THIAZOLE AND ITS DERIVATIVES

PART ONE

Edited by Jacques V. Metzger

UNIVERSITY OF AIX-MARSEILLES FRANCE

AN INTERSCIENCE (8) PUBLICATION

JOHN WILEY & SONS

NEW YORK · CHICHESTER · BRISBANE · TORONTO

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THIAZOLE AND ITS DERIVATIVES

IN THREE PARTS

PART ONE

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

This is the thirty-fourth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors



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Contributors

J. P. Aune, University of Aix-Marseilles III, France
J. Chouteau, University of Aix-Marseilles III, France
J. Crousier, University of Aix-Marseilles I, France
H. J. M. Dou, University of Aix-Marseilles III, France
L. Forlani, University of Bologna, Italy
J. Metzger, University of Aix-Marseilles III, France
R. Meyer, University of Aix-Marseilles III, France
G. Mille, University of Bologna, Italy
G. Vernin, University of Aix-Marseilles III, France
E. J. Vincent, University of Aix-Marseilles III, France

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To the memory of

ARTHUR RUDOLF HANTZSCH

great chemist and teacher and pioneer of thiazole chemistry



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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.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

Research Laboratories Eastman Kodak Company Rochester, New York

Princeton University Princeton, New Jersey ARNOLD WEISSBERGER

EDWARD C. TAYLOR

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Preface

Given their theoretical as well as practical interest, five-membered aromatic rings occupy a position of particular significance in the enormous field of heterocyclic chemistry. Thiazole is one of the important members of this family and thus merits a comprehensive study. The purpose of this book is to condense into a volume of reasonable size the chemistry of thiazole, covering the literature of approximately one century up to December, 1976. For technical reasons this present work has been limited to the study of monocyclic thiazoles, excluding thiamine and partially reduced thiazoles but including selenazoles. Though most of the important material has been published in the last twenty years, all the literature concerning thiazoles has been surveyed, and it is of special interest to see with what energy Arthur Hantzsch was obliged to defend his historical discovery of thiazole.

In the first chapter, devoted to thiazole itself, specific emphasis has been given to the structure and mechanistic aspects of the reactivity of the molecule: most of the theoretical methods and physical techniques available to date have been applied in the study of thiazole and its derivatives, and the results are discussed in detail. The chapter devoted to methods of synthesis is especially developed and traces the way for the preparation of any monocyclic thiazole derivative. Three chapters concern the nontautomeric functional derivatives, and two are devoted to amino-, hydroxy-, and mercaptothiazoles: these chapters constitute the core of the book. All discussion of chemical properties is completed by tables in which all the known derivatives are inventoried and characterized by their usual physical properties. This information should be of particular value to organic chemists in identifying natural or synthetic thiazoles. Two brief chapters concern mesoionic thiazoles and selenazoles. An important chapter is devoted to cyanine dyes derived from thiazolium salts, completing some classical reviews on the subject and discussing recent developments in the studies of the reaction mechanisms involved in their synthesis.

The importance of this work, which was begun by Dr. J. M. Swan of Monash University, Melbourne, Australia, was very quickly recognized, and in 1964 I joined him in his endeavor. Three years later, Dr. Swan was obliged to abandon, and, for the last decade, 17 distinguished scientists have labored to realize this book. I acknowledge with sincere thanks the cooperation and perseverance of all of them, but I am especially indebted to Michel Chanon and his collaborator, René Barone, for the untiring efficiency in management that they have exhibited throughout the realization of this book. I acknowledge also the help of the numerous heterocyclic chemists of the world who sent so many of their valuable reprints to Marseilles. My thanks are also due to Mrs. J. de Caseneuve and Mrs. G. Formanek, who carried out the tedious task of typing the manuscript, and to Thomas Murphy for his help in adjusting the poor original English of most of the manuscript to a hopefully acceptable one. Finally, grateful thanks are due to the University of Aix-Marseilles for financial support and library facilities.

