

# ISOTHIOCYANATES OF NATURAL DERIVATION

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## INTRODUCTION

Since ancient times and in nearly all cultures, plant products have played an important rôle and served a great variety of purposes. Organic chemists have, for obvious reasons, been particularly attracted by constituents known for their poisonous effects, or used in the cure of diseases, and remarkable results have emanated from such studies. There are, however, numerous other long-established applications of plant materials that have evoked the interest of chemists. In this category belong numerous pigments, fragrant principles, and active ingredients which have in common the ability of revealing themselves through direct stimulation of our senses: eyes, nose, or tongue; therefore, it is not surprising that these provinces of natural product chemistry have attracted much early and continued chemical interest.

This lecture deals with a limited, but uniform group of natural compounds in this category which give rise to certain pungent, sulphur-containing compounds, the mustard oils, or isothiocyanates. Chemically, these can be regarded as esters of the hypothetical isothiocyanic acid, HNCS.

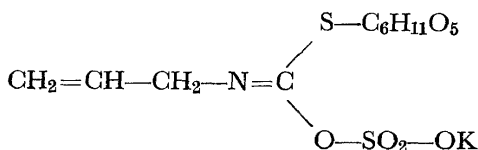
## HISTORICAL

Mustard seed was widely grown in many ancient cultures as a condiment, and many speculations on the chemical nature of the pungent ingredient can be found in the literature preceding that of the era of modern organic chemistry (*cf.* ref. 1).

About 1830, a group of French chemists reported that the pungent principle is not present as such in the plant material but rather arises as a product of secondary changes taking place after disintegration of the seed in the presence of water. In fact, Boutron and Fremy<sup>2</sup> in 1840 isolated a protein fraction, myrosin<sup>3</sup>, from black mustard seed that was shown to be instrumental in liberating the pungent mustard oil from a water-soluble, acid progenitor. The latter was isolated the same year as a potassium salt from black mustard seed by Bussy and given the name potassium myronate (myron = balsam)<sup>4</sup>. Later, this compound became known as sinigrin. About the same time, an analogous mustard oil-producing compound, sinalbin, was isolated from the seeds of white mustard (*Sinapis alba* L.)<sup>5</sup>. For nearly eighty years these two plant constituents remained the sole representatives of what is known today to be a fairly large group of related compounds.

The discovery about 1860 that sinigrin in the presence of myrosin was degraded to glucose, potassium hydrogen sulphate, and "schwefelcyanallyl" represented a major step forward in the understanding of this unique

transformation<sup>6</sup>. It remained for A. W. Hofmann to clarify the isomerism between thiocyanates and isothiocyanates in a classical paper which appeared in 1868<sup>7</sup>. However, the first structural proposal did not appear until 1897, when Gadamer<sup>8</sup> summarized the available experimental evidence in a sinigrin structure (*Figure 1*) that remained virtually unchallenged until a few years ago.



Sinigrin  
(Gadamer 1897)

*Figure 1*

## GLUCOSIDES

### Chemical structure

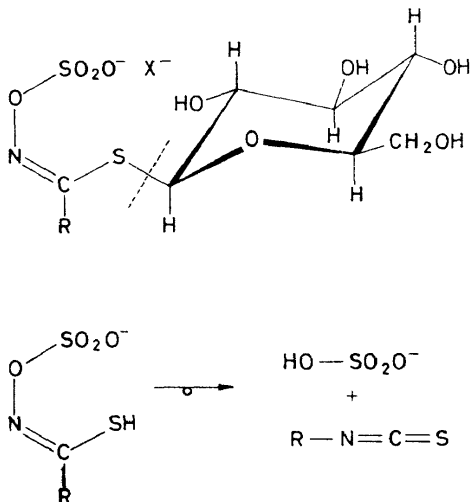
Obviously, Gadamer's formula accounts satisfactorily for the enzymic decomposition to allyl isothiocyanate, glucose and sulphate ions. On the other hand, it does not provide any ready explanation of the long-established formation of allyl cyanide, concomitant with the mustard oil, during the enzymic hydrolysis or on treatment of sinigrin with silver nitrate<sup>6</sup>. Nor is it compatible with the fact that sinigrin does *not* afford allylamine on hydrolysis. Taken together, these and other facts called for a revision of the almost generally accepted Gadamer-structure; in an important paper in 1956, Ettlinger and Lundeen<sup>9</sup> presented a revised structural expression for sinigrin and sinalbin, which, on the basis of later experience, appears to be a general one for all natural compounds of this class. Thus, glucose, attached in a  $\beta$ -thioglucosidic linkage, seems to be an invariable feature of this group of compounds, justifying their designation as glucosides.

