LOW MOLECULAR WEIGHT SULPHUR-CONTAINING COMPOUNDS IN
NATURE: A SURVEY

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Abstract – Sulphur, besides being an integral element of several macro-
molecular cell constituents, appears in a series of low-molecular weight,
partly ubiquitously distributed compounds, e. g. S-containing protein ami-
no acids, coenzyme A, S-adenosyl methionine, thiamine, and biotin, with-
out which a steady state of living cells cannot be maintained. These, how-
ever, are not included in the present discussion. Rather, an attempt is
being made to illustrate, by way of examples, the vast structural varia-
tion in other organic sulphur compounds with, as far as we know, a dis-
continuous distribution within the plant and animal kingdom. The chemi-
cal characteristics of these compounds are variegated, encompassing,
inter alia, mercaptans, thiolesters, disulphides, sulphides (linear, cyc-
lic, aromatic, and heterocyclic), amino acids, thioglycosides, terpe-
noids, sulphoxides, sulphones, and sulphates, the origin, transforma-
tions, and biological importance of which are mostly unknown. A bird's-
eye view of the area is presented in the hope that this, however incom-
plete and blurred, may reveal some less obvious relationships and thus
serve to invigorate further activity within the field.

INTRODUCTION

'Sulphur in the Bible', the title of a memorable after-dinner presentation by professor D.
Ginsburg at the previous meeting of this series, tellingly attests to the importance and an-
tiquity of the topic we are here concerned with. Sulphur-containing enzymes, structural
proteins, nucleosides, amino acids, vitamins, and coenzymes constitute an extensive ar-
ray of primary cell constituents without which a steady state of living cells cannot be main-
tained. As we know, the ability of microorganisms and plants to convert sulphate into or-
ganic sulphur compounds, unparalleled in animals, is not limited to the production of the
ubiquitous cell constituents outlined above. A vast and rapidly increasing number of addi-
tional, i. e. 'secondary' sulphur compounds, encountered in natural materials, bears wit-
ness to an amazing versatility in the synthetic capacity of non-animal tissues. Discontinu-
ous distribution and mostly poorly understood biological positions are characteristics of
the secondary sulphur compounds. The ensuing survey will be limited to selected groups
of these in an endeavour to illustrate the astounding variety in structural type and, at the
same time, to underline some prominent biosynthetic features responsible for this diversity.

The topic, thus defined, is one of rapid development and considerable recent interest.
Though the class of natural sulphur compounds has hardly ever been monographed in its
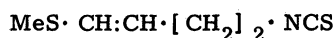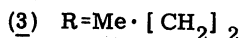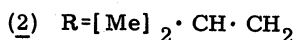entity, selected and important groups of such products have formed the subject of thorough

reviews on various occasions. The present discussion will mostly be limited to recent developments within certain areas, selected entirely according to the interests of the author, and,therefore, not necessarily representative of the field in general. The lack of detailed insight into the stream of biosynthetic processes leading to the multitude of natural sulphur compounds necessitates an alternative arrangement of these to facilitate discussion. Any such division will, perforce, be artificial. Here, chemical functionality shall, arbitrarily, serve to order the discussion.
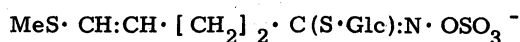
DICOORDINATE SULPHUR COMPOUNDS

The pronounced capacity of sulphur to enter into numerous molecular combinations, varying in the character and number of ligands, as well as in oxidation step, is reflected in the secondary sulphur compounds of natural origin. Most of these share with the vital, primary sulphur compounds the content of sulphur in its lowest oxidation step, $i.$ $e.$ in a sulphidic, dicoordinate arrangement, $R^1 \cdot S \cdot R^2$. We shall begin our discussion here.

Mercaptans and Thiolesters

Mercaptans. The class of mercaptans (thiols), encompassing compounds of vital biological significance (cysteine, Co-enzyme A,etc.), often occurs together with that of disulphides, $R \cdot S \cdot S \cdot R$, the oxidized counterparts. Accounts of early findings of mercaptans in biological materials arising from plants and microorganisms have previously been presented (Ref. 1, 2, 3) and shall not be repeated here. The obnoxious smell of volatile thiols is properly exemplified by the recent demonstration of crotyl mercaptan (1) and isopentyl mercaptan (2), but not,as previously maintained, butyl mercaptan (3) as parts of the odorous components of the striped skunk (Ref. 4).

$R \cdot CH_2SH$ $MeS \cdot CH:CH \cdot [CH_2]_2 \cdot NCS$

(1) $R = Me \cdot CH:CH$ (4)

(2) $R = [Me]_2 \cdot CH \cdot CH_2$ $MeS \cdot CH:CH \cdot [CH_2]_2 \cdot C(S \cdot Glc):N \cdot OSO_3^-$

(3) $R = Me \cdot [CH_2]_2$ (5)

