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**Five- and Six-Membered Compounds**  
**with Nitrogen and Oxygen**  
**(Excluding Oxazoles)**

EDITED BY RICHARD H. WILEY

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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  
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ARNOLD WEISSBERGER

## Preface

It is appropriate in a preface to this volume to comment on some of the more impressive features of the chemistry of the O—N heterocycles. For over a century, this field, as most of the branches of heterocyclic chemistry, has presented an intriguing array of remarkable discoveries and of research challenges. Substantial accomplishments—both utilitarian and theoretical—have resulted, and one has great respect for the talents of the many renowned organic chemists who have labored, with inspiration and insight, to establish the presently available body of information covered in this volume. It is with humility and appreciation that we, the authors of this volume, summarize and present this report on their research.

Foremost among the problems presented by O—N heterocyclic chemistry is that of the assignment of appropriate structures to compounds whose properties do not, or did not, fit a standard pattern. Some of these problems have been solved readily with the advent of present-day structural concepts. Thus, the *cis-trans* isomers of the nitrile oxide–stilbene and nitrile oxide–maleic or fumaric ester reaction products have been established as *cis-trans* isomers of the corresponding isoxazolines using characteristic infrared absorption bands (p. 105), and the keto-enol character of the isoxazolones has been clarified using ultraviolet absorption characteristics (page 206). The *o*-quinoid character of the anthranils (page 159); the benzofurazans (page 292), and the phenoxazonium salts (page 427) presents a structural problem of broad significance for which partially satisfactory explanations now seem at hand. Similarly, the diazophenol structure seems reasonably well explained (page 238). Other systems such as the sydnones (page 240), the furoxans (pages 296, 305), and benzofuroxan (page 308) present structural problems which still involve elements of uncertainty or controversy or a high degree of novelty. Some of the most interesting structural studies have made possible a considerable advance in the understanding of the chemistry of fulminic acid through characterization of the furoxans (pages 310, 311) and isoxazoles (page 23) derived from it.

There are also some reactions leading to O—N heterocycles, the more complete understanding of which will contribute measurably to the advance of our knowledge of organic reaction mechanisms. These are the

characteristic four-center reactions of the nitrile oxides leading to the dimeric furoxans (page 297), isoxazoles (pages 19–22), and isoxazolines (page 29). This type of reaction, with its parallels in the diene additions and azide and diazo cyclizations, is of considerable theoretical significance as its mechanism seems rather difficult to establish. Other peculiar rearrangements have been encountered in the alkaline degradation of actinomycins (page 424) and with the indole ozonides (page 360). In the chemistry of the nitric acid reactions, unusually baffling problems have been carried through to plausible explanations after much study. Some of these include the nitric acid–acetylene reactions (page 31), the nitric acid–resorcinol reactions leading to resorufin (page 417), and the products from reactions of nitric acid with acetone (page 30) and with citraconic acid (page 29).

The importance of O—N heterocycles in biological systems is evidenced by the isolations of cycloserine (D-4-amino-3-isoxazolidone) from *Streptomyces garyphalus* or *orchidaceus*; the actinomycins (polypeptide derivatives of dicarboxyphenoxazones, pages 423–4); from *streptomyces antibioticus*, *parvus*, and *chrysomallus*; xanthommatin (a pyridophenoxazone, page 425) from various insect tissues; and cinnabarin (a phenoxazone, page 426) from a red fungus pigment. The phenoxazones, at least the insect types, are apparently products of tryptophan metabolism. The relation of cycloserine to serine is structurally obvious and raises the question of the biological significance of either hydroxylamine or some *N*-hydroxy structure. Clarification of these relations between structure and activity is certainly important as a basis for further advances in the design of structures of pharmacological interest. This activity certainly is to be regarded favorably in view of the utility of such products as sulfoxazole (Gantrisin, the sulfa drug derived from 3,4-dimethyl-5-aminoisoxazole, page 225) and 5-methyl-3-phenyl-4-isoxazolympenicillin (Prostaphlin).