The revised structure (*Figure 2*), which has been verified by synthesis<sup>10</sup>, calls for a few comments\*. Clearly, the enzymic fission must be accompanied by a rearrangement of the side-chain from carbon to nitrogen, a process that is probably without precedent in enzymically induced reactions. It is noteworthy that an initial, enzymic detachment of the glucose moiety leaves a molecular fragment with structural features, including a good leaving group, that are almost ideal for an intramolecular Lossen-type rearrangement to proceed, leading to isothiocyanates (*Figure 2*). The details of the enzymic system, as well as of the mechanism involved, have been a subject of study by several groups within the last few years (*cf.* ref. 12). Without entering the somewhat controversial discussion, it seems appropriate here to mention that Ettlinger and colleagues recently provided convincing evidence for the presence in yellow mustard flour of an enzyme that catalyses the

\* A recently published X-ray analysis of sinigrin<sup>11</sup> fully confirms the proposed structure. Furthermore, it provides evidence regarding the only undecided structural detail, *viz.* the stereochemistry around the C=N bond; in sinigrin, the two sulphur atoms are located *syn* to each other.

ISOTHIOCYANATES OF NATURAL DERIVATION

hydrolysis of mustard oil glucosides to give the same products that are formed with the classical myrosin; however, the enzyme differs from myrosin in requiring vitamin C as a cofactor<sup>12</sup>. This appears to be the first well-documented case of the participation of vitamin C as a specific coenzyme in an enzymic reaction and therefore deserves attention.



(Ettlinger, Lundeen, 1956)

Figure 2

The native glucosides are usually accompanied in the plant tissues by the hydrolyzing enzymes, deposited in special cells. Only after disintegration of the cell structure do substrate and enzyme meet, leading to isothiocyanate formation. Most mustard oils are pungent, and this fact may be diagnostically useful in the search for the inconspicuous glucosidic precursors in plant materials. The general structure of the glucosides renders it immediately understandable that acid hydrolysis gives sulphur and hydrogen sulphide, glucose, sulphuric acid, hydroxylamine, and the carboxylic acids corresponding to the side-chains (Figure 3)<sup>9</sup>.

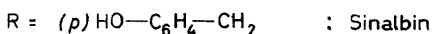
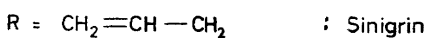
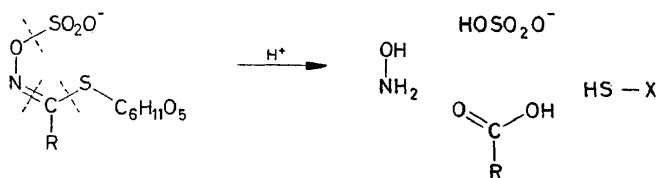


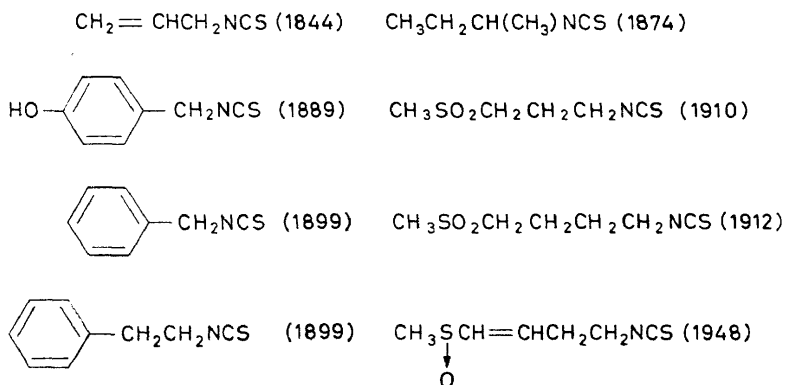
Figure 3

## Botanical sources

According to our present knowledge, the isothiocyanate-producing glucosides are of rather restricted occurrence within the plant kingdom. They seem to be present in virtually all species of the families *Cruciferae*, *Resedaceae* and *Capparidaceae*, whereas sporadic occurrences in other, mostly systematically remote families have been reported. In no case have glucosides of the present type been encountered outside the dicotyledons (for a more detailed discussion, *cf.* ref. 13). Usually, the thioglucosides are present in all parts of the plants, yet in widely varying amounts. There seems to be a tendency for glucosides to accumulate in the seeds, often the most convenient source for the isolation of the pure compounds.

## ISOTHIOCYANATES

Apart from the classical glucosides, sinigrin and sinalbin, few additional compounds of the same type became known prior to the new tide of interest in this field about ten years ago. They comprise five precursors, giving rise to the production of *s*-butyl<sup>14</sup>, benzyl<sup>15</sup>,  $\beta$ -phenylethyl<sup>15</sup>,  $\gamma$ -methylsulphonylpropyl<sup>16</sup>, and  $\delta$ -methylsulphonylbutyl<sup>17</sup> isothiocyanate, on enzymic hydrolysis (*Figure 4*). Many years after these had been discovered, Schmid



*Figure 4.* Naturally derived isothiocyanates known before 1953

and Karrer<sup>18</sup> in 1948 reported the isolation of sulphoraphen from radish seed; it is worth mentioning here that this isothiocyanate represented the first compound of natural derivation in which optical activity was attributable solely to factors other than asymmetric carbon atoms. This list up to 1953 of altogether eight compounds needs only be compared with that valid today, and comprising a total of about 45 thioglucosides (for a survey of these, *cf.* refs. 13, 19, 20), to illustrate the marked ability of certain botanical species to incorporate simpler fragments into the same unique molecular framework; at the same time the comparison indicates the rapid progress made within this field during the last decade.