Mercaptans, as encountered in living matter, are hardly uniform in their origin. We know of natural products, such as thiolesters and vinylic sulphides, that readily undergo hydrolysis to thiols, occasionally even in the absence of enzymes; the radish mustard oil (4), and the glucosinolate (5), whence it derives, are representative of the latter of these types. But we also know of the existence of C-S-lyases, catalyzing the fragmentation of naturally occurring S-substituted L-cysteines (6) into mercaptans (7), pyruvic acid, and ammonia.
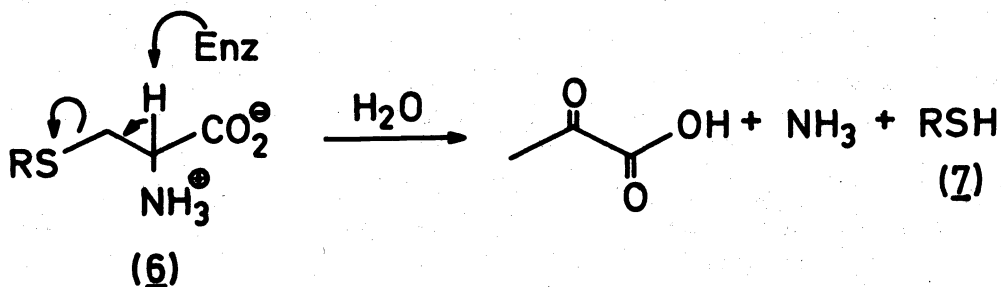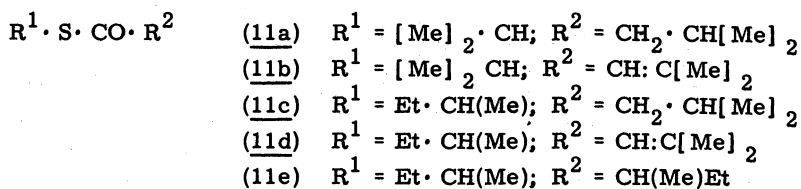
Thus, S-alkylation of L-cysteine,followed by fragmentation, attributes to cysteine the task of carrying sulphur into mercaptans and thence into sulphides, disulphides etc. In fact, the author favours the opinion, admittedly supported by intuition rather than compelling evidence that, by and large, Nature knows no other way of introducing sulphidic sulphur into organically bound form than via cysteine. In keeping herewith is the documented in vivo incorporation of sulphur from L-cysteine into several sulphur compounds, such as the penicillins, ergothioneine, glucosinolates etc. A much broader insight into the anabolic pathways to sulphur compounds is required, however, before the supposition, aired above, can be confirmed or refuted.

It would be of much interest, for example, to know the in vivo path, by which the diastereomeric p-menthane-8-thiol-3-ones (8) and (9), accompanying (−)-pulegone (10), and other monoterpene ketones, in Buchu leaf oil, are produced (Ref. 5, 6).

(8) A = H; B = [Me]$_2$·C·SH
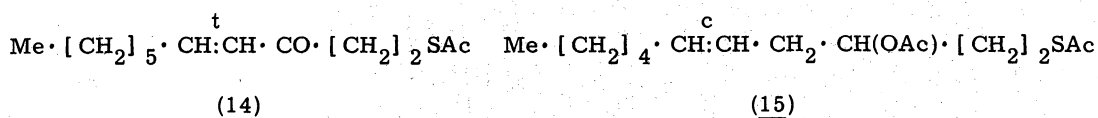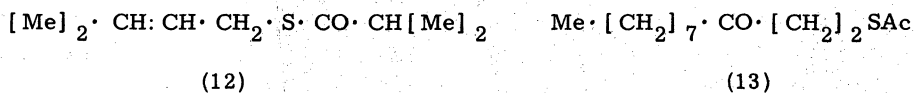
(9) A = [Me]$_2$·C·SH; B = H
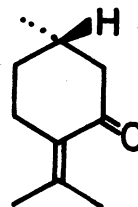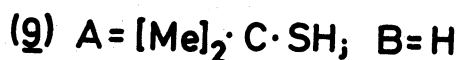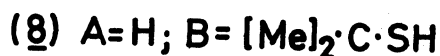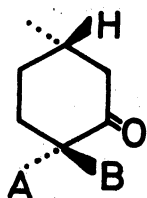
(10)

Thiolesters. Apart from esters of Coenzyme A, thiolesters (11), here regarded as acylated mercaptans, have only recently been recognized as a potentially important class of natural sulphur compounds. In 1971, Burrell et al. (7) reported the occurrence of the esters (11a)-(11e) in Galbanum oil, a volatile fraction arising from Ferula species. Only

$$R^1 \cdot S \cdot CO \cdot R^2$$

(11a)	R^1 = [Me]$_2$·CH; R^2 = CH$_2$·CH[Me]$_2$
(11b)	R^1 = [Me]$_2$CH; R^2 = CH:C[Me]$_2$
(11c)	R^1 = Et·CH(Me); R^2 = CH$_2$·CH[Me]$_2$
(11d)	R^1 = Et·CH(Me); R^2 = CH:C[Me]$_2$
(11e)	R^1 = Et·CH(Me); R^2 = CH(Me)Et

after chromatography, or under adverse gas chromatography conditions of these esters, could disulphides be detected in the essential oil (Ref. 7). To what extent and through which reactions the non-symmetrical disulphides, reported in the essential oils of Galbanum and the closely related asafetida, derive from thiolesters, remains unknown. Interestingly, Rivett (8) recently corrected a previously recorded finding of butyl 1-pentenyl disulphide in the essential oil of Agathosma species (Rutaceae) to the thiolester (12), obviously of isoprenoid origin. Other natural thiolesters are the C$_{11}$-thiolacetates (13)-(15), encountered in species of the odorous, marine alga genus Dictyopteris (Ref. 9, 10).
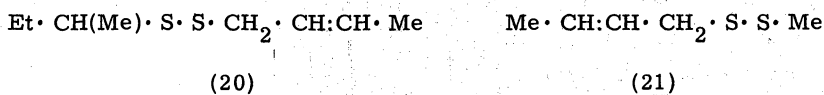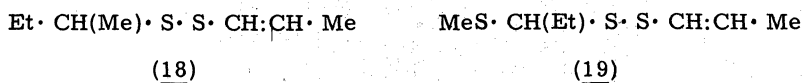
[Me]$_2$·CH:CH·CH$_2$·S·CO·CH[Me]$_2$ Me·[CH$_2$]$_7$·CO·[CH$_2$]$_2$SAc

