the commercial exploitation of essential oils from Australian eucalypts,[1] established the basic interest from which emerged the significant involvement of Australian Organic Chemistry research in natural products.

The stimulus in the marine field also derived from an early involvement by scientists from overseas. Apart from the "Endeavour" visit from 1768 to 1771 when so many excellent botanical observations were made by Banks, the first marine scientific expedition appears to have been that by the French vessel "Astrolabe" from 1826 to 1829 when the naturalists Quoy and Gaimard sampled dredgings off Jervis Bay and Port Jackson in New South Wales.

From 1826, scientific oceanographic expeditions by HMS ships "Fly", "Rattlesnake", "Herald", the Austrian frigate "Novara", then HMS "Challenger", SMS "Gazelle" and HMS "Alert" all reported collections of marine species before the first Australian collection in the S.S. "Manly" in the area of Port Stephens.[2]

In the early 1900's the Australian coast attracted visits by German, Swedish, Danish and English marine expeditions and in more recent years expeditions from the United States and from Japan to Australian waters have become relatively commonplace. To this date in 1975 Australia does not have a single major vessel equipped for marine or oceanographic research and much of the knowledge of the Australian marine environment continues to be derived from the results of overseas expeditions. However, the CSIRO and several universities in Australia, as well as State Government Departments of Fisheries, do have smaller vessels which are adequate for near off-shore exploration.

As with terrestrial natural product research, research in the marine environment by chemists has followed preliminary investigation by biologists and it is interesting to note that in 1899 Waite reported[2] in his paper on the scientific results of the trawling expedition of HMCS "Thetis" off the coast of New South Wales in February and March 1898, that "south of the equator few waters if any had been as thoroughly investigated as those of Port Jackson in NSW and it has been proved that its fauna is an extremely rich one".

In his review of Australian natural product research in 1961, Price[1] gave brief reference to the work of Sutherland, which had then only recently begun on the examination of marine animal pigments, but Price gave no suggestion that Australia should become more involved in this field of research. Nor did Lord Todd, in his presidential address "Natural Product Chemistry—Retrospect and Prospect",[3] specifically stress the potential of the marine environment for chemical research.

From these facts it can be seen that Australian chemical involvement in marine natural product research received little consideration prior to 1960. This should not necessarily be interpreted, at that stage in time, as a failing to capitalise on a natural advantage, because facilities had only recently been developed to stimulate underwater exploration, and there was little evidence in the literature of international interest in marine natural products.

Sutherland and Wells, in 1959 reported[4] on the anthraquinone pigments from a Queensland crinoid *Comatula pectinata*, and since that date Sutherland has retained an interest in a variety of marine pigmentations. Sutherland may therefore be regarded as the progenitor of marine natural product chemistry in Australia.

In contrast to the development of interests in Australian essential oils at the beginning of the century, Sutherland's results have, to this stage, not shown compounds which are of potential commercial interest.

Consistent with modern practice he has displayed a distinct interest in the development of biogenetic theories in the relationships of structures of the various pigments reported.

Apart from Sutherland and his co-workers,[4–13] the only Australian workers to report on the elucidation of structures of compounds from marine organisms, prior to 1971, were D.H.S. Horn and co-workers[14–16] on crustecdysone from a South Australian crayfish, and B. J. Ralph and colleagues on non-protein amino acids from Australian seaweeds.[17]

During the 1960's, P. R. Burkholder from the University of Puerto Rico was particularly active in collections from the Great Barrier Reef and although many of the collections have not yielded publishable results, Sharma, Vig and Burkholder[18] did report to the "Food-Drugs from the Sea" Symposium in 1969 on antimicrobial substances from marine sponges, and illustrated the formulae of the phakellins isolated from the Australian sponge *Phakellia*

flabellata. During this same period Ciereszko from the University of Oklahoma was also involved in collections from the Great Barrier Reef and he published[19] on the isolation of gorgosterol from a gorgonian (*Isis hippuris*) and from a soft coral (*Lobophytum* sp.) collected in the region of Heron Island, in 1968.

Since 1971, publications by Australian workers on structures of substances from Australian marine organisms have come from Sutherland's laboratory,[20] and from our group,[21-24] which grew directly from the Sutherland training and influence, at the James Cook University of North Queensland. Similarly the interest of overseas workers has been maintained with further reports by Sharma and Burkholder,[25] Ciereszko[26-28] and Sims.[29-31] Webb from the Lederle Laboratories in New York has indicated preliminary findings on some halogenated compounds from Burkholder's collections.[32]

On the basis of published work it may appear that Australia is still lagging behind the rest of the world in its interest in marine natural products.

Significant internal development has been the promise of the Australian Government to establish an Australian Institute of Marine Science, which after several years of controversy on the location of the Institute, has now been established on a site near Townsville in North Queensland. This site gives access to an area which may be regarded as central to the 1200 mile length of the Great Barrier Reef. This Institute will be funded directly from the Commonwealth Government and when the direction of its research interest is known, one will be better able to appraise the significance of its role in the future of Australian Marine Chemistry. Additionally, the Australian Museum has established a Research Station on Lizard Island which is some 400 miles north of Townsville and therefore gives access to a northern area of the Great Barrier Reef, whilst the well-established Heron Island Research Station on the southern extremity of the Great Barrier Reef, allows visiting scientists adequate research facilities, at least for collection purposes.

Thus, there is adequate access for Australian workers to the Great Barrier Reef, which although it has been a focal point for overseas involvement, should not necessarily be regarded as the area of greatest potential for interesting marine natural products.