As in many other areas of natural product chemistry, the powerful tools of chromatography and ion-exchange techniques have been of decisive

## ISOTHIOCYANATES OF NATURAL DERIVATION

importance for this rapid progress (*cf. e.g.* ref. 20). Nearly 450 individual botanical species have thus far been screened for their contents of isothiocyanate-producing glucosides by chromatographic methods\*. Frequently, several thioglucosides occur together in a given plant, and many species-characteristic patterns have been established. The large number of known thioglucosides renders the unambiguous analytical identification of the individual constituents in a given species a matter of considerable difficulty. Recently, however, the combination of gas-liquid chromatography<sup>21, 22</sup> and mass spectrometry<sup>23</sup> of the enzymically produced isothiocyanates has proved to be almost uniquely useful for the rapid identification of unknown mixtures of mustard oils. The structural types encountered thus far may be conveniently treated groupwise, according to the chemical nature of the side-chains. The remaining part of this paper will be devoted to such a discussion.

### Aliphatic side chains

The simplest possible side chain, *viz.* a methyl group, has been repeatedly encountered in the thioglucoside glucocapparin<sup>24</sup>, which appears to be an almost constant constituent of Old-World species of the family *Capparidaceae*<sup>25, 26</sup>. It is remarkable that this simple glucoside has not yet been encountered with certainty in any cruciferous species. The *ethyl* side chain has only been found once, *viz.* in a North-American species of the genus *Lepidium*<sup>27</sup>. In contrast, the thioglucoside possessing an *isopropyl*-grouping, appears to be rather widely distributed and is often accompanied by the long known glucocochlearin, producing *s-butyl* isothiocyanate on enzymic hydrolysis (*cf.* ref. 20). The latter mustard oil is dextrorotatory and its

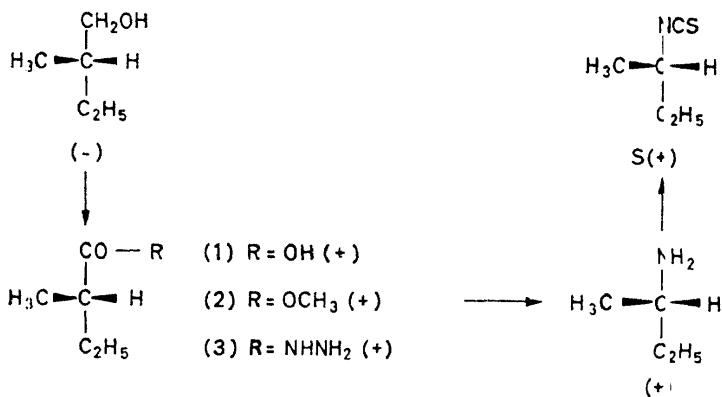


Figure 5

absolute configuration follows from its synthesis from dextrorotatory 2-butylamine<sup>28</sup>. The absolute configuration of the latter, the formally simplest optically active, aliphatic amine, was established for the first time by purely chemical correlations on this occasion<sup>29</sup> (Figure 5). It may be significant

\* A survey of the results as published up to the end of 1959 is presented in ref. 20. A substantial amount of additional data, unpublished and mainly obtained during the last few years, has been collected in various laboratories, including that of the author.

that the configuration of the naturally derived mustard oil is identical with that prevailing around the  $\beta$ -carbon atom of natural isoleucine. A recent addition to the aliphatic type of side chains is the *2-methylbutyl*-analogue, a higher homologue of the *s*-butyl compound, possessing the same absolute configuration. It was recently shown to be a minor constituent of the volatile mustard oil fraction of the Indian tree *Putranjiva Roxburghii*, belonging to the family *Euphorbiaceae*<sup>30</sup>. In summary, the monofunctional aliphatic isothiocyanates hitherto reported are presented in the annexed table (*Figure 6*) together with the names of the glucosidic precursors.

<i>Isothiocyanate</i>	<i>Parent glucoside</i>
$\text{H}_3\text{C}-\text{NCS}$	Glucocapparin
$\text{H}_3\text{C}-\text{CH}_2-\text{NCS}$	Glucolepidin
$\text{H}_3\text{C}-\underset{\text{CH}_3}{\text{CH}}-\text{NCS}$	Glucoputranjivin
$(S)-\text{H}_3\text{C}-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{NCS}$	Glucocochlearin
$(S)-\text{H}_3\text{C}-\text{CH}_2-\underset{\text{CH}_3}{\text{CH}}-\text{CH}_2-\text{NCS}$	Glucojiaputin

*Figure 6*

### Keto side-chains

Lately, three individual thioglucosides have been discovered with straight carbon chains containing a *keto-grouping*; they are presented in *Figure 7*. All

