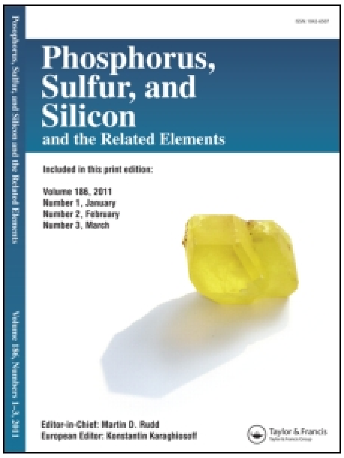

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BIOLOGICALLY ACTIVE SULFUR COMPOUNDS FROM MARINE ORGANISMS

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Abstract The isolation and structure elucidation of selected naturally occurring marine organic sulfur compounds exhibiting biological activity are discussed.

INTRODUCTION

Historically, natural products chemistry heralded the rise of modern organic chemistry. In contrast the appearance of a significant number of investigations of marine natural products is of a comparatively new date reaching back only about 30 years[1]. The first marine natural product to have its structure correctly deduced and proven, Tyrian purple, was isolated during the summer of 1908. Although Tyrian purple does not contain sulfur, it is produced from sulfur-containing precursors. Consequently, the fixpoint for the birth of the chemistry of marine natural sulfur compounds can be identified quite exactly as the year 1909 where Friedländer's paper appeared.[2] The rate of progress may be illustrated by the fact that the immediate precursor of Tyrian purple, tyriverdin, was finally identified in 1978.[3]

Concomitantly with the elevated activity in marine natural products research the number of papers on marine natural sulfur compounds has grown considerably. The following account highlights the author's own involvement within this area. The interested reader is referred to a recent review for further details, an overview of the whole area and a state of the art.[4]

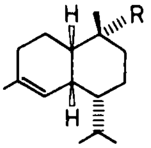
MARINE ISOTHIOCYANATES

In the early 1970'ies intensive research was carried out by Scheuer and co-workers in Honolulu to determine the nature of the chemical defence substances in nudibranch mollusks. Nudibranchs lack a protective shell and are often brightly colored. In spite of these disadvantages they are rarely preyed upon by other marine animals. The reason for this apparent paradox is, at least in some cases, the presence of toxic feeding deterrents in the mollusk.

The structure determination of a toxin from the nudibranch *Phyllidia varicosa* was severely hampered by the inavailability of sufficient quantities of toxin. Simultaneously a marine sponge *Halichondria* sp. was examined owing to an established antibacterial activity. The investigation of the sponge concluded in the identification of a sesquiterpenoid- and a diterpenoid isothiocyanate (**1** and **2**) accompanied by the corresponding isocanides (**3** and **4**) and formamides (**5** and **6**).[5,6] The sesquiterpenoid isothiocyanate is derived from the 4-amorphene skeleton and the diterpenoid from geranyllinalool.

Data secured in the *Halichondria* investigation were helpful in determining the identity of the nudibranch products.

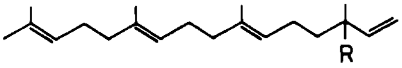
The identity of the nudibranch allelochemicals was established as a pair of isomeric sesquiterpenoid iso-



1: R= -N=C=S

3: R= -N=C

5: R= -NHCHO



2: R= -N=C=S

4: R= -N=C

6: R= -NHCHO

cyanides. The idea that the mollusk sequestered these compounds from a prey organism was substantiated by the finding of isocyanides in a sponge and the sponge, preyed upon by *P. varicosa*, was eventually located by numerous explorative divings around Oahu, Hawaii. The latter sponge was shown to contain the isocyanides isolated from the nudibranch.[7,8]

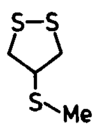
This work was the first to chemically investigate the allelochemical relationship between a nudibranch and a marine sponge. It has later been succeeded by numerous comparable studies.[9]

INSECTICIDAL AND HERBICIDAL COMPOUNDS

Ecological investigations of green algae of the order Charales sustain the hypothesis of the presence of chemicals capable of controlling the growth of phytoplankton, zooplankton as well as bacteria.

Charales are freshwater species although some members will tolerate brakish conditions.

In the case of *Chara globularis* Thuillier 1799 we found these activities associated with 4-methylthio-1,2-dithiolane (**7**), 5-methylthio-1,2,3-trithiane (**8**)[10,11] and charamin (**9**, 4-azoniaspiro[3,3]heptane-2,6-diol)[12].



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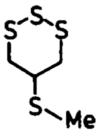

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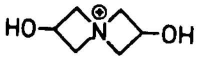

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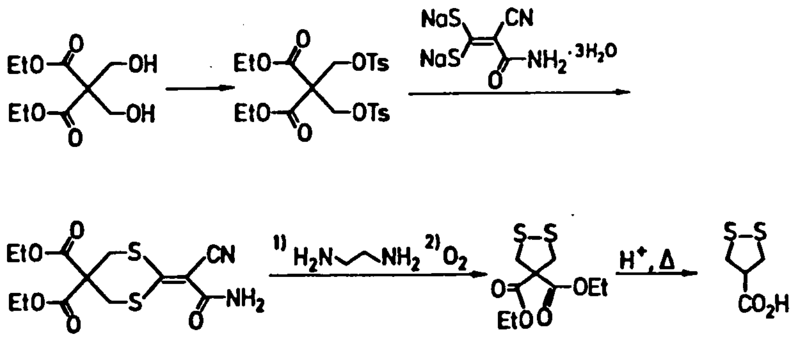
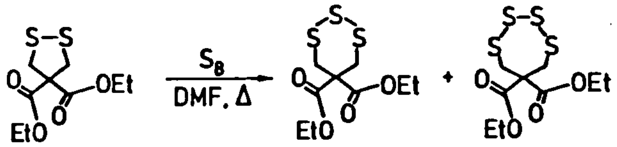
In order to gain access to larger amounts of especially 7, which showed promise as a commercial insecticide, a synthesis of the sulfur compounds was developed.[13] The mechanism of the insecticidal activity was investigated[14] and a series of related compounds was prepared and tested for activity.[15]