Another aspect of importance to Marine Science is the recognition by the Australian Research Grants Committee that special grants should be made available in the field of marine science. It is logical to expect that initial grants in this area will go predominantly to biological sciences but some grants have been given to chemical work, particularly on the isolation of active compounds from the Crown-of-Thorns Starfish (*Acanthaster planci*) and to the established groups such as those of Sutherland, and later Baker in Townsville, and Howden[52] at Macquarie University in Sydney.

At present the work being undertaken under these A.R.G.C. Grants is predominantly within one of a number of disciplines but recent moves in different Universities have indicated an interest in inter-disciplinary research in marine sciences and such a major project is under way at the James Cook University of North Queensland, involving the Departments of Engineering, Biological Sciences, Geography, Geology and Chemistry.

The Victorian Institute of Marine Sciences has been established and this should be operative as a viable institute in the near future.

From the co-ordination point of view the establishment of the Australian Marine Sciences Association in 1962 gave promise of the development of a group within Australia whose interest will relate directly to the marine environment. To date this Association encompasses mainly the biological sciences, but in recent years there has been an increasing membership from chemists and biochemists.

Chemical activities of the CSIRO in the field of natural compounds appear to be related to the traditional areas of research in essential oils and alkaloids from Australian flora and there is little indication of any strong move towards marine natural product chemistry in this organization. Within State Government Departments there is an increasing awareness of the need for chemists to monitor marine environmental changes but, at the present, research within these groups appears to be concentrated on the detection of heavy metals and of traces of halogenated pesticides.

On the commercial front the development of the Roche Research Institute of Marine Pharmacology in 1974 at Dee Why in Sydney, provides an integrated research group for the study of marine natural products of potential biological interest.

Other commercial groups express their interest by collecting activities in Australian waters.

When one considers the geographical location of the principal Australian Universities one cannot help but be impressed by the fact that these are in many cases ideally suited to the pursuit of marine chemistry. However, to date this resource has been largely ignored. With the advent of demonstrated Federal and State Government support for Marine Science projects we see in several Australian Universities and Colleges of Advanced Education the desire to attract Government financial support by establishing Degree Courses in Marine Science, and the inevitable consequence of this should be a greater involvement by university chemists in the marine field.

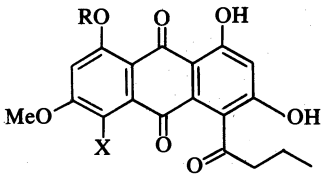
In discussion of specific secondary metabolites from Australian marine organisms it is natural that the first portion should deal with that work undertaken by Sutherland and his group at the University of Queensland in Brisbane.

Sutherland and Wells[4] initially worked on the pigments of the crinoid *Comatula pectinata* Linnaeus which was collected in sheltered waters of Moreton Bay. The hydroxyanthraquinone pigments isolated were previously unknown from animal sources, except in insects of the Coccidae family, and similar pigments were subsequently extracted from a second species of crinoid, *C. cratera* A. H. Clark, collected during long uncomfortable nights on prawn trawlers operating in open waters near the Queensland–New South Wales border.

To aid in the unambiguous assignment of structure of these indicator-type pigments, Sutherland and co-workers synthesised[6] 1, 3, 6, 8-tetramethoxyanthraquinone and its 4-methoxy- and 4-methoxycarbonyl-derivatives and subsequently elucidated[7,8] the structures of the three major naturally occurring pigments as I, II and III.

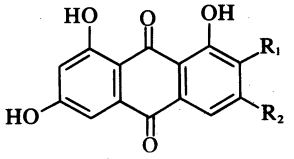
The paper by Sutherland and Wells[7] provides a comprehensive review of the history of investigations of crinoid pigments, and that by Powell, Sutherland and Wells[8] gives excellent detail on the methods used to resolve the different types of pigment mixtures from the different species of crinoids investigated.

Powell and Sutherland[9] examined the pigments of the crinoids *Ptilometra australis* Wilton and of *Tropiometra afra* Hartlaub, both of which are common off the South



I X = H, R = H Rhodocomatulin-6-methyl ether
II X = H, R = Me Rhodocomatulin-6,8-dimethyl ether
III X = OH, R = H Rubrocomatulin monomethyl ether

Queensland coast, and from the complex mixture derived from *P. australis*, characterized the three principal components as IV, V and VI.



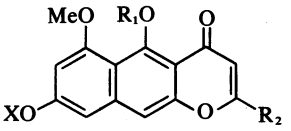
IV $R_1 = H$, $R_2 = CH(OH)—CH_2—CH_3$ Rhodoptilometrin
V $R_1 = H$, $R_2 = CH_2—CH(OH)—CH_3$ Isorhodoptilometrin
VI $R_1 = COOH$, $R_2 = CH_2—CH_2—CH_3$ Ptilometric acid

Specimens of *T. afra* contained ptilometric acid (VI) but did not contain rhodoptilometrin (IV) or isorhodoptilometrin (V).

Sutherland[9] noted that *P. australis* and *Comatula cratera*, while yielding characteristic, but different classes of anthraquinones, are taken from the sea bed in the same trawl net, and that *T. afra* and *C. pectinata*, again each yielding the different classes of anthraquinones, are found intermingled on the rocky reefs off the South Queensland coast. He therefore regards as untenable, any suggestion that crinoidal anthraquinones represent accumulating residues from phytoplankton or other plant foodstuff and postulates that the crinoid anthraquinones are endogenous in origin.

The rhodocomatulin series of compounds (I), (II), (III) isorhodoptilometrin (V) and ptilometric acid (VI) conform to the Birch polyketide rule[33] whereas rhodoptilometrin (IV) is considered as plausibly arising by oxidation of ptilometric acid at the labile benzylic position, and decarboxylation of the acid function.[9] The topic of distribution and biogenesis of anthraquinones has been well covered by Thomson,[34] as has the integration of research results on all classes of naturally occurring quinones.