(12)   (13)

                              t   c
Me·[CH$_2$]$_5$·CH:CH·CO·[CH$_2$]$_2$SAc   Me·[CH$_2$]$_4$·CH:CH·CH$_2$·CH(OAc)·[CH$_2$]$_2$SAc

(14)   (15)

A problem of long standing: the chemical identity of the odoriferous principle, produced
in the urine of some humans, after ingestion of asparagus has recently found its solution.
The ability to produce the odour, long attributed to methyl mercaptan, is apparently con-
trolled by a single autosomal dominate gene, supposedly possessed by slightly less than
half of all humans. About a year ago, White (11) presented convincing evidence that the
two methylthiol esters, (16) and (17), in approximately equal amounts, are the compounds
responsible for the urine odour. Their metabolic origin, however, remains an unsolved
problem.

CH$_2$:CH·CO·SMe   MeS·[CH$_2$]$_2$·CO·SMe

(16)   (17)

Disulphides

Linear. Symmetric disulphides, RS·SR, most likely produced from mercaptans by oxida-
tion, are rather common in natural materials. The recent demonstrations of dimethyl di-
sulphide as an attractant pheromone in the vaginal secretion of the hamster (Ref. 12), and
of diisopentyl disulphide as a component of the odorous secretion of the mink (Ref. 13), sug-
gest a broader biological significance of even simple sulphur compounds.

Non-symmetric disulphides, R^{1}S·SR^2, have been repeatedly recorded from plant sources,
notably in essential oils (cf. Ref. 2). Their origin is obscure and not easy to comprehend.
As pointed out above, the claim as to the presence of unsaturated disulphides in essential
oils from species of Agathosma (Rutaceae) has lately been retracted (Ref. 8), whereas re-
cent studies (Ref. 14, 15) have served to specify the structure and detailed stereochemi-
stry of the disulphides (18), (19), and (20), present in the essential oil of asafetida.

Et·CH(Me)·S·S·CH:CH·Me   MeS·CH(Et)·S·S·CH:CH·Me

(18)   (19)

Et·CH(Me)·S·S·CH$_2$·CH:CH·Me   Me·CH:CH·CH$_2$·S·S·Me

(20)   (21)

The finding of crotyl methyl disulphide (21) in the volatile skunk scent (Ref. 4) reminds
us that non-symmetrical disulphides are not restricted to the plant kingdom.

Cyclic. Ring systems incorporating the disulphide linkage, illustrated by α-lipoic acid as example, are not uncommon in products of natural derivation. Lenthionine (22), an important constituent of the odorous principle of the Japanese mushroom Lentinus edodes ('shiitake') (Ref. 16), derives enzymically, in the fruiting bodies, from lentinic acid, formulated as (23) (Ref. 17).
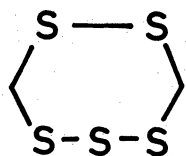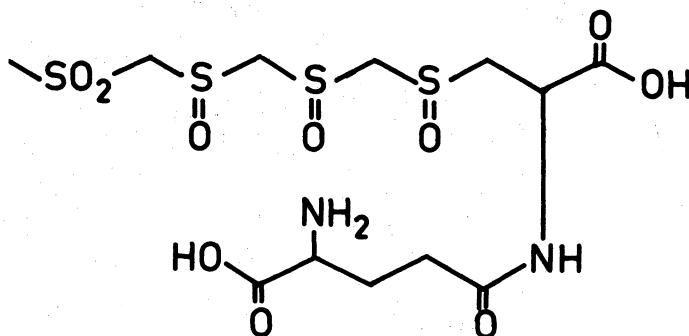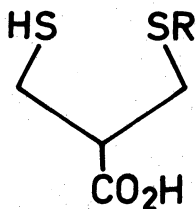
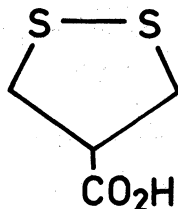A number of closely related plant growth inhibitors, isolated from asparagus end exerting activities comparable to that of abscisic acid, are disulphides, or obvious derivatives thereof: (24)-(28) (Ref. 18, 19).
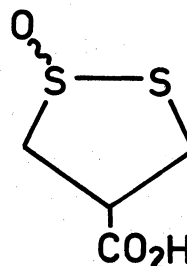
Members of the mangrove family (Rhizophoraceae) possess a striking capacity to elaborate cyclic disulphides in varying disguises. Nitrogeneous representatives, classifiable as alkaloids, have been previously reviewed (Ref. 20); the simple carbinols (29)-(31) constitute novel additions to the class (Ref. 21, 22). The biosynthetic origin of the dithiolanes is unknown. One might speculate on a relationship between the unique habitat of the mangrove and the curious synthetic specialization.
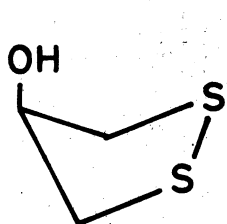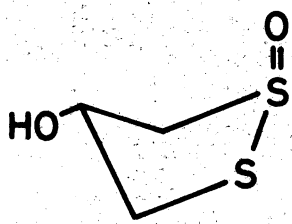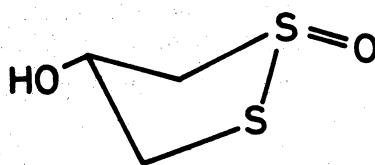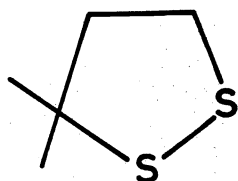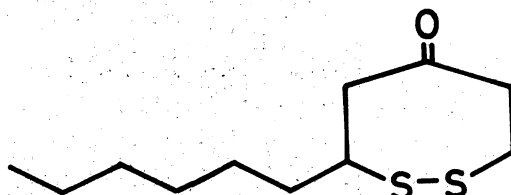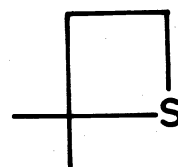
(29)   (30)   (31)