Marseilles, France December 1978 JACQUES V. METZGER

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R. GUGLIELMETTI

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THIAZOLE AND ITS DERIVATIVES

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PART ONE

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THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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Introduction

This volume is intended to present a comprehensive description of the chemistry of thiazole and its monocyclic derivatives, based on the chemical literature up to December, 1976. It is not concerned with polycyclic thiazoles, such as benzo- or naphthothiazole, nor with hydrogenated derivatives, such as thiazolines or thiazolidines: later volumes in this series are devoted to these derivatives. The chemistry of thiamine has also been excluded from the present volume because of the enormous amount of literature corresponding to the subject and is developed in another volume. On the other hand, a discussion of selenazole and its monocyclic derivatives has been included, and particular emphasis has been given to the cyanine dyes derived from thiazolium salts.

The first chapter discusses thiazole itself, its structure, and its physical and chemical properties. The second chapter describes the general synthetic methods for thiazoles and thiazolium salts.

Chapters III to VII discuss the general properties of thiazoles having hydrocarbon and functional substituents, respectively. A special chapter (Chapter VIII) is devoted to *meso*-ionic thiazoles, and Chapter IX describes the thiazolium salts and their numerous cyanine dyes derivatives. The last chapter concerns the monocyclic selenazoles.

Although unsubstituted thiazole is not found in nature, naturally occurring thiazoles are numerous and are described in the chapters corresponding to their structure. Their origin has often been related to the cyclization of a peptide chain at cysteine residue with formation of a thiazoline ring and thence, by dehydrogenation, of a thiazole ring: Several antibiotics, such as althiomycine (1) and micrococcin (2, 3), contain a thiazole ring, as do many metabolic products of living organisms (4, 5); numerous natural aromas contain thiazole derivatives: tomato (6), roasted coffee (7, 8), roasted peanuts (9), the basic fraction of Scotch whisky and Jamaica rum (10) and so on. Thiazoles have also been separated from nitrogen bases of some petroleums (11). Many thiazole derivatives possess biological activity, and numerous medicaments contain a thiazole ring in their structure.

Among the pentaatomic heterocyclic rings, thiazole is one of the most intensively investigated, and its chemistry maintains steadily its intensive development. The number of annual publications dealing with monocyclic thiazoles is continuously growing, and the excellent but condensed review published in 1957 by Sprague and Land (12) is now quite obsolete. The Card Index of Thiazole Compounds edited by Prijs in 1952 (13) described the 2100 individual thiazolic compounds known at that time; unfortunately more recent editions have not been published, and the present number of known compounds is greater than 12,500. Since 1970 a condensed but comprehensive biannual review of the published work concerning thiazole appears in the collection, "Organic compounds of S, Se and Te," edited by The Chemical Society under the signature of F. Kurzer (14-16): this excellent review calls with insistence for "the volumes concerning the chemistry of thiazole, in the series of monographs edited by A. Weissberger." This book is an attempt to fill this gap.

Most chapters contain tables giving an inventory of all known derivatives of the family concerned. The classification of substituents in these tables is made according to the following hierarchy:

- 1. Nature of the heteroatom bonded to the ring: C(N)O(S)P.
- 2. Simply bonded doubly bonded substituents.

3. Size of the substituent: $-H \rightarrow -CH_3 \rightarrow -CH_2R \rightarrow -CHR_2 \rightarrow -CR_3 \rightarrow -CH =$ CR =aryl $\rightarrow -C =$ halogeno $\rightarrow -NH_2 \rightarrow -NHR \rightarrow -NR_2 \rightarrow -OH$ $OR \rightarrow -SH \rightarrow -SR \rightarrow -PR_2$

In these tables most of the reference numbers are accompanied with small letters, the significance being that the paper concerned deals with one or several of the following topics:

- a. Practical application
- c. Cotton effect, circular dichroïsm
- d. Dipole moment
- e. Medicament, pesticid
- f. Fluorescence, phosphorescence

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- g. Vapor-phase chromatography
- h. HMO and other theoretical evaluations
- i. Infrared spectrometry
- k. Kinetic data
- 1. Living material
- m. Mass spectrometry
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- z. Optical properties