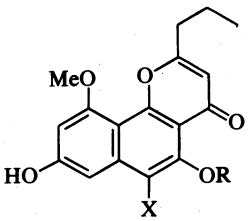
Kent, Smith and Sutherland[13] obtained the mustard-yellow coloured crinoid, *Comantheria perplexa* Clark, from prawn trawlers off the South Queensland coast. Acetone extraction of the flesh of this crinoid yielded the sulphuric ester of a substituted naphthopyrone (VII) as the sodium salt, and acid hydrolysis yielded the corresponding phenol (VIII), which has been synthesised by Japanese workers.[35] Hydrolysis of the crude extract from *C. perplexa* yielded VIII, IX and X. Sulphation of neocomantherin (X) gave a sulphuric ester[13] which is comparable in characteristics with the natural water-soluble colouring matter, and it is suggested that neocomantherin occurs in nature as the sulphuric ester. Similar experiments involving anhydrofonsecin (IX) did not yield an unambiguous result because of a fortuitous coincidence of the R_f value of the product with that of



VII X = ^-O_3S, R_1 = Me, R_2 = Me Comantherin sulphate
VIII X = H, R_1 = Me, R_2 = Me Comantherin
IX X = H, R_1 = H, R_2 = Me Anhydrofonsecin
X X = H, R_1 = Me, $R_2 = CH_2—CH_2—CH_3$ Neocomantherin

comantherin-*O*-sulphate in the chromatography system used.

Angular naphthopyrones were isolated by Smith and Sutherland,[20] from the crinoid *Comanthus parvicirrus timorensis* Muller, collected in Moreton Bay. Acetone extraction yielded three yellow water-soluble colouring matters which were each shown to be *O*-sulphates, giving, on mild acid hydrolysis XI, XII and XIII respectively. The structures were assigned largely on the basis of spectral data.



XI X = H, R = H Comaparvin
XII X = OMe, R = H 6-Methoxycomaparvin
XIII X = OMe, R = Me 6-Methoxycomaparvin 5-methyl ether

Sutherland[36] currently has in preparation a publication on the synthesis of the methyl ethers of the linear and angular naphthopyrones from *Comantheria perplexa* and *Comanthus parvicirrus timorensis.*

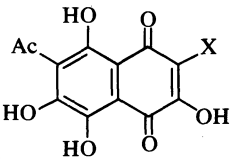
He has postulated[13] that the naphthopyrones originate from C_{14} and C_{16} polyketides and thus provide further evidence of the remarkable similarity already noted[7,9] between crinoidal and fungal secondary metabolites.

Gough and Sutherland[5] in their work on the naphthoquinone pigments from the Australian echinoid *Salmacis sphaeroides* Lovén recognized the confusion in the literature relating to the numerous spinchromes, and were able to demonstrate that the reported spinochromes B, B_1, M_2, N and P_1 were identical. They proposed that spinochrome B, be the accepted trivial name.[5]

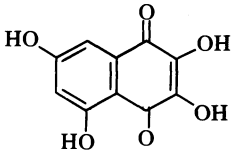
S. sphaeroides yielded three known hydroxy naphthoquinone pigments spinochrome A (XIV)[37,38] spinochrome C (XV)[37,38] and spinochrome B (XVI)[5,37] together with a new hydroxynaphthoquinone, spinochrome S (XVII),[10] and several minor unidentified pigments.

In both the crinoids and the echinoids only the major pigments have been classified from the Australian species, and a combination of spectral and synthetic studies may be necessary to fully elaborate the structures of all minor pigments.

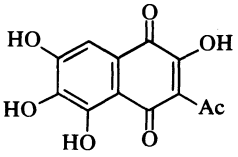
Sutherland's interest in pigments derived from marine organisms extended beyond those naturally present in the live animal and prolonged investigation preceded the report by Baker and Sutherland[11] on precursors of 6,6'-dibromoindigotin (Tyrian purple) (XVIII) from the mollusc *Dicathais orbita* Gmelin, this purple pigment being well characterized by Friedländer[39,40] from Mediterranean molluscs.



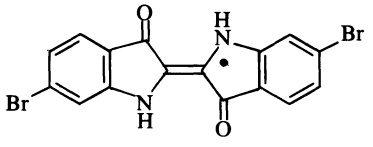
XIV X = H, Spinochrome A
XV X = OH, Spinochrome C



XVI Spinochrome B

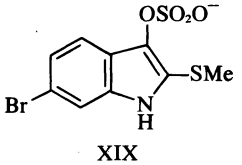


XVII Spinochrome S

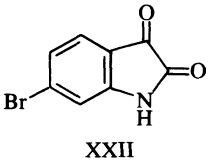


XVIII 6,6′-Dibromoindigotin

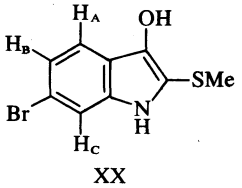
Baker and Sutherland characterized the substance present in the hypobranchial gland of *D. orbita* as the salt of tyrindoxyl sulphate (XIX) and postulated that enzymatic hydrolysis produced the corresponding tyrindoxyl (XX), which could partially oxidise to the corresponding tyrindoleninone (XXI).[11]



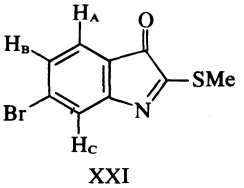
XIX



XXII



XX



XXI

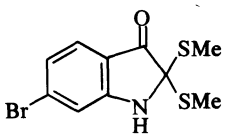
A 1:1 molecular complex of a quinhydrone type involving XX and XXI was postulated to explain the insoluble photosensitive material (tyriverdin) deposited from extracts of the autolysed hypobranchial glands. Irradiation in sunlight of a solution of tyriverdin produced 6,6′-dibromoindigotin (XVIII), dimethyldisulphide and 6-bromoisatin (XXII), the yield of XVIII decreasing with increasing oxygen availability in the solution.