(32)   (33)   (34)

The occurrence of the cyclic disulphides (32) and (33), along with the mono-sulphur spe-
cies (34) and (14), in the mink secretion (Ref. 13) and Dictyopteris algae (Ref. 9), respec-
tively, is compatible with the biosynthetic intermediacy, in these cases, of molecular spe-
cies such as $R^1R^2C{:}CH{\cdot}[X]{\cdot}S{\cdot}SH$, or their formal equivalents. Other, and unknown,
routes must apply in the in vivo production of trithiolaniacin (35) (Ref. 23) and the linear
trisulphide (36) (Ref. 24), both isolated from root material of Petiveria alliaceae (Phyto-
laccaceae).
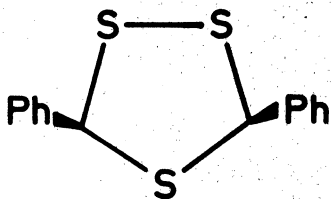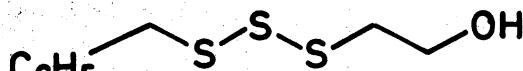
(35)   (36)

(37)

Important disulphides, which shall not be discussed here, however, are the fungal epidi-
thio-compounds, comprising e. g. the sporidesmins, aranotins, and gliotoxin.

Sulphides

Simple aliphatic sulphides. Dimethyl sulphide, Me· S· Me, is widely encountered as a product of chemical or enzymic decomposition of non-volatile precursors, often S-methylsulphonium salts, in lower and higher plants (cf. Ref. 1, 2, 3). Nature's predilection for S-methyl derivatives is obvious. Thus, bis-methylthiomethane (37) appears to contribute significantly to the unique and cherished odour of white truffle (Tuber magnatum) (Ref. 25). Though unproven, an in vivo derivation of (37) from djenkolic acid, accomplished through a C-S-lyase action followed by methylation, seems conceivable and should be subjected to experimental studies.

Mustelan, the major component of the secretion from the anal glands of the mink (Mustela vison) and fitchew (M. putorius), has recently been identified as 2, 2-dimethylthietane (34) (Ref. 13), suggesting the involvement of 3, 3-dimethylallyl mercaptan in its formation.

Polyacetylenes, abounding, above all, in Compositae, are widely accompanied by vinylic methyl sulphides (38) and thiophenes (39), arising in vivo by the formal addition of one or two molecular equivalents of hydrogen sulphide, followed by S-methylation or eliminative cyclization:
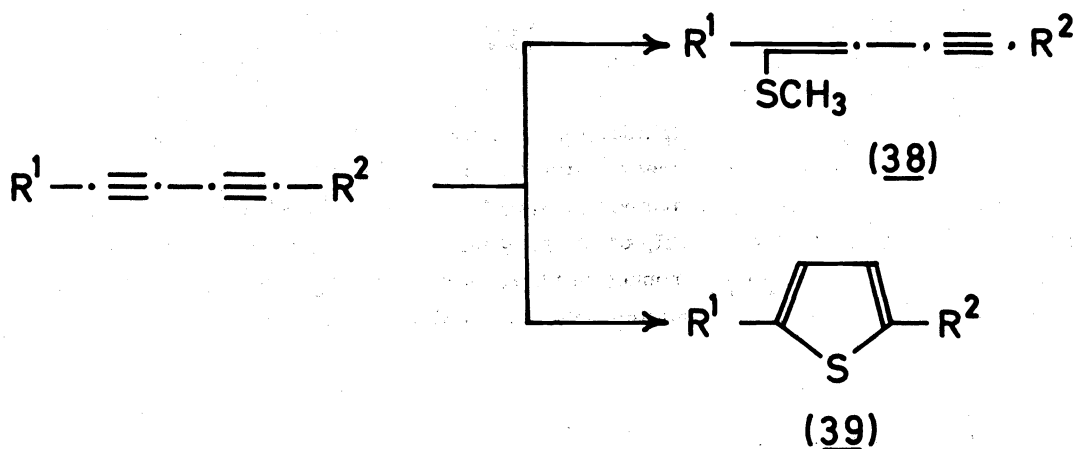

A complete list of naturally occurring polyacetylene-derived sulphur compounds would call for several additions, from within the last years, to the previous compilations (Ref. 20, 26). Though these shall not be specified here, an updated over-all picture would not show fundamental changes.