REFERENCES

- 1. H. A. Kirst, E. F. Szymanski, D. E. Dorman, J. C. Occolowitz, N. D. Jones, M. O. Chaney, R. L. Hamill, and M. M. Hoehn, J. Antibiot., 28, 286 (1975).
- 2. P. Brookes, A. T. Fuller, and J. Walker, J. Chem. Soc., 689 (1957).
- 3. M. N. G. James, and K. J. Watson, J. Chem. Soc. C, 1361 (1966); Chem. Abstr. 65, 12189H.
- 4. J. Jadot, J. Casimir, and R. Warin, Bull. Soc. Chim. Belges, 78, 299 (1969).
- 5. Y. Yamada, N. Seki, T. Kitahari, M. Takahashi, and M. Matsui, Agric. Biol. Chem. Japan, 35, 780 (1970); Chem. Abstr. 73, 35265.
- R. Viani, J. Bricout, J. P. Marion, F. Mueggler-Chavan, D. Reymond, and R. H. Egli, Helv. Chim. Acta, 52, 887 (1969), Chem. Abstr. 71, 11875
- 7. O. G. Vitzthum, and P. Werkhoff, J. Food Sci., 39, 1210 (1974).
- 8. O. G. Vitzthum, and P. Werkhoff, Z. Lebensm. Forsch., 156, 300 (1974).
- J. P. Walradt, A. O. Pittet, T. E. Kinlin, R. Muralidhara, and A. Sanderson, J. Agric. Food Chem, 19, 972 (1971); Chem. Abstr. 75, 108666.
- 10. H. J. Wobben, R. Timmer, R. Ter Heide, and P. J. De Valois, J. Food Sci., 36, 464 (1971); Chem. Abstr. 75, 3997.
- S. L. Gusinskaya, V. Y. Telly, and A. Aidogdyev, Uzbek. Khim. Zhur., 11, 21 (1967). Chem. Abstr. 67, 4551.
- 12. J. M. Sprague, and A. H. Land, "Heterocyclic Compounds," R. C. Elderfield, ed., Wiley, New York, 1957, Vol. 5, p. 485.

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- 13. B. Prijs, "Kartothek der Thiazol Verbindungen," Karger, Basel, 1952, Vols. 1-4,
- 14. F. Kurzer, "Organic Compounds of Sulphur, Selenium and Tellurium," D. H. Reid, Ed., Chemical Society, London, 1970, Vol. 1, p. 378.
- F. Kurzer, "Organic Compounds of Sulphur, Selenium and Tellurium," D. H. Reid, Ed., Chemical Society, London, 1973, Vol. 2, p. 587.
- 16. F. Kurzer, "Organic Compounds of Sulphur, Selenium and Tellurium," D. H. Reid, Ed. Chemical Society, London, 1975, Vol. 3, p. 566.

Properties and Reactions of Thiazole

I

JACQUES V. METZGER

Laboratoire de Chimie Organique, Faculté des Sciences et Techniques de Saint-Jérôme, Marseille, France

EMILE-JEAN VINCENT

Laboratoire de Chimie Organique Physique, Faculté des Sciences et Techniques de aint-Jérôme, Marseille, France

with the collaboration of

JACQUES CHOUTEAU AND GILBERT MILLE

Centre de Spectroscopie Infra-rouge, Faculté des Sciences et Techniques de Saint-Jérôme, Marseille, France

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I. GENERAL ASPECTS

1. Introduction

This chapter follows the general pattern of the series, starting in Section I with a historical survey of the most important points in the discovery of thiazole and the long-known derivatives of this molecule, followed by its preparations and the description of its electronic structure. The second section presents the most interesting physical properties of thiazole and some of its simple derivatives. The third section is devoted to the chemical reactivity of the thiazole molecule; it is followed by a short section relating the effect of the thiazole ring on substituents, and finally a brief discussion of free-energy relationships in this system is given. Most of the general aspects of thiazole chemistry are only briefly discussed here: they are developed in the following chapters.

A. Numbering the Thiazole Ring

First described by A. Hantzsch and J. Weber (1) as "the pyridine of the thiophene series," thiazole (1) received a nomenclature conforming to this definition (2): the letters α and β were justified by the great analogy of both positions with the corresponding ones of pyridine, while the *meso* position, to which μ was assigned, had no equivalent in the pyridine ring. In Richter's *Lexikon*, as well as in the second edition of Meyer-Jacobson's *Lehrbuch der Organischen Chemie*, the sulfur atom was numbered 1 and the nitrogen 3 (2). Other nomenclatures have also been used: T. B. Johnson (3) proposed the numbering **3**, whereas J. Metzger et al. (4-14) used another system (4) then recommended by Grignard's *Traîté de Chimie Organique* (15). The correct numbering is that given by The Ring Index (16) and Chemical Abstracts, and corresponds to **2**.