In addition to the pharmaceuticals derived from isoxazole structures, there are other O—N heterocycles of technical utility. Among these are several phenazone dyestuffs: Gallocyanine (page 418), Nile Blue A (page 420), and Meldola's Blue (page 428), which have established markets, and the one product in the class which may well be classified as a bulk commodity—morpholine. Available from ethylene oxide and ammonia, morpholine has found numerous practical applications and is used as an intermediate in the manufacture of several products.

The volume was originally planned to cover all of the O—N heterocycles including the oxazoles. However, as the various parts of the text were being completed, the section on oxazoles had not yet been submitted. A late change of authorship was certain to delay the complete volume,

and, at the same time, the amount of material for the other sections exceeded our original estimates. These problems seemed best resolved simply by excluding the oxazoles, thereby assuring the prompt publication of a reasonably sized volume of pertinent material. It is hoped that this compromise will not be confusing, and that a companion volume on oxazoles will be prepared for the series.

The literature surveys on which the various parts of this volume are based were completed prior to 1960 using the then available indexes. They are, thus, hopefully reasonably complete through the 1958 indexes. No claim as to exhaustive coverage of this vast segment of the chemical literature is made. Many selections from the available material were made to include those things deemed to be of general interest. In the intervening years the literature has been followed by the authors of the separate parts of the volume with the intent of adding as many significant references as possible up to the last moment. This has made possible the addition of a selection of references into 1962. Again complete coverage is not claimed. It is hoped that those whose research, through oversight or inaccessibility, has not been cited will feel free to send reprints to the authors and will accept our apologies for this difficult situation.

The R.I. (Ring Index) numbers cited are the number from the second (1960) edition of the Ring Index and correspond to the RRI numbers given in the conversion Tables on pages 1411-1425 and in the text of the second edition. A complete compilation of O—N ring types given in the Ring Index has not been made and the compilation has been treated somewhat differently by the authors of the three Parts to accommodate problems of different dimensions.

The authors wish to thank the many persons who have assisted in the preparation of this volume. We are grateful for the careful assistance of our several secretaries in typing the manuscripts, to those authors who generously made reprints available, to the staff of the Interscience Division of John Wiley & Sons for the patient help with the handling of the manuscript and proofs, and to Miss Dorothy Ellison of the University of Louisville who retyped the revised English version of Part I and the tables therein.

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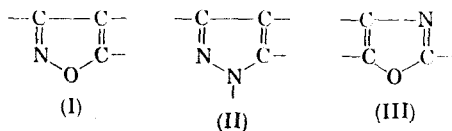
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## ISOXAZOLES AND RELATED COMPOUNDS

ADOLFO QUILICO

## INTRODUCTION

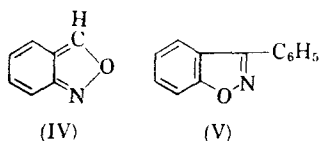
The chemistry of isoxazole is associated with the name of Ludwig Claisen, who recognized in 1888 the cyclic structure of the product (3-methyl-5-phenylisoxazole) that Ceresole<sup>1</sup> had obtained in 1884 from the action of hydroxylamine on benzoylacetone. He advanced the hypothesis that it might contain the five-membered ring  $C_3NO$  (I), the oxygen analog of the  $C_3N_2$  ring of *pyrazole* (II).<sup>2</sup> Claisen suggested for it the name of *monoazole*, which was eventually modified by Hantzsch<sup>3</sup> to *isoxazole*, from the already known isomeric ring of the *oxazole* (III) (Ring Index 118).