The unique α-dicarbonyl methyl sulphide (40), identified as a volatile secretion from the anal scent gland of the striped hyena (Hyaena hyaena) (Ref. 27), presents a real challenge with regard to origin and biological significance. Though still in its infancy, the detailed study of mammalian scent materials has already produced results that augur well for an exiting development, also within the field of naturally derived sulphur compounds, including a better understanding of their biological origin and natural function.
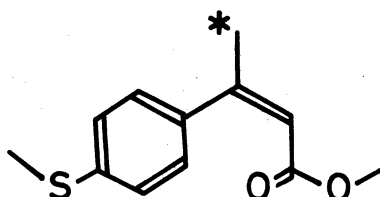
Aromatic sulphides. Thioanisols as natural products are rare, albeit not totally unknown. The in vivo conversion, within Anthemis tinctoria, of dehydromatricaria ester (41) into the thioanisol (42) represents the first documented case of aromatic biosynthesis from a

(40)

(41)

$$H_3\overset{*}{C}\cdot C : C\cdot C : C\cdot C : C\cdot CH : CH\cdot CO_2CH_3$$
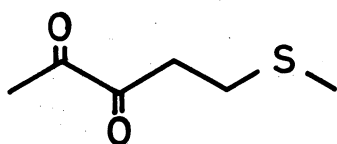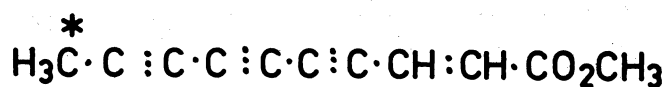
(42)

polyacetylene. The transformation, presenting an intriguing mechanistic problem, invol-
ves specific transfer of a methyl group from a terminal position in (41) to the benzylic
carbon of (42) (Ref. 28). The micrandols A and C are phenanthrene derivatives, possess-
ing the structures (43) and (44) and occurring, together with the 9,10-dihydro derivative
of (43) (micrandol B), in root material of the South American tree Micrandopsis sclero-
xylon (Euphorbiaceae). By inspection, the substitution pattern suggests a mevalonate ori-
gin of the micrandols (Ref. 29). It would be of much interest to learn how the sulphide
functionality is introduced into micrandol C (44).

(43)

(44)

$\left.\begin{array}{l} -SCH_3 \\ \\ -C_{30}H_{61} \end{array}\right.$
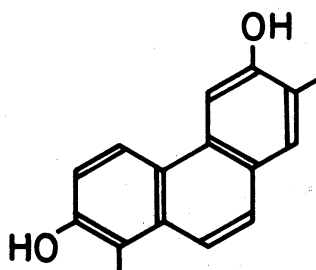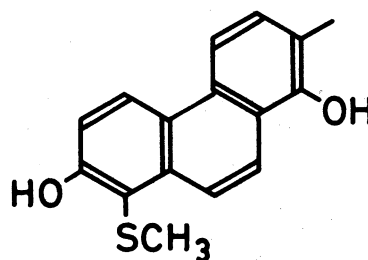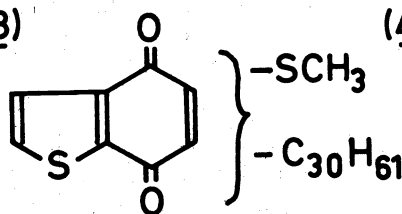
(45)

The bacterium <u>Caldaria acidophila</u>,living in volcanic areas under marginal conditions (pH 1.5-3.5; 75-90°C), elaborates a sulphur-containing pigment, for which the partial structure (<u>45</u>) has been advanced (Ref. 30). Further details, regarding the chemistry and possible biological significance of (<u>45</u>), are awaited with interest.

<u>Sulphur-containing amino acids and alkaloids</u>. No other group of natural sulphur compounds has attracted more interest than that of amino acids, derived, more or less obviously, from cysteine and, to a smaller degree, methionine. The key rôle attributed to cysteine in the <u>in vivo</u> assemblage of organic sulphur compounds is reflected quite obviously in the structures of an impressive series of amino acids from plants. They can be accommodated within the general structures (<u>46</u>) (encompassing a number of sulphoxide analogues) and (<u>47</u>), and include acids of great significance, <u>e.g.</u> as precursors of odoriferous principles. The structurally simple cysteine derivatives have been repeatedly reviewed (cf. <u>e.g.</u> Ref. 2.3) and we shall not discuss them further. The excretion of felinine (<u>48</u>), to