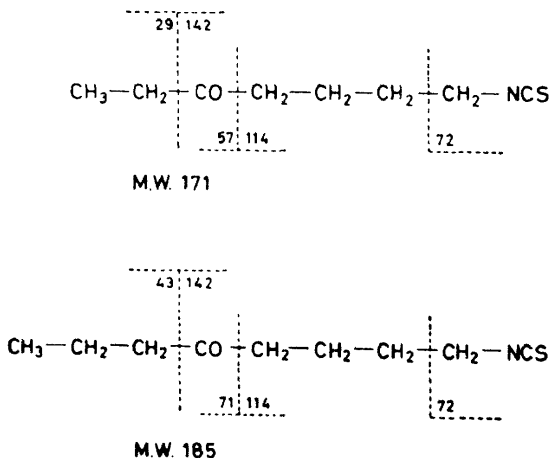
<i>Isothiocyanate</i>	<i>Parent glucoside</i>
$\text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{O}}{\parallel}{\text{C}}\text{CH}_2\text{CH}_2\text{CH}_2-$	Glucocapangulin <sup>31</sup>
$\text{CH}_3\text{CH}_2\text{CH}_2\underset{\text{O}}{\parallel}{\text{C}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	Glucocappasalin <sup>32</sup>
$\text{CH}_3\text{CH}_2\underset{\text{O}}{\parallel}{\text{C}}\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$	Gluconorcappasalin <sup>33</sup>

*Figure 7*

## ISOTHIOCYANATES OF NATURAL DERIVATION

three have been encountered in closely allied South-American species of the genus *Capparis* (family *Capparidaceae*) whereas they seem to be entirely absent from Old-World species of the same genus, a considerable number of which have been examined<sup>26</sup>. It remains to be seen to what extent the reverse be true, namely, that glucocapparin, producing methyl mustard oil, occurs exclusively in Old-World species of the genus.

The identification of the keto side-chains has mostly been performed on a microgram scale due to the very limited quantities of botanical material available, and has been based mainly on mass-spectral data. Typical fragmentation patterns<sup>23</sup> are shown in *Figure 8*.



*Figure 8*

### Unsaturated side chains

The classical sinigrin, with its allyl side-chain, has since been supplemented with two higher homologues, *viz.* the 3-butenyl<sup>34, 35</sup> and 4-pentenyl glucosides<sup>36</sup>, both occurring in seed of rape, the former as the major constituent (*Figure 9*). It is noteworthy that sinigrin does not appear at all in rape seed.

<i>Isothiocyanate</i>	<i>Parent glucosid.</i>
$\text{CH}_2=\text{CHCH}_2\text{NCS}$	Sinigrin
$\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{NCS}$	Gluconapin
$\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{NCS}$	Glucobrassicinapin

*Figure 9*

### $\omega$ -Methylthioalkyl side chains

A remarkable series of closely related glucosides has been established as a constituent of cruciferous species. Chemically, they represent a considerable extension of a type of mustard oils identified several years ago and

exemplified by the sulphones presented in *Figure 4*. Characteristic for this class of thioglucosides is the terminally located methyl-sulphur grouping. In *Figure 10* a survey is presented of the individual compounds of this type



<i>n</i>	X	<i>n</i>	X
3	S (ref. 37), SO (ref. 38), SO <sub>2</sub> (ref. 16)		
4	S (ref. 39), SO (refs. 18, 40), SO <sub>2</sub> (ref. 17)	8	SO (ref. 46)
5	S (ref. 41), SO (refs. 42, 43)	9	SO (ref. 47)
6	S (ref. 44), SO (ref. 45)	10	SO (ref. 48)

*Figure 10*

known today. There are good reasons to believe that the missing homologue, containing seven methylene groups, will be established as a species of natural derivation before long. Obviously, the side chain sulphur atom may assume different oxidation stages. The series of sulphoxides all contain an asymmetric sulphur atom, as is apparent from the conspicuous optical activity of the corresponding mustard oils and the derived thiourea-derivatives. The plain, negative rotatory dispersion curves of several series of such derivatives clearly indicate that they all belong to the same stereochemical series<sup>49</sup>. The determination of their absolute configuration, however, is still a matter of investigation in our laboratory. This remarkable series of strictly homologous natural products poses, of course, a biogenetic problem of considerable interest. Biosynthetic experiments have, however, not yet proceeded to a stage permitting definite conclusions to be drawn.

### Aromatic side-chains

Again, several additions to the classical aromatic side-chains: benzyl, *p*-hydroxybenzyl and  $\beta$ -phenylethyl can be recorded as results of more recent studies (*Figure 11*). The pair of *meta*-derivatives<sup>51, 52</sup> deserves more attention than the *O*-methyl-derivative of sinalbin<sup>50</sup>, in view of the rather rare occurrence of *meta*-compounds in Nature.

From a practical point of view, much interest has recently been associated with  $\beta$ -phenylethyl isothiocyanate, a mustard oil produced from a glucosidic precursor present in, *e.g.*, watercress and turnip root. Apparently, this compound ranks among the most potent insecticides and may well acquire practical importance in the future<sup>53</sup>.

Recently, several groups of investigators have studied the biosynthesis of glucotropaeolin, a glucoside which produces benzyl isothiocyanate on enzymic hydrolysis; evidence has been adduced that phenylalanine functions as a precursor of the side-chain of glucotropaeolin<sup>54, 55</sup> as well as of the next higher glucoside, namely that which furnishes  $\beta$ -phenylethyl isothiocyanate<sup>55</sup>.