Charatoxin, 7, is reminiscent of nereistoxin (4-dimethylamino-1,2-dithiolane) isolated from the marine annelids *Lumbriconereis heteropoda* and *Lumbrinereis brevicirra*.[16] A derivative of nereistoxin has been marketed as an insecticide for 20 years. Another member af this exclusive class of natural products, asparagusic acid (1,2-dithiolane-4-carboxylic acid) from etiolated *Asparagus officinalis*, is a powerful growth inhibitor for several plants. Generally speaking, the 4-substituted 1,2-dithiolanes seem to have specific physiological activities.[4]

Owing to the standing interest in the potential biological activity of these sulfur compounds a more controled preparation of 1,2-dithiolanes was made[17] (Eq. 1). Simultaneously, a procedure for the synthesis of the hitherto unknown 1,2,3,4-tetrathiepanes was carried out (Eq. 2).[18] The latter compounds are at present being investigated with respect to their pharmacological activity.



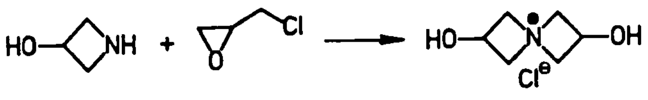
(1)



(2)

The potential ecological significance of 9 was demonstrated by the determination of the photosynthesis inhibiting activity towards a natural population of phytoplankton where concentrations around 3 μM completely arrested photosynthesis.[11]

Charamin (9) was isolated by a bioassay-guided procedure and synthesized (Eq. 3.).[12]



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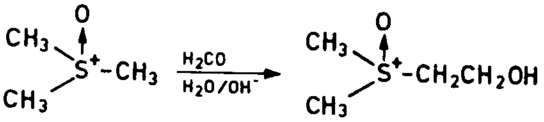
(3)

An improved synthesis is at present being explored in order to produce sufficient material for further biological studies and to explore the stereochemistry of 9.

A SULFOXONIUM ION - DOGGER BANK ITCH

Dogger Bank itch is an eczematous contact dermatitis contracted mainly by fishermen working in the Dogger Bank area of the North Sea. This allergy may be totally disabling. The sensibility, once aquired, is lifelong and there is no cure for outbreaks of the allergy. Using path tests on sensibilized volunteers, the activity of extracts of the cuasative organism, the bryozoan *Alcyonidium gelatinosum*, was eventually traced to a fraction of the aqeuous extracts. Further bioassay guided fractionation finally resulted in a mixture, which according to instrumental neutron activation analyses contained only common salts and an organic compound. The structure of the latter was deduced from spectroscopic studies and verified by synthesis (Eq. 4.). The synthetic product displays the full biological activity of the natual agent.[19]

From a structural point of view the hapten, (2-hydroxyethyl)dimethylsulfoxonium ion (**10**), is interesting as it is the first example of a naturally occurring sulfoxonium ion. As a class sulfoxonium ions are only represented by a few synthetic examples.



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(4)

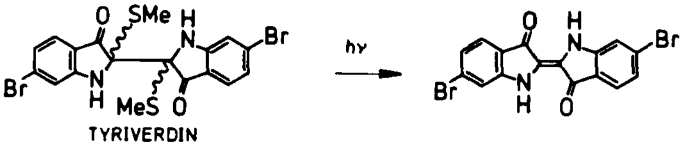
The synthesis was performed by carefully controlled base catalyzed addition of formaldehyde to trimethylsulfoxonium ion. Access to the synthetic hapten has allowed the identification of the allergy as a Type 4 reaction and in addition has made possible the unambiguous diagnosis of the condition.[19-23]

TYRIVERDIN - TYRIAN PURPLE

Tyrian purple has been used for dying for at least 3500 years. The coloring matter originates from the hypobranchial gland of various mollusks of the families Muricidae and Thaisidae. Precursors present in the gland during the coloring process go through a series of reactions evidenced by a series of color changes ending in a deep purple-red.[24,25] Friedländer in his work on the structure succeeded in isolating 1.4 g Tyrian purple (**11**) from 12,000 snails of the species *Murex brandaris*.[2]

The immediate precursor for Tyrian purple is green and is therefore named tyriverdin. The structure of tyriverdin (**12**) has been the subject of debate for many years. The last reaction in the formation of Tyrian purple is a photochemical reaction and the smell accompanying the process strongly indicates that dimethyl disulfide is released.

By synthesizing **12** we found it to be photochemically reactive forming Tyrian purple and dimethyl disulfide with a quantum yield in excess of 5 (Eq. 5). The synthetic compound on comparison with tyriveridin isolated from *Nucella lapillus* proved identical in all respects.[3]



(5)

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