<u>(46)</u>

<u>(47)</u>

<u>(48)</u>
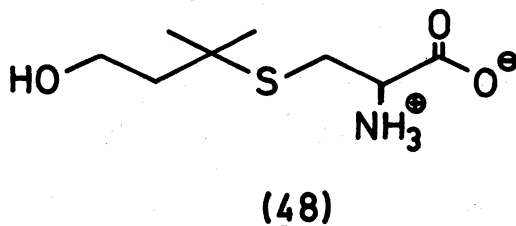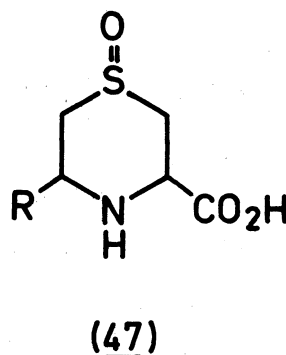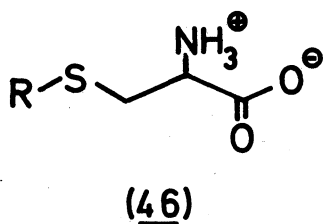
the extent of 175 mg/100 ml, in the urine of members of the cat genus (<u>Felis</u>) (Ref. 31) clearly shows that selective <u>in vivo</u> modification of cysteine is not limited to the plant world.

A vast number of other natural sulphur compounds undoubtedly derive from cysteine, albeit in an often far less transparent fashion. Admittedly, this supposition is supported today more by structural inspections and speculation than by unassailable evidence. However, a gratifying increase in experimental studies within the last few years gives hope that we shall soon possess a more profound understanding of the detailed paths by which cysteine is so multifariously modified in living cells. The biosynthesis of penicillins and cephalosporins, studied for nearly thirty years, has been known for quite some time to involve cysteine (cf. Ref. 32). In the <u>Amanita</u> toxins, a cysteine residue in the peptide

array is curiously attached to the 2-position of a tryptophan unit (<u>49</u>) (Ref. 33), an arran-
gement reminiscent of that prevailing in tyrindoxyl sulphate (<u>50</u>), the precursor of Tyrian
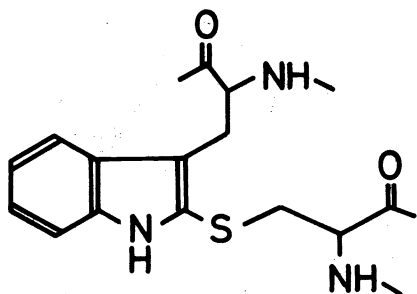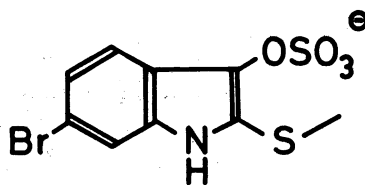
(**49**)   (**50**)

purple in the hypobranchial glands of the Australian mollusc <u>Dicathais</u> <u>orbita</u> (Ref. 34).
The implication of cysteine in the production of (<u>50</u>), possibly <u>via</u> an oxindole intermedi-
ate, can easily be envisaged. Again, cysteine is almost certainly involved in the <u>in</u> <u>vivo</u>
synthesis of the firefly luciferin (<u>51</u>); a successful biomimetic synthesis lends credence
to the suggestion that benzoquinone functions as the second reactant in the biosynthesis
(Ref. 35).
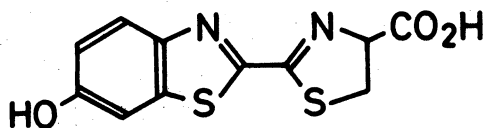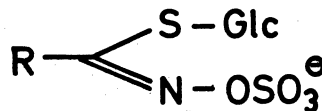
(**51**)   (**52**)

Sulphur-containing alkaloids are still rare when judged on the basis of reported represen-
tatives (cf. the review, Ref. 20). It may very well be, however, that a more systematic
search for such bases should prove highly rewarding.

<u>Thioglycosides</u>. The glucosinolates (<u>52</u>) constitute a large and uniform group of thiogluco-
sides, today encompassing close to 80 individual compounds. Their botanical distribution,
chemical character, reactions, and <u>in vivo</u> synthesis have been formerly discussed (<u>e. g.</u>
Ref. 20,36) and shall not be repeated here.

Apart from the glucosinolates, thioglycosides are rare in Nature. Lincomycin (<u>53</u>) (Ref.
37) and celesticetin (<u>54</u>) (Ref. 38), two antibiotics produced by different actinomycetes,
both possess thioglycosidic linkages, the origin of which seems a matter of considerable
interest.

(53) X= CH$_2$CH$_2$CH$_3$; R^1=H; R^2=CH$_3$

(54) X = H, R^1=CH$_3$

R^2=CH$_2$CH$_2$·O·CO·
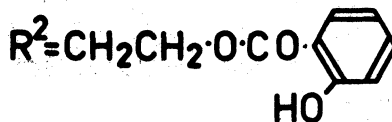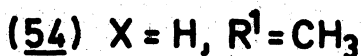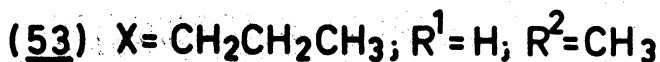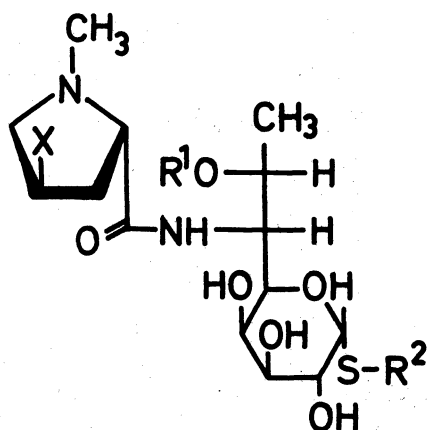
Isothiocyanates. On enzymic hydrolysis, glucosinolates (52) typically give rise to the production of isothiocyanates (mustard oils)(55), the practical and biological importance of which is generally appreciated. As far as we know, however, isothiocyanates as such are not pr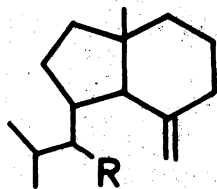esent in undamaged, glucosinolate-containing plant materials. It hence occasioned surprise when a sesquiterpenoid isothiocyanate, axisothiocyanate-1 (56), was first identi-