It is interesting in this connection that both mustard oils are derived from the C<sub>6</sub>—C<sub>2</sub> portion of phenylalanine (*Figure 12*). In neither case, however, is the carboxylic acid group of the amino-acid retained. The methyl carbon



ISOTHIOCYANATES OF NATURAL DERIVATION

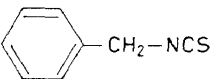
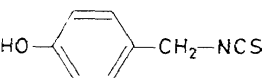
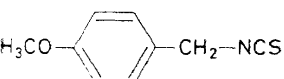
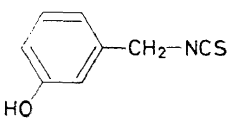
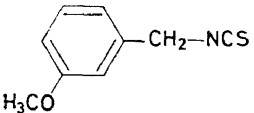
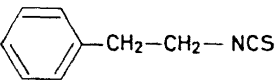
<i>Isothiocyanate</i>	<i>Parent glucoside</i>
	Glucotropaeolin
	Sinalbin
	Glucoaubrietin
	Glucolepigramin
	Glucolimnanthin
	Glucouasturtiin

Figure 11

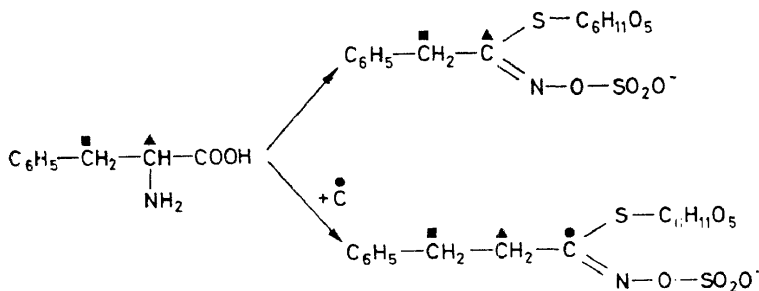


Figure 12

atom of acetate serves as an effective source of the extra carbon atom in the  $\beta$ -phenylethyl derivative<sup>55</sup>.

Although it has thus been clearly demonstrated that the simple aromatic thioglucosides are biosynthesized from phenylalanine, far too few data are yet at hand to permit any conclusion to be drawn regarding the extent to which amino-acids, or closely related compounds, function generally as

biosynthetic precursors for thioglucosides of the type discussed here\*. If this, in fact, should turn out to be the case, the future discovery of many previously unknown amino-acids, or their biochemical equivalents may be anticipated. However, preliminary investigations of the amino-acid pools in a number of thioglucoside-producing species have not been rewarding in this respect. Further progress in current studies on the biosynthesis of the unique thioglucoside structure must therefore be awaited with considerable interest.

An interesting and somewhat related thioglucoside is *glucobrassicin*, first isolated by Virtanen and Gmelin from cabbage leaves a few years ago<sup>57</sup>. In fact, this compound constitutes the sole thioglucoside known today with a heterocyclic side-chain (Figure 13). Other properties, however, necessitate

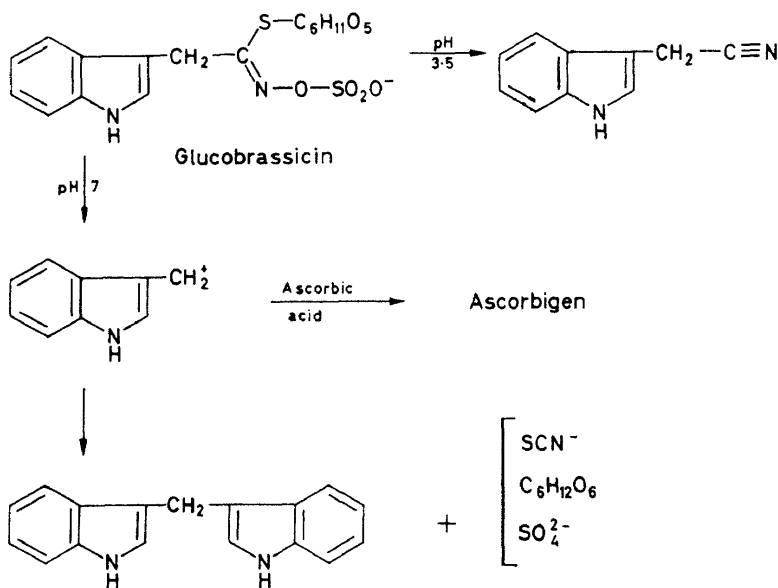


Figure 13

a few additional comments on this compound. Upon enzymic hydrolysis, two alternative paths may be followed, depending on the pH, neither of them, however, orthodox when regarded in terms of end products. At pH-values close to neutrality, the expected skatyl isothiocyanate is probably produced initially, but it immediately suffers hydrolysis to a thiocyanate ion and, presumably, 3-hydroxymethylindole, which then reacts *via* a known intermolecular condensation to give di-indolyl-methane as the stable end product. This series of events also affords an explanation of the production of ascorbigen, a long-studied, bound form of ascorbic acid in cabbage species. It now seems clear that ascorbigen, the definite structure of which has not yet been established, is nothing but an artefact, resulting from a secondary

\* The incorporation of tryptophane into the corresponding thioglucoside, glucobrassicin, has been similarly demonstrated<sup>56</sup>.

