MULTI-SULFUR AND SULFUR
AND OXYGEN FIVE- AND
SIX-MEMBERED HETEROCYCLES

Part One

David S. Breslow
Herman Skolnik

Hercules Research Center, Hercules Incorporated, Wilmington, Delaware

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FIVE- AND SIX-MEMBERED HETEROCYCLES

In Two Parts
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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds and accommodate the specific interests of the authors.

Research Laboratories
Eastman Kodak Company
Rochester, New York

Arnold Weissberger
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PREFACE

On accepting the assignment to write a definitive chemistry of five- and six-membered heterocycles containing more than one sulfur, oxygen and sulfur, and their selenium and tellurium analogs, we went through the Ring Index by A. M. Patterson and L. T. Capell (2nd edition, 1960, by A. M. Patterson, L. T. Capell, and D. F. Walker), page by page, compound by compound. We found over 200 parent rings within the defined scope of this volume. We assigned to them the RRI (Revised Ring Index) number in the text and provided an index to them in the second part of this volume. Many parent rings in the volume, however, had not yet been assigned RRI numbers. Most of these entered the literature since the coverage of the Ring Index and are undoubtedly in the supplements, which issued after the manuscript went to press; only a relatively small number are without RRI numbers because the Ring Index missed them or chose to consider them uncertain.

An assignment that covers over 200 parent heterocycles meant that this number was the minimum number of subjects that we had to consult in the indexes of the standard reference works, such as Chemical Abstracts, Chemisches Zentralblatt, and Beilstein. Our burden of searching the literature was lightened considerably by the Index of Ring Systems in Chemical Abstracts. There were two major difficulties in finding the references in the standard reference works: the plethora of names for a given compound and the unrelatedness of the nomenclature in the many classes of a heterocyclic moiety. Because nomenclature of the heterocyclics is a major problem, we devoted considerable attention to it throughout the volume and in the subject index. Chemical Abstracts nomenclature was followed, particularly for the heterocyclics. In the case of reactants used in the synthesis of a heterocyclic moiety, we carefully avoided nomenclature which might be confused with a heterocyclic name. For example, we preferred dimercaptoethane over ethanedithiol when it was used in the synthesis of the dithiole ring.

Although the assignment per se essentially dictated the scope for the contents of this volume, the order of arrangement and method of treatment are the result of our own deliberations. There are a number of variables which might influence the order of arrangement, such as size of the heterocyclic ring, kinds of heteroatoms, number of heteroatoms, synthetic methods, reactions and reactivity, etc.

Fortunately, these and other variables are not mutually exclusive. Each of us, having been heavy users of the chemical literature for the past twenty-five years, tended to think in terms of the reader's viewpoint and how he might want to consult this volume. These considerations led us to the arrangement which is best known to users of the Ring Index and of the Index of Ring Systems in Chemical Abstracts, viz., the size of the ring and the number of heteroatoms. Consequently, five-membered rings are together in the first part and six-membered rings in the second part of this volume. As in the Ring Index and Index of Ring Systems in Chemical Abstracts, the heterocyclic systems are
Preface

classified in order of increasing carbon atoms. Our logic divided the heterocyclic systems into twelve major units. The selenium and tellurium heterocyclics, because of their relatively small literature, were treated similarly in one unit.

Our experience as readers of the chemical literature, particularly in heterocyclic chemistry, led us to adopt the heterocyclic moiety pattern within each of the major heterocyclic systems. For example, Chapter 4, on the C₂OS ring system, is in two parts: the 1, 2-oxathiole moiety and the 1, 3-oxathiole moiety. The arrangement within a moiety is in ascending order by number of rings and number of atoms in each ring. We did make an exception, however, in this order, viz., spiro compounds are treated as derivatives of the heterocyclic class. Thus, spiro derivatives of 1, 3-dithiolane are discussed under 1, 3-dithiolane (Chapter 5, Section II A-4) and spiro derivatives of 1, 3-benzodithiole under 1, 3-benzodithiole (Chapter 5, Section II D-3).