R·N=C=S

(55)

(56) R= NCS

(57) R = NC

(58) R = NH·CO·H
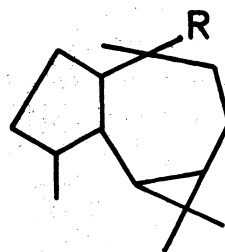
(59) R= NCS

(60) R= NC

(61) R = NH·CO·H

fied in the marine sponge <u>Axinella cannabina</u>, where it cooccurs with larger quantities of the corresponding isocyanide (57) and formamide (58) (Ref. 39,40). The same sponge also produces a similar set of nitrogenous species, (59)-(61), (Ref. 40,41), suggesting a common biosynthetic sequence within the two series. Parallel herewith, two identical sets of nitrogen-containing olefins have independently been established in species of the marine sponge <u>Halichondria</u> from the Pacific, viz. (62)-(64) (Ref. 42,44) and (65)-(67) (Ref. 43, 44).
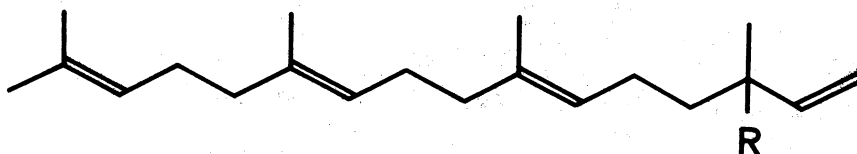
(65) R = NCS

(66) R = NC

(67) R = NH·CO·H
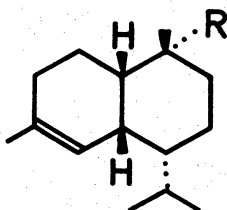
(62) R = NCS

(63) R = NC

(64) R = NH·CO·H

It would indeed be interesting to learn whether Nature knows ways of simulating the well-known, high-temperature conversion of isocyanides and elementary sulphur into isothiocy-anates. At any rate, the sponge isothiocyanates seem to possess no other relationship to the mustard oils, deriving enzymically from glucosinolates, than a purely formal one.

TRI - AND TETRA - COORDINATE SULPHUR COMPOUNDS

Of the many known classes of stable tri- and tetra-coordinate sulphur compounds, several are represented among the constituents of living cells. Sulphonium ions, sulphoxides, sul-phones, sulphonic acids, and organic sulphates all occur in Nature, more or less widely distributed. Most of the tricoordinate species are chiral and hence occur in high enantio-meric purity. The stereochemical aspects of some biologically important sulphur com-pounds have recently been discussed (Ref. 45). The present account has as its limited ob-jective to delineate the chemical groups and draw attention to a few recent developments.

Tri-coordinate sulphur compounds
Sulphonium ions. S-Adenosyl-L-methionine, the reactive species in the biological methyl group transfer, is, of course, the natural sulphonium ion par excellence. The structural-ly simpler S-methyl methionine (68) and β-dimethyl-propiothetin (69) can both serve as natural sources of dimethyl sulphide, resulting from base- or enzyme - induced elimina-tion reactions (cf. Ref. 1). A better understanding of their natural distribution and possib-le biological significance would be welcome. There are reasons to believe that the future has several additions to the list of natural sulphonium compounds in store.
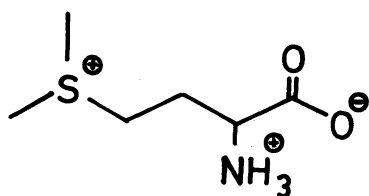
(68)
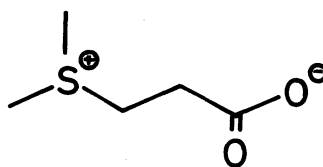
(69)

Sulphoxides. In 1951, the garlic amino acid alliin (70) was reported as the first sulphoxide of natural provenance (Ref. 46). Since then, a great many sulphoxides have been encountered within various classes of natural products, such as amino acids, glucosinolates, poly-
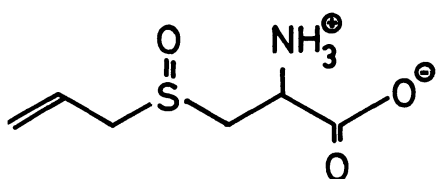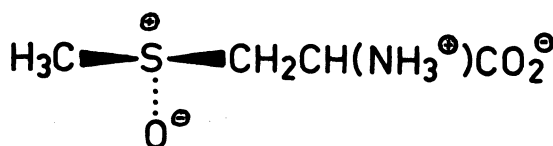

(70)

$$H_3C \blacktriangleright S \blacktriangleleft CH_2CH(NH_3^{\oplus})CO_2^{\ominus}$$
$$\overset{\oplus}{\underset{\ominus}{\vdots}}$$
$$O^{\ominus}$$