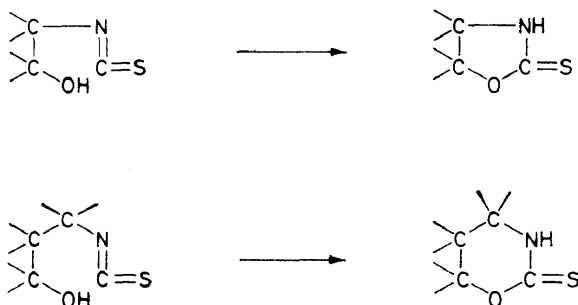
## ISOTHIOCYANATES OF NATURAL DERIVATION

reaction between ascorbic acid and hydroxymethylindole, or, possibly, the skatyl ion precursor. In fact, the synthesis of ascorbigen can easily be achieved *in vitro* from ascorbic acid and hydroxymethylindole.

In a lower pH-range, however, the enzymic fission takes a different course leading to the formation of indolylacetonitrile, a compound isolated several years ago from Brussels sprouts by Jones and his group<sup>58</sup> and shown to have strong growth-promoting properties. It now seems clear that this compound also should be looked upon as a secondary product, originating from the enzymic decomposition of glucobrassicin on disintegration of the cell structure. More recently, the Finnish authors<sup>59</sup> have characterized a minor thioglucoside, neoglucobrassicin, occurring in a number of *Brassica* species, as the indole-*N*-methoxy derivative of glucobrassicin.

### Hydroxy-substituted side chains

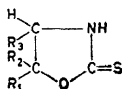
It may be foreseen that thioglucosides, carrying hydroxy-groups in  $\beta$ - or  $\gamma$ -positions in the side chains, on enzymic hydrolysis will produce hydroxyalkyl isothiocyanates which undergo spontaneous cyclization to five- or six-membered heterocyclic rings, respectively (*Figure 14*). In fact, a series of such thioglucosides has been encountered in Nature.



*Figure 14*

In the cruciferous species *Malcolmia maritima*, a close relative of ordinary wallflower, the benzoate of the 3-hydroxypropyl thioglucoside appears<sup>60</sup>. All other thioglucosides of the present type so far detected are hydroxylated in the  $\beta$ -position. The resulting 2-oxazolidinethiones, summarized in *Figure 15*, may carry substituents either in the 4- or 5-position. Structural studies on these compounds pose some problems, in particular ones of stereochemistry.

The 5,5-dimethyl-derivative was isolated by Hopkins<sup>61</sup> several years ago from a Canadian crucifer; its origin from a thioglucoside was hardly appreciated at that time (*cf.* ref. 62). More recently, the 5-vinyl-derivative, named goitrin, was isolated by Astwood, Ettlinger and Greer<sup>63</sup> as the compound responsible for the long observed antithyroid factor in yellow turnip and various *Brassica* seeds. Its derivation from a thioglucosidic precursor was suggested by these authors and has subsequently been confirmed by several groups<sup>62, 64, 65</sup>. Through chemical correlations, the



R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Parent glucoside
CH <sub>2</sub> =CH	H	H	Progoitrin
C <sub>6</sub> H <sub>5</sub>	H	H	Glucobarbarin
CH <sub>3</sub>	CH <sub>3</sub>	H	Glucocongringiin
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	H	Glucocleomin
H	H	CH <sub>3</sub>	Glucosisymbirin
H	H	C <sub>2</sub> H <sub>5</sub>	Glucosisaustriцин

Figure 15

absolute configuration of the naturally derived goitrin has been established in our laboratory<sup>66</sup> and is shown in Figure 16. Accordingly, the glucosidic progenitor of goitrin is a  $\beta$ -hydroxy-derivative of the thioglucoside affording 3-butenyl isothiocyanate, the predominant volatile mustard oil of rape seed.

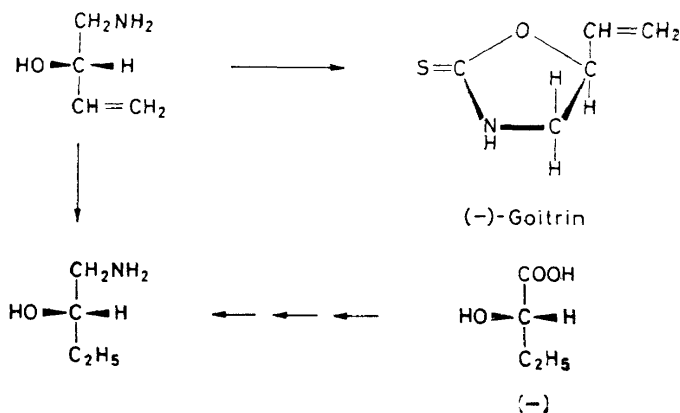


Figure 16

The thioglucoside, glucobarbarin, discovered in various *Barbarea*-species and in *Reseda luteola*, on enzymic hydrolysis gave a 5-phenyl-2-oxazolidinethione, the absolute configuration of which was likewise established by stereospecific synthesis as indicated on Figure 17<sup>67, 68</sup>. Consequently, glucobarbarin is a  $\beta$ -hydroxy-derivative of gluconasturtiin, the precursor of  $\beta$ -phenylethyl isothiocyanate.