Chemical proof of the presence of tyriverdin could not be achieved, but supporting spectral evidence was gained from both mass spectra and Fourier transform ^{1}H NMR which showed the following characteristics

	δ	No. of protons	J
SCH_3	1.88	3	—
H_B	6.96	1	J_{BA} = 8 Hz
			J_{BC} = 1.5 Hz
H_C	7.28	1	J_{CB} = 1.5 Hz
H_A	7.47	1	J_{AB} = 8 Hz
O..H..N	8.20	1	—

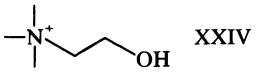
1:1::XX:XXI

Baker and Duke[21–24] continued investigations on *D. orbita, Mancinella keineri* Deshayes and on other Australian gastropod molluscs and succeeded in isolating the tyrindoleninone (XXI) as well as tyrindolinone (XXIII) from the gland extracts of *D. orbita*.

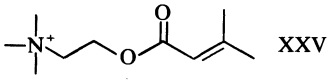


XXIII

Their work also revealed the apparently specific association of tyrindoxyl sulphate with different organic bases in the case of *D. orbita* (with choline) XXIV and in the case of *M. keineri* (with β,β-dimethylacrylylchloline) XXV.

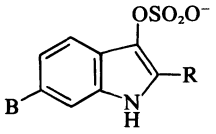


XXIV



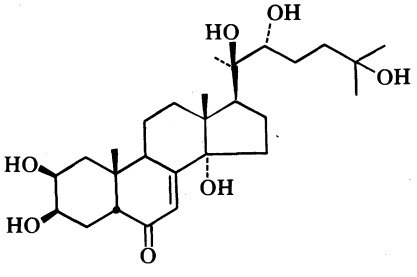
XXV

The opportunity to work on Mediterranean gastropod molluscs has revealed significant differences in hypobranchial gland constituents from species to species.[23] The following summary information based on published results[11,41] for *D. orbita* and *M. trunculus* is no longer consistent with our as yet unpublished results.

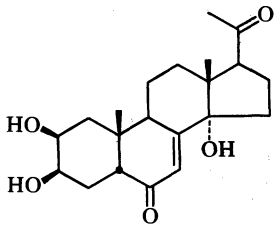


R = SCH_3	B = Br	*Dicathais orbita*	
R = H	B = H	*Murex trunculus*	Fouquet and Bielig Nov. 1971
R = SCH_3	B = H	*Murex trunculus*	
R = H	B = Br	*Murex trunculus*	
R = SO_2CH_3	B = Br	*Murex trunculus*	
R = SO_2CH_3	B = H	Not yet confirmed	

Hampshire and Horn[14] in 1966 reported the isolation of 2 mg of crustecdysone (XXVI), a crustacean moulting hormone, from 1 ton of crayfish waste, the crayfish being *Jasus lalandei* Milne-Edwards from the seas off South Australia.



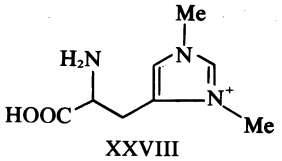
XXVI



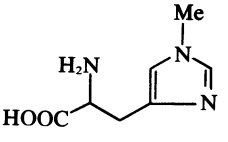
XXVII

The structure (20 R-hydroxyecdysone) was proposed[14,15] partly on biogenetic grounds, and partly from a comparison of its properties with those of the insect moulting hormone, ecdysone. Further evidence for the structure was obtained by oxidising crustecdysone to a synthetic ketone of known structure (XXVII)[42] and by synthesis of crustecdysone,[43] which was identical with the natural product.

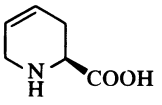
The final example of published work by an Australian group is that due to Madgwick, Ralph, Shannon and Simes[17] who investigated the free amino acids of some 50 species of red, brown and green algae occurring along the New South Wales coast, and reported on four non-protein amino acids XXVIII, XXIX, XXX and XXXI.



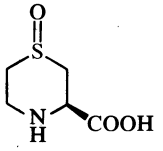
XXVIII
Dimethyl histidine



XXIX
1-Methyl histidine



XXX L-Baikiain

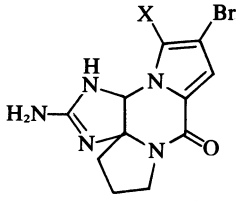


XXXI
Chondrine(1,4-thiazane-3-carboxylic acid-1-oxide)

It should be stressed that Australian work referred to in this section, is only that which has led to structure elucidation of marine natural products.

With reference to overseas interest in Australian marine organisms, it is probable that many years will elapse before the true extent of collections organized by Burkholder and by other groups representing pharmaceutical companies, will be known.

In reporting the structure of 4,5-dibromophakellin (XXXII) and of 4-bromophakellin (XXXIII),[18,25] isolated from the Great Barrier Reef sponge *Phakellia flabellata*, Sharma and Burkholder[25] drew attention to the fact that although their proposed structures contain a guanidine unit in a 5-membered ring, the compounds do not possess the usual high basicity of guanidinium compounds.

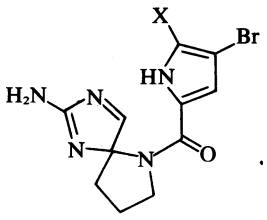


XXXII X = Br
XXXIII X = H

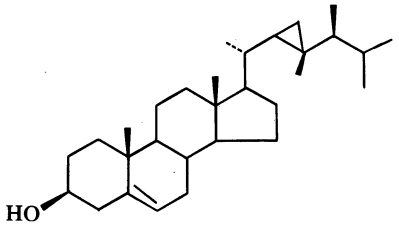
However, on the basis of spectroscopic analysis including 220 MHz ^{1}H NMR data, and supported by X-ray diffraction analysis of a single crystal of a monoacetyl derivative, the above structures were proposed.