2. A Brief History of the Discovery of the Thiazole Ring

On November 18, 1887, Arthur Rudolf Hantzsch with his collaborator, J. H. Weber, signed the birth certificate of thiazole. Under the title, "Ueber Verbindungen des Thiazoles (Pyridins der Thiophenreihe)," Hantzsch and Weber (1) gave the following definition: "Unter Thiazolen verstehen wir diejenigen Stickstoff und Schwefel in ringförmiger Bindung enthaltenden Substanzen von Formel (CH)₃NS, welche sich zum Pyridin verhalten, wie das Thiophen zum Benzol." They proved the existence of both thiazole (5) and isothiazole (6), although neither of these was then known in the free state, compared them to glyoxaline and pyrazole, respectively, and proposed to name benzothiazole the "Methenylamidophenylmercaptan" just discovered by A. W. Hofmann (17). Extending this definition they proposed naming the three azole derivatives of thiophen, pyrrole, and furan: thiazole, imidazole and oxazole, respectively, and their benzo-derivatives, benzothiazole, benzimidazole, and benzoxazole. Making allowance for the high reactivity of the groups attached to the carbon atom placed between sulfur and nitrogen they proposed the prefix meso for this position in the normal azole series. They noted that numerous derivatives of thiazole could already be known without their constitution being correctly described: they ascribed all the so-called α -thiocyano derivatives of ketones and aldehydes (7) ("Rhodanketone") to being thiazole derivatives, especially meso-oxythiazoles (8).



Hantzsch and Weber began their description with the compound which led them indirectly to the discovery of the thiazoles: the α thiocyanoacetone imine ("Rhodanpropimin") of J. Tcherniac and C. H. Norton, C₄H₆N₂S, obtained by reaction of ammonium thiocyanate with chloroacetone. After Tcherniac and Norton (18), the α thiocyanoacetone (9) first formed would react with a second molecule of ammonium thiocyanate to give the thiocyanate of α -thiocyanoacetone imine (10). The physical properties of the new base prompted Hantzsch and Weber to study its structure carefully, and they discovered it to be cyclic and derived from the thiazole nucleus (11):



m-aminomethylthiazole. Although most of the classical reactions of primary amines were unsuccessful, reaction with methyl iodide showed the presence of two (and only two) hydrogens fixed at nitrogen, and the acetylation proved them to be attached to the same nitrogen atom. The dimethylamino derivative (12) thus obtained reacted with bromine to give a monobromo compound (13) the constitution of which was only compatible with the formula of a trisubstituted thiazole.



Looking back to the precursor of the aminomethylthiazole (11), Hantzsch and Weber studied the so-called thiocyanoacetone (9). This compound had been already prepared by Tcherniac and Hellon (19) by the action of barium thiocyanate with chloroacetone and was described by these authors as an oily product ("Rhodanacetone"). Hantzsch and Weber, introducing a *slight* modification to the preparation given by Tcherniac and Hellon (salting out the product from its aqueous solution by adding Na_2CO_3), obtained a white solid (m.p. 98°) that did not show the classical properties of ketones but contained an hydroxyl group exchangeable with chlorine under the action of PCl_5 , and to which they attributed the structure of *m*-oxymethylthiazole (14). The cyclic nature of



the compound was compatible with the analogous formula attributed eight years earlier by C. Liebermann and A. Lange (20) to the product called "Senfölessigsaüre" (senevolacetic acid) (17), obtained, according to Claesson (21) and Nencki (22, by hydration of sulfocyanoacetic acid (15) to give 'carbaminthioglycolic acid" (16) and its subsequent dehydration: Hantzsch and Weber proposed the name dioxythiazole for 17. In the

same way one could consider the similar structure of the "rhodaninacetic acid" of M. Nencki (22), the constitution of which was demonstrated by Liebermann and Lange (20) to be that of a sulfur derivative of dioxythiazole (18). Finally, in a subsequent paper (23), Hantzsch and Weber recalled the thiazolic structure of the long-known thiohydantoïne of Maly (24) to which Liebermann and Lange (20) attributed the cyclic formula 19. Shortly after, Arapides (25), a collaborator of Hantzsch,