Recently, a structural study has been completed of the laevorotatory 5-methyl-5-ethyl-2-oxazolidinethione, named cleomin and formed as the end product of the enzymic hydrolysis of the thioglucoside glucocleomin, present in many species of the capparidaceous genus *Cleome*<sup>69</sup>, as well as in the Indian *Pulranjiva*<sup>30</sup> mentioned previously in this review. Since the chemical correlations involved include some simple molecules which may be of

## ISOTHIOCYANATES OF NATURAL DERIVATION

more general interest, the principal features of this work will be sketched briefly.

Synthetic access to the oxazolidinethione in question requires production of the parent amino-alcohol, which, in its turn, may be produced *via* the amide from 2-hydroxy-2-methylbutyric acid. This represents the simplest,

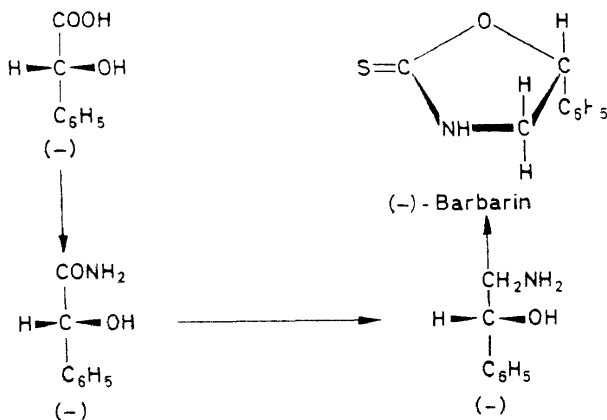


Figure 17

optically active, tertiary  $\alpha$ -hydroxy-acid (Figure 18). For this reason, and also because it has been repeatedly recorded as an esterifying acid in more complex natural esters, such as various *Veratrum* alkaloids and the bitter principle glaucarubin, it appeared of interest to establish its absolute

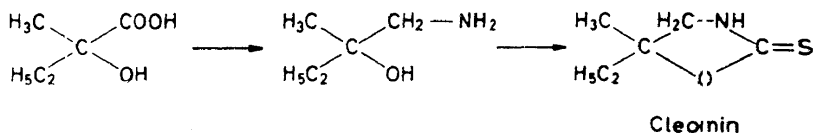


Figure 18

configuration by direct correlation, as indicated in Figures 19 and 20. Tiglic acid was selected as a convenient starting material (Figure 19); it was *cis*-hydroxylated to *threo*-2,3-dihydroxy-2-methylbutyric acid, and this was further resolved into its enantiomers according to known procedures. Reduction of the dextrorotatory enantiomer afforded a triol, which, after some trials, could be selectively tosylated on the primary hydroxy-grouping. Hydrogenolysis of this with lithium aluminium hydride now afforded a monoasymmetric, dextrorotatory diol, which was easily correlated with

lactic acid of known absolute configuration *via* a Grignard carbinol synthesis. Thus, the absolute configuration was established for the *threo*-dihydroxy acid, which, incidentally, also occurs in certain *Veratrum* alkaloids<sup>70</sup>.