Weigele[44] has proposed that the alternative structure XXXIV may well be consistent with the 220 MHz ^{1}H NMR and spectroscopic data for the 4,5-dibromophakellin. The structure XXXIV would then be proposed as cyclising to XXXII during acetylation.

Ciereszko and co-workers of the University of Oklahoma, have noted the presence of gorgosterol (XXXV) in the gorgonian *Isis hippuris* and in a soft coral (*Lobophytum* sp.) both species being collected at Heron Island.[19]

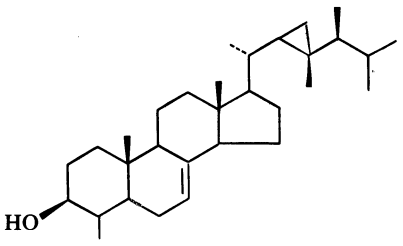


XXIV

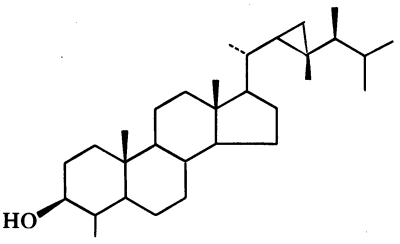


XXXV

Steudler, in his M.S. thesis with Ciereszko,[26] identified, on the basis of GC-MS records, gorgosterol (XXXV), 4-methylacanthasterol (XXXVI) and 4-methylgorgostanol (XXXVII) in the Australian soft coral *Xenia elongata* and IR the crab *Caphyra laevis* which is normally associated with the soft coral.

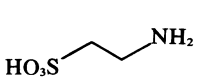


XXXVI

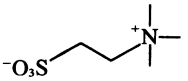


XXXVII

Taurine (XXXVIII) which is widely distributed in marine organisms[45] and taurobetaine (XXXIX) which has been previously reported[46,47] in a gorgonian *Briareum asbestinum* and in the sponge *Geodia gigas*, were reported by Ciereszko[27] as occurring in the soft coral *Sarcophytum trocheliophorum*, from Heron Island.



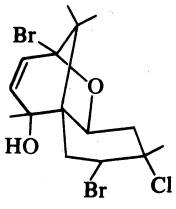
XXXVIII



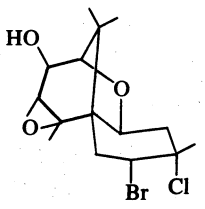
XXXIX

Sims, during the 1971–1972 tenure of a research fellowship at the Australian National University, had the opportunity to apply his experience in marine natural product chemistry, to Australian species.

Previous to his work on Australian algae, Sims had been involved in the isolation and characterization of pacifenol (XL) from *Laurencia pacifica*[48] and of Johnstonol (XLI) from *L. johnstonii.*[49]

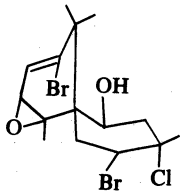


(XL)



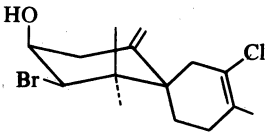
(XLI)

From the Australian red alga *L. filiformis*, Sims[30] isolated the probable precursor of pacifenol, prepacifenol (XLII), finding that the original procedure involving the use of silica gel chromatography for the resolution of the extract from *L. pacifica* had isomerised prepacifenol to pacifenol. However, Sims was able to demonstrate[30] that pacifenol (XL) occurs naturally in *L. tasmanica.*



XLII

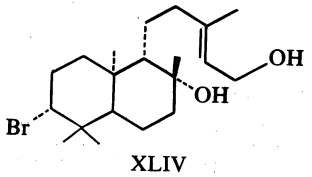
From another species of Australian red alga, *L. elata*, collected from the New South Wales coast, Sims[31] isolated another halogenated sesquiterpene, elatol, (XLIII), which features a vinyl chlorine. The structure was verified by X-ray crystal analysis.



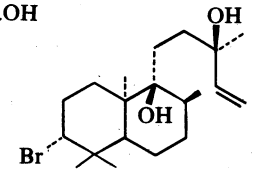
XLIII

L. concinna is another red alga found off the New South Wales coast and in 1973 Sims[29] isolated the relatively rare class of compound—a haloditerpene. Previous to Sims' report[29] only one bromoditerpene had been isolated from a marine organism, this being aplysin-20 (XLIV) from the sea hare *Aplysia kurodai.*[50,51] It has been noted in other studies on *Aplysia* that they ingest algae and that they may be able to modify the structure of halogen-containing substances of the algae.

Concinndiol (XLV) crystallized from a hexane extract of dry *L. concinna*, and the structure, isomeric with that of aplysin-20 (XLIV), was confirmed by X-ray crystal analysis.



XLIV

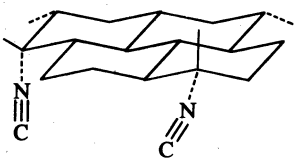


XLV

To date no papers have appeared from the chemistry group at RRIMP, this fact being accounted for by the relatively brief period of operation of the Institute since its opening on 20 April, 1974.

Some work was achieved prior to this opening by Roche-supported staff at Australian universities, principally by R. J. Wells, (as distinct from J. W. Wells who had worked with Sutherland) and to some extent by Baker, Murphy and Hawes at James Cook University of North Queensland, and by Hofheinz and Dunstan at the University of Queensland.