The study of the action of hydroxylamine on benzoylactaldehyde<sup>4</sup> and acetoacetaldehyde<sup>5</sup> led Claisen to the discovery of monosubstituted isoxazoles and of the so-called "sesquioximes," intermediate products of the reaction between hydroxylamine and  $\beta$ -ketoaldehydes. In 1891 he published his classical paper "Ueber Isoxazole,"<sup>6</sup> in which was reported the fundamental outline of isoxazole chemistry and the first example of a *bis-isoxazole*. A new synthesis of the isoxazole ring was discovered by Dunstan and Dymond in 1888:<sup>7</sup> on heating nitroethane with aqueous alkalies, they isolated a liquid base to which they assigned the correct structure of 3,4,5-trimethylisoxazole after demonstrating that it was different from the isomeric, already known trimethyloxazole.<sup>8</sup>

The first benzisoxazole, *anthranil* (IV), was described in 1882.<sup>9</sup> A phenyl derivative of  $\alpha,\beta$ -benzoisoxazole, *phenylindoxazene* (V), was prepared in 1892 by Cathcart and Meyer<sup>10</sup> (Ring Index 1123, 1124).





To Claisen we are also indebted for the discovery of *isoxazolones*, the oxygen analogs of pyrazolones. By treating benzoylacetic ester with hydroxylamine he obtained 3-phenylisoxazolone.<sup>11</sup> This reaction also had been investigated in the same year by Hantzsch,<sup>12</sup> who found that  $\beta$ -ketonic esters when treated with hydroxylamine do not form oximes, but yield dehydration products of acidic character, isoxazolones, which he studied thoroughly.

A simple isoxazole derivative, *4-nitroisoxazole*, had been prepared in 1899 by Hill and Torrey<sup>13</sup> from nitromalondialdehyde and hydroxylamine. The parent member of the series, *isoxazole*, was synthesized by Claisen in 1903 from propargylic aldehyde acetal and hydroxylamine.<sup>14</sup> By extending this reaction to other acetylenic aldehydes and ketones, Moureu and associates achieved the synthesis of a number of homologs.<sup>15</sup> New routes to the isoxazole synthesis were shown by the researches of Wieland on the action of nitrous acid on ethylenic aldehydes and ketones<sup>16</sup> and of Schmidt on the action of nitric acid on  $\gamma$ -dicarbonyl derivatives.<sup>17</sup> Further important contributions to isoxazole chemistry are: von Auwers studies on the action of hydroxylamine on ethylenic ketones<sup>18</sup> and on the structure of "sesquioximes";<sup>19</sup> the discovery by Kohler of the *isoxazoline oxides*;<sup>20</sup> and the synthesis of the isoxazole ring from benzohydroxamyl chlorides and acetylenic derivatives<sup>21</sup> (Weygand and Bauer, 1927).

More recently, the development of isoxazole chemistry has advanced from the discovery of new synthetic methods. Most of these are based on the capacity of substances containing the highly reactive group  $\text{—C}\equiv\text{N}\rightarrow\text{O}$ , found in nitrile oxides<sup>22</sup> and fulminic acid,<sup>23</sup> to react with aliphatic triple and double bonds forming respectively the isoxazole and isoxazoline ring. Substances such as hydroxamyl chlorides<sup>24</sup> and nitrolic acids,<sup>25</sup> capable of releasing nitrile oxides under suitable conditions, have been used also. The nitrile oxide synthesis of isoxazoles has taken its origin from earlier investigation on the action of nitric acid on acetylene and other unsaturated compounds which leads to isoxazole derivatives (Quilico and associates, 1929–1946).

From the historical point of view it is worth mentioning that two representatives of this series had been isolated as early as 1852 and listed in the Beilstein Handbuch among the "*corps à sérier*" of unknown constitution. It was demonstrated (Quilico and Fusco, 1946) that *eulite* and *dislite*, obtained by Baup<sup>26</sup> from the action of concentrated nitric acid on citraconic acid, are actually polynitro derivatives of isoxazole (VI)<sup>27</sup> and 3,3'-bis-isoxazole (VII).<sup>28</sup>