Consequently, the *threo*-acid was available for further stereochemical

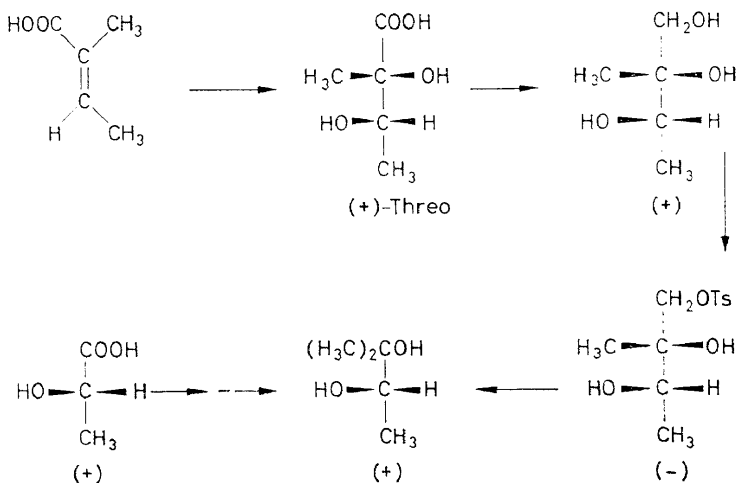


Figure 19

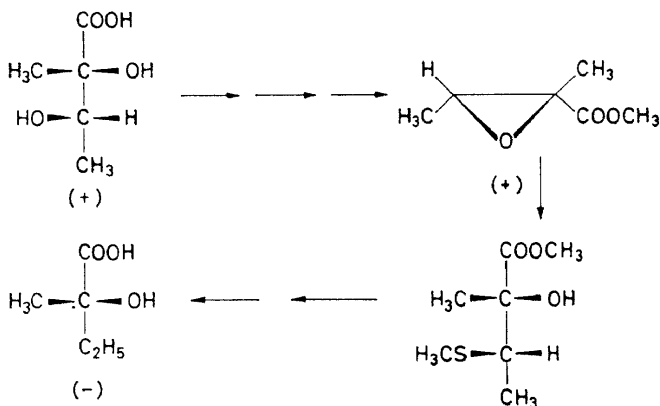


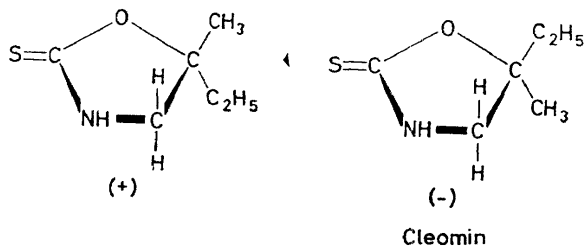
Figure 20

conversions. Tosylation of its methyl ester (Figure 20), followed by base-induced epoxidation, yielded an epoxy-ester which could easily be opened nucleophilically by a mercaptide ion to give a sulphide ester. This, on hydrolysis yielded a sulphur-free ester and thence the free 2-hydroxy-2-methylbutyric acid with the absolute configuration indicated<sup>71</sup>. From here it was a simple matter to extend the synthesis *via* the ester, amide, and amino-alcohol, to the (+)-5-methyl-5-ethyl-2-oxazolidinethione possessing

## ISOTHIOCYANATES OF NATURAL DERIVATION

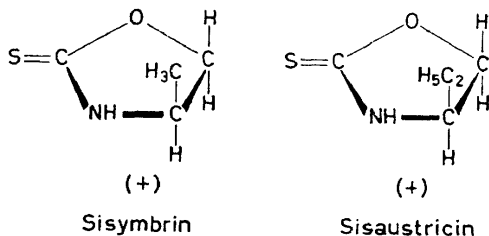
the absolute configuration shown in *Figure 21*. The synthetic specimen proved to be the enantiomer of natural cleomin, which consequently possesses the configuration indicated<sup>72</sup>.

Similarly, stereospecific syntheses proceeding from  $\alpha$ -amino-acids with known configurations, served to establish the absolute configurations of the two known 4-substituted-2-oxazolidinethiones, both isolated from seed extracts of the European crucifer *Sisymbrium austriacum*. The 4- $\alpha$ -methyl-<sup>73</sup> and 4-ethyl-derivatives<sup>74</sup> (sisymbrin and sisaustriecin, respectively) possess the



*Figure 21*

configurations depicted in *Figure 22*. The corresponding hydroxy $\gamma$ -substituted thioglucosidic precursors, as well as the benzoates<sup>75, 76</sup> of the latter, occur together in the intact plant material.



*Figure 22*

Knowledge of the absolute configurations of the heterocyclic end products is, of course, tantamount to knowledge of the configurations about the asymmetric,  $\beta$ -hydroxy-substituted centres of the original side chains. The various data have been summarized in *Figure 23*.

Clearly, the side-chains are reminiscent of those of the amino-acids valine, isoleucine and phenylalanine. Furthermore, the hydroxylated derivatives have their counterparts in certain intermediates on the accepted anabolic pathways of these amino-acids, and there are good reasons for believing that the two groups of natural compounds will eventually prove to converge biosynthetically. It is noteworthy in this connection, that isobutyl isothiocyanate, the expected analogue of leucine, has not yet been recorded as a mustard oil of natural derivation.

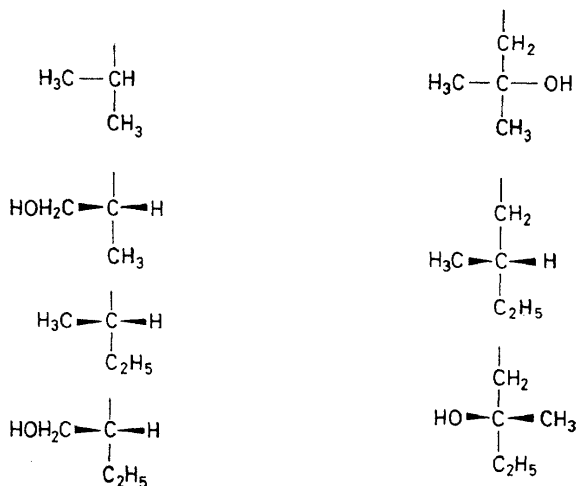


Figure 23

### CONCLUDING REMARKS

The present account of the botanical distribution and chemical character of a uniform and highly characteristic group of constituents from higher plants is considered to be no more than the opening chapters of a much longer story. Many additions to the list of natural thioglucosides are to be expected in the near future. As in so many other fields of natural product chemistry, the powerful tools and methods of today will most likely reduce the structure determinations, until recently a major challenge to organic chemists, almost to a matter of routine. Fortunately, however, this development will only accelerate the rate at which insight will be gained into other aspects of the problem, such as the biosynthesis and metabolism of this unique class of natural products. There are several indications that the thioglucosides, traditionally considered as little more than the sources of a few odd, pungent principles, may play a much more central rôle in plant biochemistry. Every attempt to increase our knowledge in this area must, therefore, be welcomed as a contribution to our understanding of the diverse and fascinating chemistry behind the life processes in higher plants.

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