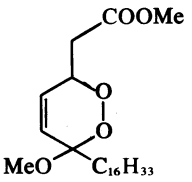
In one of his first contacts with marine natural product chemistry, R. J. Wells joined Baker and Hawes in the investigation of constituents of a Queensland sponge (*Adocia* sp) and they succeeded in crystallising a novel $C_{22}H_{32}N_2$ substance which was saturated in the tetracyclic ring system and confirmed by Oberhänsli as hexadecahydro - 1α,2β,5β,3α - tetramethyl - 1,8 - pyrenediyl-diisocyanide (XLVI) by X-ray crystal analysis.[53] This unsymmetrically substituted hexadecahydropyrene was the first reported diisocyanide isolated from a marine organism.



XLVI

Wells has subsequently isolated two isomeric monoisocyanides from the same sponge, and Fattorusso,[54,55] Minale[56] and Scheuer[57] have since reported on isocyanides from sponges found in areas other than in Australian waters.

From a sponge of the genus *Chondrilla* from the Queensland coast Wells[58] isolated a novel peroxyketal (XLVII), chondrillin, in 6% dry weight yield. A representative of the rare series of C_{22} lipids, the compound was optically active, and was therefore formed by an enzyme mediated process.

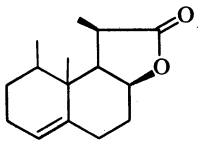


XLVII

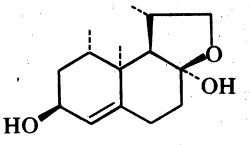
Chondrillin (XLVII) was stable at room temperature, slowly decomposed by acids and extremely sensitive to inorganic bases and to amines.

In this early period at James Cook University of North Queensland, Wells continued to locate novel marine substances, when with Dunstan he isolated from an alcyonarian, *Paralemnalia digitiformis*, a new sesquiterpene lactone (XLVIII), which crystallised from the original hexane extract.[59]

During 1975 Tursch and coworkers[60] isolated from sundried specimens of the Indo-Pacific alcyonarian *Lemnalia carnosa*, (collected in the Lesser Sunda Islands (Indonesia)), a sesquiterpene alcohol (XLIX) having the same novel nonisoprenic carbon skeleton as the lactone (XLVIII). Tursch[60] has named the alcohol (XLIX) lemnacarnol and Wells and Dunstan[59] have adopted the derived name lemnalactone for (XLVIII).



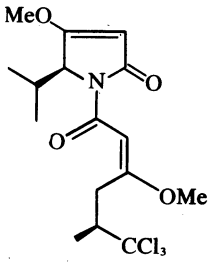
XLVIII



XLIX

The stereochemistry of lemnacarnol (XLIX) was established by X-ray crystal analysis, and the stereochemistry of lemnalactone (XLVIII) is currently under investigation.

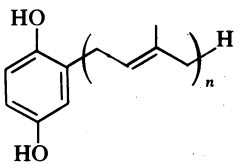
During 1971 Hofheinz undertook analyses of extracts from a variety of marine organisms, while working in the Department of Zoology, University of Queensland with Endean. From a sponge *Dysidea herbacea* Dunstan and Hofheinz isolated the novel compound 5 - isopropyl - 4 - methoxy - 1 - (6,6,6 - trichloro - 3 - methoxy - 5 - methyl - 2 - hexenoyl) - 3 - pyrrolin - 2 - one (L), the structure of which was confirmed by Oberhänsli by X-ray crystal analysis.[61] At this time the compound (L) was the only marine derived substance in which chlorine was present as the only covalently bound halogen, although several examples existed where chlorine and bromine were both present.



L

Subsequent to this early yield of novel compounds, the more detailed and systematic screening of marine organisms within RRIMP has produced a preponderance of organic compounds of structural types similar to those found in related species from other shorelines, the Australian compounds often providing missing links in examples known to date.

For example the prenyl-1,4-benzoquinols of formulae



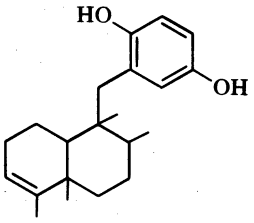
LI

are found in marine sponges. To the end of 1973 four members of this series had been reported from "overseas" species.

(LI) $n = 4$ 2-tetraprenyl-1,4-benzoquinol: *Ircinia muscarum*[62]
(LI) $n = 6$ 2-hexaprenyl-1,4-benzoquinol: *I. spinosula*[63]
(LI) $n = 7$ 2-heptaprenyl-1,4-benzoquinol: *I. spinosula*[63]
(LI) $n = 8$ 2-octaprenyl-1,4-benzoquinol: *I. spinosula*[63]

Kazlauskas, Murphy, Quinn and Wells, the RRIMP chemists involved in isolations and characterizations up to July 1975, found LI ($n = 2$), 2-diprenyl-1,4-benzoquinol, LI ($n = 4$), and LI($n = 5$), 2-pentaprenyl-1,4-benzoquinol in the sponge *Ircinia ramosa*. Whilst overseas workers have subsequently reported the occurrence of LI ($n = 2$) in a tunicate (*Aplydium* sp),[64] the member LI ($n = 5$) remains, at this stage, unique to Australian species.

Other more complex 1,4-benzoquinols have been isolated by the RRIMP group, e.g. avarol (LII), the novel sesquiterpenoid-1,4-benzoquinol from a sponge (*Dysidea* sp).