(71)

acetylenes, cyclic sulphides (e. g. biotin) and disulphides (cf. Ref. 2, 3, 20, 45, and the present chapter). Though supported by convincing evidence in only a few cases, it seems probable that sulphoxides normally result from in vivo oxidation of sulphides. The facile formation of sulphoxides presents an inherent difficulty in ascertaining the true natural product character of the former. In oxidized, chiral sulphides, a typical natural product situation , optical activity, traceable to the sulphoxide grouping, does not per se preclude non-enzymic oxidation in view of the inherent possibility of asymmetric induction. Through X-ray crystallography, (+)-S-methyl-L-cysteine sulphoxide, a constituent of many crucifers, became the first sulphoxide with unequivocally established chirality, viz. (S), around sulphur (71) (Ref. 47). Subsequently, the absolute configuration has been determined for several other sulphoxides of natural origin. It is noteworthy that both stereochemical series are represented in Nature; thus all ω-methylsulphinylalkylglucosinolates possess (R)-configuration, whereas in the S-substituted L-cysteine sulphoxides, the (S)-configuration prevails around the sulphur atom.

Sulphoxides in terpenoid arrays are of recent date. We should be pleased to know how the β-hydroxysulphoxide system in the norditerpenoid dilactones podolactone D (72) and C (73), isolated from a Podocarpus species (Ref. 48), are biologically manufactured. Equally intriguing is the ability of horses to convert caffeine into the sulphoxide (74) and the corresponding sulphide and sulphone, through metabolic steps that are not obvious, although perhaps more general in character (Ref. 49). The structure of sparsomycin (75), an antibiotic from Streptomyces sparsogenes, contains an interesting oxidized thioacetal grouping (Ref. 50).

(72)

(73) 1,2-α-epoxy

(74)

(75)
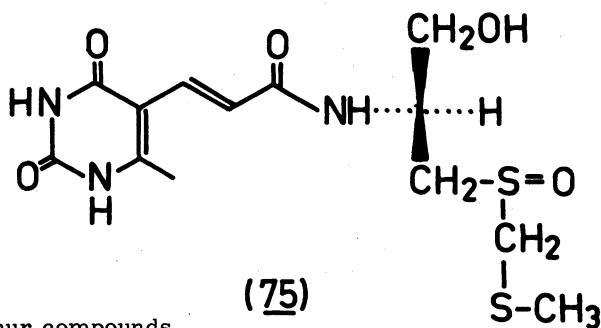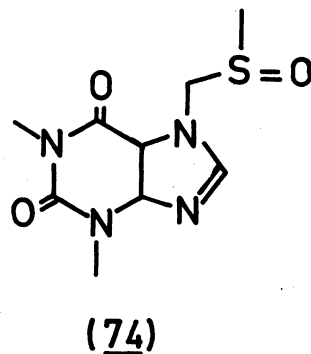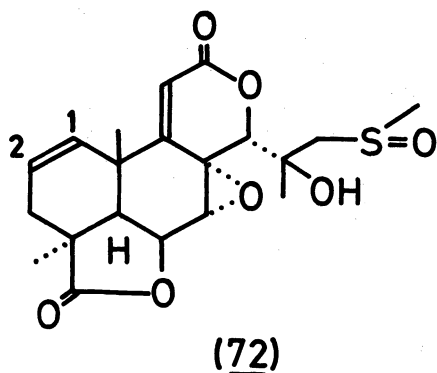
Tetra-coordinate sulphur compounds

Sulphones. Extensive oxidation of sulphides leads, via sulphoxides, to sulphones. Dimethyl sulphone is known as a constituent of several species of Equisetum (Ref. 51, 52), and the ω-methylsulphonylalkylglucosinolates (76) and (77) are present in certain crucifers (Ref. 20).

(76) n = 3

(77) n = 4
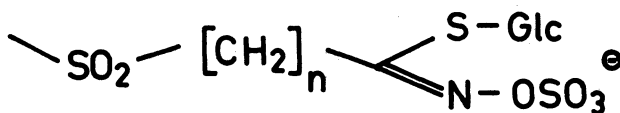
Moreover, a few sulphones have been encountered within the classes of natural polyacetylenes (Ref. 26) and the Tyrian purple progenitors (Ref. 34). Mostly, the sulphones are accompanied by lower oxidized counterparts. It seems likely that additional sulphones will be unveiled as natural products in the future.

Organic sulphates. A remarkable variety of organic mono-O-sulphates occur in Nature, comprising polysaccharide sulphates and the curious sulphate lipids found in several groups of algae. Here, it suffices to draw attention to the tyroxindol sulphate (50), discussed above, to the uniform collection of O-oxime sulphates constituting the class of glucosinolates (52), and to the increasing awareness, within the last years, of the wide natural distribution of flavonoid sulphates (Ref. 53).

Epilogue

Merely on structural inspection, the major part of the collection of natural compounds discussed above appears to have little more in common than the contents of one or more sulphur atoms. Even when far from complete, the same collection, therefore, may leave an almost kaleidoscopic impression on the reader. Yet, it is the author's hope that a collocation as this, however artificial and inadequate, may trigger off associations that may prove helpful in deepening our understanding of the origin and function of naturally occurring sulphur compounds, comprising those included here, the ones omitted for various reasons, as well as the many yet to be discovered.

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