Scheme 10

prepared thiocyanoacetophenone (20) (m.p. 74°C) (cf. R. Dyckerhoff (26) and proved it reactive in hot concentrated hydrochloric acid, forming the soluble "carbaminthioacetophenone" (21) (m.p. of the chlorhydrate, 175 to 180°C), which by further heating of the solution eliminated 1 mole of water to give 2-oxy-4-phenylthiazole (22) (m.p. 204°C). He isolated thiocyanoacetone (9) working in accordance with the data of J. Tcherniac and



R. Hellon (19) but using anhydrous reagents. He obtained an oil that reacted exothermically with hydroxylamine (oxime of m.p. 135°) and that isomerized to 2-oxy-4-methylthiazole (14) upon heating with diluted hydrochloric acid. The thiazolic nature of oxymethylthiazole was clearly demonstrated by its reduction by zinc powder distillation into 4-methylthiazole (23), the first free thiazole ever described.



Tcherniac did not readily accept the conclusions of Hantzsch and his collaborators (1, 25) and four years later, in July, 1892, published a series of papers (27-30) opening a polemic that was to continue for 36 years! A few details concerning this historical controversy merit being related to give an insight into the development of the chemistry of thiazole. In July, 1892, Tcherniac condemned the unsparing criticism of Hantzsch, who asserted (1) that the product obtained by Tcherniac and Hellon (19) was an impure sample of 4-methyl-2-oxythiazole; the impudence of Arapides (25) who claimed the discovery of the true thiocyanatoacetone; and explained the failure of the method of Tcherniac and Hellon by the ability of thiocyanoacetone to isomerize into methyloxythiazole by a hydration-dehydration process, catalyzed by strong acids. Tcherniac, again taking up his preparation of thiocyanatoacetone, used highly purified material and

careful conditions of extraction of the product. He asserted that he had obtained an analytically pure sample of thiocyanoacetone that resisted isomerization either by contact with water or even by heating in a waterbath with dilute HCl. On the contrary, isomerization took place upon contact with a basic reagent, like the Na₂CO₃ used by Hantzsch and his collaborators to extract the product of reaction, or CaCl₂ (always containing traces of Ca(OH)₂) used to dehydrate their etheral solutions. To determine the purity of these samples of thiocyanoacetone Tcherniac measured the elevation of temperature caused by their isomerization to methyloxythiazole under the influence of Na₂CO₃.

Three months later, in October, Hantzsch published an impetuous response (31) to the series of papers by Tcherniac, in which his work with J. Weber (1) and Arapides (25) had been severely criticized. He emphasized the correctness of the structure proposed for "Rhodanpropimin" and, as for the thiocyanoacetone of Tcherniac, he recalled the scarcity of the data given by Tcherniac and Hellon concerning the purity and the properties of the so-called "Rhodanacetone." He defended both his collaborators, showing how Arapides was able to discover the isomerization of thiocyanoacetone to thiazole. Finally he protested vehemently against "the attitude of that chemist who had not been able to note the inconsistency between the wrong formula he attributed to Rhodanpronimin and its chemical behavior, who had not been able to pick up oxymethylthiazole, though well crystallized, and who accused of crude errors conclusions that corrected, in several essential points, his own statements and thus allowed opening the field, then new, of thiazole." Two months later, December 5, 1892, Tcherniac, in an overbearing paper (32), described with self-satisfaction an accurate method using NaHCO₃ as a basic reagent to induce the isomerization of thiocyanoacetone into methyloxythiazole. Operating on large quantities he was able to obtain, with a yield of 40%, a sample of 2-oxy-4-methylthiazole melting at 105 to 106°C, whereas Hantzsch reported a melting point of 98°.

The controversy seemed then to be closed. In 1890 Hantzsch had already started his work on the structure of oximes, and his synthetic work on heterocycles was practically ended. However, 27 years later, in July 1919, Tcherniac published a new paper entitled 'Thiocyanoacetone and its derivatives as isomerides'' (33), where, after the description of improved and generalized methods for the preparation of thiocyanoacetone he came to the explosive conclusion that "the substance which has been known since 1887 as hydroxymethylthiazole is not a thiazole at all. It might be called 2-imino-4-methylthioxole, but for the sake of simplicity, and in view of the now proved existence of two other isomerides of thiocyanoacetone, it seems preferable to adopt the generic