LII

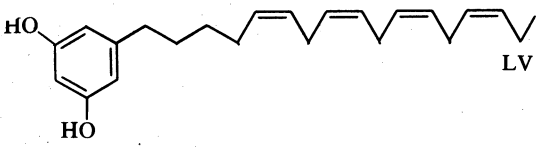
The same compound was reported by Minale and coworkers from the sponge *Dysidea avara*, and they have proposed that the rearranged drimane skeleton could be derived from farnesylpyrophosphate, by cyclisation to an intermediate drimane skeleton cation, followed by a "Friedo" rearrangement and subsequent deprotonation.[65]

An unclassified Australian brown alga has been found to contain an extensive series of compounds including the known 1,6,9,12,15-heneicosapentaene (LIII) and 1,6,9,12,15,18-heneicosahexaene (LIV), which have been reported from marine algae.[66,67]

LIII

LIV

The principal constituent (*ca.* 40% of the total petroleum ether extract) was the novel heptadecatetraenylresorcinol (LV).

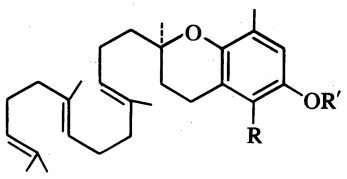


LV

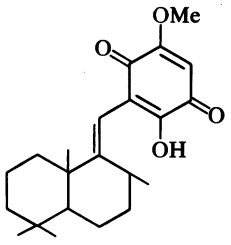
Of the four other substances isolated, two have been characterized (LVII and LVIII) and may be considered as derived from aromatic ring substituted tetraprenyl-1,4-benzoquinols. The compound LVII is the methyl ether of the recently described δ-tocotrienol (LVI), isolated from a Japanese marine alga *Sargassum tortile* and believed to be an active component which induces the settling of the swimming larvae of the hydrozoan *Coryne uchidai*.[68,69]

Australian marine organisms have also yielded a series of compounds which may be regarded as derivatives of 2,5-dihydroxy-1,4-benzoquinones.

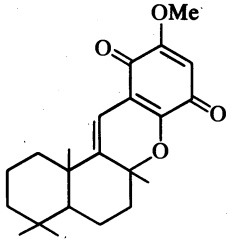
The sponge Stelospongia canalis occurs in an orange-coloured form and also in a yellow-coloured form. From the orange-coloured form, the RRIMP chemists characterised four novel quinones, LIX, LX, LXI, and LXII. These quinones were absent from the yellow-coloured



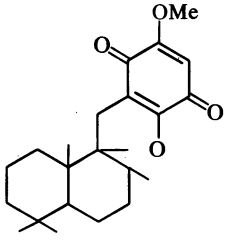
(LVI) R = H, R′ = H
(LVII) R = H, R′ = Me
(LVIII) R = Me, R′ = Me



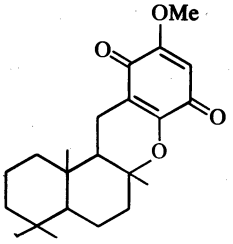
LIX



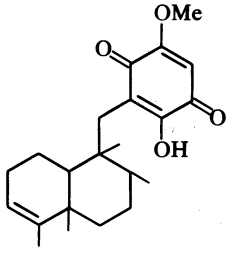
LX



LXI



LXII



LXIII

form which contained the hydroxyquinone LXIII featuring a rearranged drimane skeleton.

It is significant that those sponges which contain terpenoid compounds formed by successive head-to-tail linkages of isoprene units have very low content of sterols, and it must be concluded that, in these species, tail-to-tail dimerisation of two farnesyl units to give triterpenes and sterols, is not a favoured process. Rather, terpenes from C_{15} to C_{45}, formed by head-to-tail condensation of isoprene units, are found in several species.

In this presentation we have already noted several structures which result from polyprenyl units linked to a 1,4-quinol or a 1,4-quinone.

Minale and co-workers in Naples have reported a large number of C_{21} furanoterpenes and Minale has postulated that these C_{21} furanoterpenes should be considered biogenetically as truncated sesterterpenes.[76]

In this conference Dr. R. J. Wells will present detailed evidence concerning the furans isolated and characterised within RRIMP.

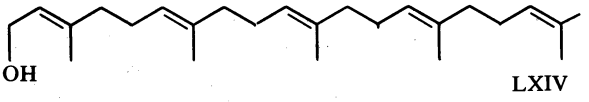
A significant finding has been that an Australian *Fasciospongia* contains the first reported example of geranylfarnesol (LXIV) from marine sources, geranylfarnesol being a probable precursor of sesterterpene tetronic acids derived from sponges of the genus *Fasciospongia.*

Wells has noted that if one considers the C_{25} terpenoids these fall into two main groups.

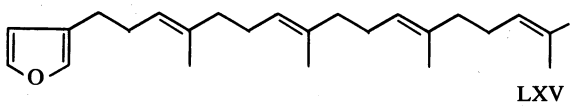
(i) The essentially linear series of sesterterpenes terminated by a furan at one end and containing a tetronic acid moiety at the other end and

(ii) the tetra- or pentacyclic analogues which do not terminate in furan moieties but always in groups which might be regarded as furan synthons.

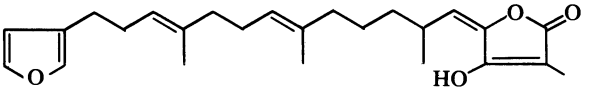
In the Australian sponge *Fasciospongia fovea* geranylfarnesol (LXIV) cooccurs with the known compounds furospinosulin-1 (LXV)[63] and variabilin (LXVI).[77]



LXIV

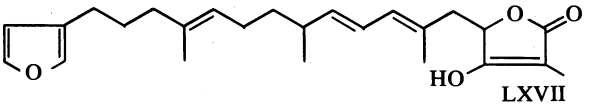


LXV

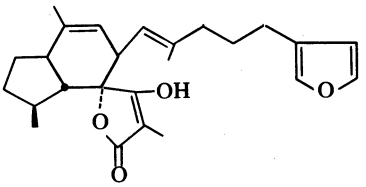


LXVI

New tetronic acid derivatives have been found in Australian *Ircinia* species. From *I. halmiformis* the tetronic acid LXVII has been characterised and from a Barrier Reef *Ircinia* species the tetracyclic tetronic acid LXVIII has been isolated as a crystalline substance, the structure of which was established by X-ray crystal analysis.[78] Clearly LXVIII could be derived from a 4+2 cyclisation of a didehydrofasciculatin.