The treatment of subject matter for each heterocyclic class is in the order: preparation, structure, properties, reactions, and uses. Our method of treatment, however, was not to summarize the literature completely and thoroughly in the text, but to review the literature selectively and eclectically, to establish the soundness and validity of what is known, and to point out what needs to be confirmed and extended. To the best of our ability and within the confines of the sources available to us, the literature has been exhaustively covered through most of 1962. The details of this coverage, such as preparation, yields, and properties (melting point, boiling point, index of refraction, density, etc.) are thoroughly tabulated and referenced. Physiological properties are noted in the text. The emphasis of the text is on the chemistry of the many ring systems within the scope of the assignment. Particular attention has been directed to the updating of the chemistry and to the elucidation of reaction mechanisms in terms of modern concepts. Because of this emphasis and direction, the text includes discussions of crystallographic studies, conformational analyses, and spectroscopic studies.

Unfortunately, this type of arrangement separates similar compounds from each other. For example, any one interested in the chemistry of sulfite esters must consult many sections in at least two chapters. A similar problem arises in the chemistry of 1, 2-disulfides. Although this was unavoidable, we hope the Contents and Subject Index will ease the problem of finding the desired information.

Because the subject index to this volume is different from other book indexes, we think a brief description may be to the reader's advantage. Every heterocyclic covered in the text is indexed specifically and the heterocyclics cited in the tables are indexed generically. The page citation designates that the page pertains to synthesis (s), property (p), or reaction (r) of the chemical or to a listing in a table (t). The heterocyclics are indexed by the heterocyclic parent compound with the sub-
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stituents inverted. Thus, 4-methyl-1, 3, 2-dioxathiolane 2-oxide is indexed as

1, 3, 2-Dioxathiolane 2-oxide, 4-methyl-

Reactants used in the syntheses of the heterocyclics are indexed, but not chemicals reacted with the heterocyclics. We think the indexing of the reactants is a real advantage as they are a common basis for relating the syntheses of heterocyclics. Uses and application of the heterocyclics and of their reaction products are indexed under the use or application, such as detergent, dye, pesticide, pharmaceutical, etc. A use or application is designated by the letter u following the page citation under the heterocyclic entry in the index. Spectroscopic properties, such as ultraviolet, infrared, nuclear magnetic resonance, and X-ray, are also subjects in the index.

From the perspective of the end of our assignment, we are acutely aware of the genius and labor of the hundreds of chemists whose contributions through time and space have constituted the facts and design of this volume. We are all the more impressed with the continuing and cumulative nature that the whole of chemistry imposes on any given area of chemistry, such as that encompassed by this volume, and how well the essence of this nature has been captured by our heritage, the chemical literature.

We gratefully acknowledge the encouragement of our friends and of the Research Department of Hercules Incorporated. We are grateful for the typing assistance the Hercules Research Center provided.

Most of all, we gratefully acknowledge the encouragement and support of our families. Their patience and understanding were completely essential for this undertaking.

Wilmington, Delaware
January, 1966

David S. Breslow
Herman Skolnik
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CHAPTER 1

C₂O₂S RING SYSTEMS

Five-membered rings containing two oxygens and a sulfur are known with only one arrangement of the hetero atoms, 1, 3-dioxa-2-thia. The compounds with this arrangement are cyclic sulfite and sulfate esters of 1, 2-dihydroxy compounds, cyclic anhydrides of acid sulfite esters of 2-hydroxy acids, and glyoxal sulfate.

I. C₂O₂S 1, 3, 2-DIOXATHIOLANE (1) AND 1, 3, 2-DIOXATHIOLE (2)

\[
\begin{align*}
\text{H}_2\text{C} & \text{5} \text{2} \text{S} \\
\text{H}_2\text{C} & \text{4} \text{3} \text{O}
\end{align*}
\]

(RRI 105)

Chemical Abstracts indexes this ring system under the above names. Alternative names are 1, 3-dioxa-2-thiacyclopentane and -pentene. However, the compounds are invariably found under the parent hydroxy compounds and these names are rarely used.