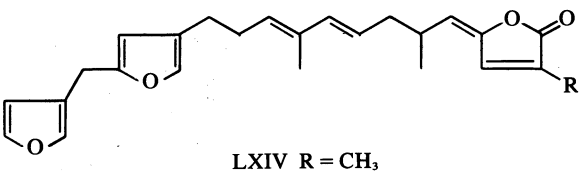


LXVII



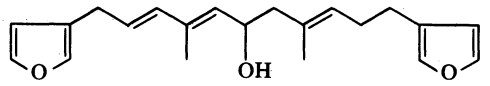
LXVIII

Two new sesterterpenes (LXIX) and (LXX) in which the usual tetronic acid moiety occurs in each case as a γ-lactone have been identified from an unclassified Australian sponge.

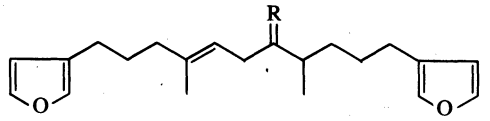


LXIV R = CH_3
LXX R = CH_2OH

The presence of C_{21} degraded furanoterpenes in Australian *Spongia* species has been demonstrated by tetradehydrofurospongin-1 (LXXI) and by the novel unsymmetrically oxygenated C_{21} furanoterpenes, furospongenol (LXXII) and furospongenone (LXXIII).

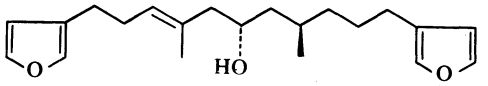


LXXI



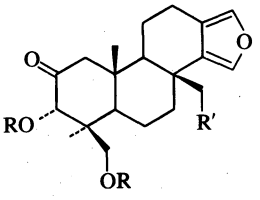
LXXII R = H, OH
LXXIII R = O

Five Australian *Spongia* species investigated at RRIMP have yielded different major metabolites: furospongin-1 (LXXIV), tetradehydrofurospongin-1 (LXXI), a series of tetracyclic diterpenefurans (LXXV-LXXXII), and the compound furospongenol (LXXII). The taxonomic identification of *Spongia* and related species has caused many problems, and it is hoped that further chemical work may yield a consistent pattern which would facilitate taxonomy.

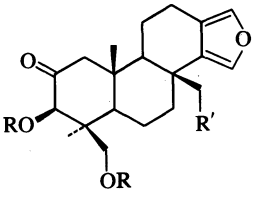


LXXIV

A series of eight tetracyclic diterpene furans has been obtained from various extractions of a common Barrier Reef sponge (*Spongia* sp). Structures LXXV-LXXXII have been proposed on the basis of spectral and chemical evidence, and confirmed by X-ray single crystal structure of LXXVIII.



LXXV to LXXVIII

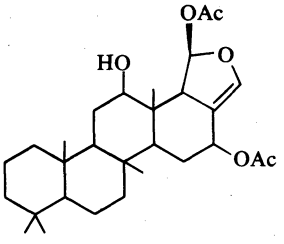


LXXIX to LXXXII

LXXV R = R′ = H
LXXVI R = Ac, R′ = H
LXXVII R = H, R′ = OH
LXXVIII R = Ac, R′ = OAc

LXXIX R = R′ = H
LXXX R = Ac, R′ = H
LXXXI R = H, R′ = OH
LXXXII R = Ac, R′ = OAc

An example of a furan synthon is provided by heteronemin (LXXXIII) from the sponge *Heteronema erecta.*

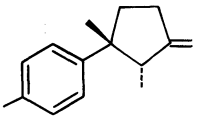


LXXXIII

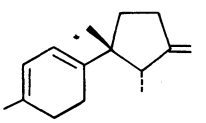
Little work has been published on sterols from Australian sponges but an extensive survey based on GC–MS analysis has been undertaken by Bergquist and Hofheinz, and publication of this study is expected in the near future.

Preliminary work at RRIMP indicates that the local red algae will provide interesting supplementary information to that obtained on "overseas" species.

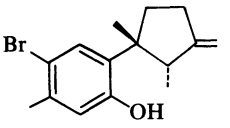
Red algae have been shown to give rise to an extensive series of halogenated sesquiterpenes, and *Laurencia glandulifera* and *L. nipponica* give rise to the hydrocarbon laurene[70–72] which is found substituted and isomerised in many examples of *Laurencia* sp. In Australia an unidentified red alga yielded laurene, (LXXXIV), dihydrolaurene, (LXXXV), *allo*-laurinterol, (LXXXVI) and (LXXXVII).



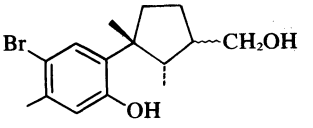
LXXXIV



LXXXV

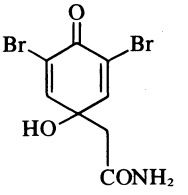


LXXXVI



LXXXVII

Another halo-compound isolated at RRIMP, from an unclassified sponge, is the known compound 4-acetamido-2,6-dibromo-4-hydroxycyclohexadienone, LXXXVIII.[73–75]



LXXXVIII

The work of RRIMP has considerably expanded the knowledge of natural products from Australian marine organisms.

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