A. SULFITE ESTERS

1. Preparation

1, 3, 2-Dioxathiole 2-oxides, cyclic sulfites of enediols, have not been reported. 1, 3, 2-Dioxathiolane 2-oxides, cyclic sulfites of 1, 2-glycols, are prepared in excellent yields by treating a glycol with thionyl chloride.¹⁹,²⁴,⁴¹,⁵²,⁵⁷,⁵⁸,⁷⁴,⁷⁸,⁸⁸

\[
\text{C-} + \text{SOCl}_2 \rightarrow \begin{array}{c}
\text{H} \\
\text{C}
\end{array} + 2 \text{HCl}
\]

The use of methylene chloride as a solvent has been reported to improve the yield.⁴¹ Pyridine has been used frequently,³⁴,⁵²,⁶⁷,⁶⁹ but it appears to have little if any effect, in contrast to its effect on the reaction of simple alcohols with thionyl chloride, where its use leads to the formation of alkyl halides. The synthesis has been applied to primary, secondary, and tertiary alcohols. Pritchard and Lauterbur⁶⁷ᵃ raised the yield of 4, 4-dimethyl-1, 3, 2-dioxathiolane 2-oxide (2a) from 20% to 60% by carrying out the reaction in benzene and sweeping out hydrogen chloride with an inert gas.

[For references, see pp. 57-61.]
Chapter 1

It is interesting that even pinacol, which is prone to undergo acid-catalyzed rearrangement, was reported by Szmant and Emerson\textsuperscript{80} to give a 55\% yield of cyclic sulfite (3).

Majima and Simanuki\textsuperscript{57} reported that glycerol yields 4-chloromethyl-1, 3, 2-dioxathiolane 2-oxide (4). De la Mare, Klyne, and co-workers,\textsuperscript{32} obtained the same compound from 3-chloro-1, 2-propanediol; in this instance pyridine had a deleterious effect, a mixture of dichlorohydrin and trichloropropane being obtained.

Majima and Simanuki\textsuperscript{57} found that \textit{d}-erythritol gave a bis(cyclic sulfite) (5); according to Kitasato and Sone\textsuperscript{52} a bis(cyclic sulfite) (6) was also formed from diethyl mucate.

\textit{d}-Mannitol\textsuperscript{52, 57} yielded a tris(cyclic sulfite) (7). According to Majima and Simanuki\textsuperscript{57} treatment of the sulfite with thionyl chloride and pyridine, presumably at an elevated temperature, yields a tetrachlorohexylene glycol sulfite of undetermined structure, either (8) or (9), providing no rearrangement has taken place.
C₂O₂S Ring Systems

It should be pointed out that there is no direct evidence that these polyhydroxy compounds yield five-membered cyclic sulfites, and not six-membered. Thus, Zinner, Sych, and Schneider suggested that the bis(cyclic sulfites) prepared from D-xylose mercaptals might be 1,3,2-dioxathianes (9a) rather than 1,3,2-dioxathiolanes (9b), by analogy with the reaction of these sugar derivatives with acetone.

However, the fact that glycerol yields a five-membered cyclic sulfite and that cyclic sulfites are prepared more readily from 1,2-glycols than from 1,3-glycols (see Chapter 8, section I A-1a) suggests that the 1, 3, 2-dioxathiolane structure is more reasonable for these compounds and they are therefore listed here. Nevertheless, there is some evidence that 1,4-anhydroxylitol forms a six-membered cyclic sulfite rather than a five (see Chapter 8, section I B), and more definitive evidence as to the structure of these compounds is required.

Asselineau prepared the cyclic sulfite esters of a number of esters and amides of mycolic acid. Inasmuch as the structure of mycolic acid is unknown, it is not known whether these compounds are derivatives of 1,3,2-dioxathiolane or 1,3,2-dioxathiane. Boehm chlorinated cellulose with thionyl chloride and pyridine; he postulated the intermediate formation of a cyclic sulfite, which then reacted with pyridine hydrochloride to yield the chlorinated cellulose.

Several novel syntheses of cyclic sulfites have been reported. Bis-singer, Fredenburg, and co-workers, prepared 4-vinyl-1,3,2-dioxathiolane 2-oxide (10) by the alcoholysis of dimethyl sulfite with erythrol.

[For references, see pp. 57-61.]
In a somewhat related synthesis, Hesse\textsuperscript{50,50a} found that treatment of an alcohol with sulfur dioxide and diazomethane gave a mixed sulfite ester. Presumably the alcohol and sulfur dioxide are in equilibrium with the half-ester of sulfurous acid, which is methylated by diazomethane. When applied to ethylene glycol, methyl 2-hydroxyethyl sulfite (11) was formed, and this on heating was converted into ethylene sulfite.

\[
\text{HOCH}_2\text{CH}_2\text{OH} + \text{SO}_2 \rightarrow \text{HOCH}_2\text{CH}_2\text{OSO}_2\text{H} + \text{CH}_2\text{N}_2 \rightarrow \text{HOCH}_2\text{CH}_2\text{OSO}_2\text{CH}_3
\]

Several patents have appeared on the synthesis of ethylene sulfite from ethylene oxide and sulfur dioxide. Thus, according to Viard\textsuperscript{76,85} the 1:1 complex of ethylene oxide and sulfur dioxide, formed from the two reagents at room temperature, is treated with a tertiary amine. A polymer is formed, and this on heating is converted into ethylene sulfite; both reactions are essentially quantitative.

Gruschke\textsuperscript{48} has reported the direct preparation of ethylene sulfite by passage of ethylene oxide and sulfur dioxide over silver oxide on charcoal catalyst at 220°. According to Dietrich and Höfermann,\textsuperscript{36} however, the conversion is incomplete by this process, and better results are obtained by carrying out the reaction in the liquid phase under pressure.

Razuvaev, Éllis, and Grobov\textsuperscript{68a} were unable to obtain ethylene sulfite by these procedures. According to these authors the reaction is catalyzed by quaternary ammonium salts. Heating equimolar quantities of ethylene oxide and sulfur dioxide for 3 hours at 110–120° in the presence of a catalytic quantity of tetraethylammonium bromide yielded a polymer which, on distillation with a free flame, gave a 57% yield of ethylene sulfite plus some dioxane and acetaldehyde. In this manner they prepared 4-methyl-, 4-chloromethyl-, and 4-hydroxymethyl-1,3,2-dioxathiolane 2-oxide from propylene oxide, epichlorohydrin, and glycidol, respectively.
England, Dietrich, and Lindsey\textsuperscript{36b} reacted tetrafluoroethylene with undistilled sulfur trioxide, and found that three products were formed: 3, 3, 4, 4-tetrafluoro-1, 2-oxathietane 2, 2-dioxide (11a); 4, 4, 5, 5-tetrafluoro-1, 3, 2-dioxathiolane 2-oxide (11b); and 5, 5, 6, 6-tetrafluoro-1, 3, 2, 4-dioxadithiane 2, 2, 4, 4-tetroxide (11c).

\[ \text{F}_2\text{C}==\text{CF}_2 + \text{SO}_3 \xrightarrow{38^\circ} \]

11a \quad 11b \quad 11c

Although 11b could not be separated from 11a by distillation, both a neutral equivalent determination on the mixture and NMR indicated its presence. This was confirmed by treatment with amines, aniline yielding oxanilide and cyclohexylamine \( N, N' \)-dicyclohexyloxamide, neither product being formed from pure 11a. With freshly distilled sulfur trioxide 11a was formed in nearly quantitative yield.

The cyclic sulfites which are reported in the literature are listed in Table 1.

2. Structure and Physical Properties

1, 3, 2-Dioxathiolane 2-oxides very probably exist as slightly puckered five-membered rings, although the actual structure has not been determined. Ethylene sulfite has been reported by Arbuzov and co-workers\textsuperscript{8,8a} to have a dipole moment of 3.65 D, and a parachor of 194.3. Using bond lengths and angles determined on open-chain sulfites, it was calculated that a planar ring structure had a dipole moment (3.48 D) closest to the experimental value. They concluded, however, that the ring is puckered, with the sulfur atom about 40° out of the plane and with 11d (4.56 D) contributing more to the structure than 11e (2.04 D).

\[ \]

11d \quad 11e

Pritchard and Lauterbur\textsuperscript{67a} found a dipole moment for ethylene sulfite of 3.74 D, which they claimed is in agreement with a planar or a slightly puckered ring. Inasmuch as the three oxygens on the sulfur are not in a plane, the four hydrogens are not equivalent, and these authors found a very complicated proton magnetic resonance spectrum for ethylene sulfite attributable to this dissymmetry. 4, 4-Dimethyl-1, 3, 2-dioxathiolane 2-oxide (2a) gave a simpler spectrum, a quadruplet for the two ring protons and two singlets for the non-equivalent methyl groups.

[For references, see pp. 57-61.]
<table>
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<th>Substituent</th>
<th>Glycol</th>
<th>Yield (%)</th>
<th>M. p. (°C)</th>
<th>B. p. (°C)</th>
<th>Other properties</th>
<th>Ref.</th>
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<td>64-66.5</td>
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<td>57</td>
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<td>n_0^2 1.4446</td>
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