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Nitroazoles: Synthesis, Structure and Applications

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Preface

The present monograph is devoted to the chemistry of nitroazoles, one of the most interesting series of heteroaromatic compounds. The azoles hold a special position in the chemistry of heterocycles. Their unique properties and specific biological activity attract much attention of research chemists all over the world. During the last years the interest in the chemistry of nitroazoles has increasing. The nitro derivatives of azoles have found a wide application in various fields of industrial chemistry, agriculture, and medicine. Medical products developed by nitroazoles incluce azomycin, metronidazole, misonidazole, tinidazole, nitazole, etc., ionic liquids, high-energy materials, synthons for nanocompounds, universal bases in peptide nucleic acids, plant growth regulators, and intermediates for organic synthesis.

The investigations in the field of energetic compounds have received enormous interest in recent years. Energetic materials on the base nitroazoles – explosives, propellants, and pyrotechnics – are widely used for both civilian and military applications. Nitroazoles, especially polynitroazoles, possess higher heat of formation, density, and oxygen balance than their carbocyclic analogs. A number of ongoing research programs worldwide are aimed for the development of new explosives and propellants with higher performance characteristics or enhanced insensitivity to thermal or shock insults and pyrotechnics with reduced smoke. The preparation of nitroazoles demonstrates its great synthetic potential. At the same time, feasibility and availability of the starting molecules make this strategy a powerful method for high-energy material construction. The introduction of electron-withdrawing nitro groups into azole cycle tends to produce energetic materials with high density, low sensitivity, and good thermal stability. Synthesis, molecular design, and explosive characteristics of new energetic compounds based on nitroazole have been studied in the famous Lawrence Livermore National Laboratory (USA). The investigations of research teams of A. Katritzky, A. Pozharskii, J. Elguero, S. Shevelev, V. Semenov, A. Sheremetev and so on, unveil the wide synthetic possibility of producing nitroazoles.

We consider azoles as five-membered heteroaromatic compounds and their annelated derivatives containing at least two endocyclic heteroatoms, one of which is nitrogen (pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, thiazole, selenazoles, tetrazole, indazole, benzimidazole, benzoxazole, benzothiazole, benzoselenazoles, benzotriazole, etc.).

A large body of information on the methods of synthesis, application, structure, and properties of all known five-membered nitroazoles – pyrazoles, imidazoles, triazoles, tetrazoles, oxazoles, isoxazoles, oxadiazoles, thiazoles, isothiazoles, thiadiazoles, selenazoles, selenadiazoles, and their benzo analogs – indazoles, benzimidazoles, benzoxazoles, benzisoxazoles, benzoxadiazoles, benzothiazoles, benzoisothiazoles, benzothiadiazoles, benzotriazoles, benzoselenazoles, and benzoselenadiazoles has been systematized, summarized, and critically discussed in this monograph.

Chapters 1 and 2 give comprehensive data on the preparation methods of all known *C*- and *N*-nitroderivatives of five-membered azoles and their condensed analogs. This book focuses on the nitration reaction, one of the main synthetic routes to nitroazoles. General information on the theory of nitration is given prior to the chapter covering synthetic methods. A separate section in the monograph is given to the special class of nitroazoles – polynitroazoles.

The critical evaluation of a large body of the information on the study of nitroazoles by physical/chemical methods (NMR, NQR, ESR, UV, IR- spectroscopy, X-ray, mass spectrometry, polarography, dipole moments, and other methods) is presented in Chap. 3.

Chapter 4 is devoted to the application of nitroazoles, many of which are important building blocks in drug discovery, well-known medicines, and hypoxic cell radiosensitizers.

Special attention is paid to those nitroimidazole derivatives among which are medicines with a vividly expressed therapeutical activity (azomycine, metronidazole, ipronidazole, carnidazole, dimetridazole, secnidazole, and many others) and to nitrotriazoles, nitrotetrazoles, and polynitroazoles used as high-energy compounds.

Our extensive investigations of the tautomerism, reactivity, electrochemistry, and structure of nitro derivatives of azoles are also included. Enormous number of facts are covered in the book.

This treatise constitutes the first complete collection of information on the chemistry of azoles containing a nitro group in the cycle. The monograph of Prof. Boyer (1986) on nitroazoles deals with only the *C*-nitro derivatives of *N*- and *N*,*O*-containing five-membered heterocycles, whereas the *N*-nitro derivatives presenting a new class of the oxide nitrogen generators (in particular, *N*-nitropyrazoles), as well as also thia- and selenazoles and all benzazoles remained unheeded. Prof. J.H. Boyer has noted that "that 'rapid development' of the chemistry of the nitroazoles in the Soviet Union began about 1960 and has provided more journal publications of research in the area than were found for any other country" and "the Russian emphasis on investigating" nitroazoles "has been outstanding."

This monograph provides comprehensive systematization of data on *C*- and *N*-nitroazole chemistry with in-depth information on structure and preparation, that is, nitration reactions and heterocyclization.

The monograph is mainly addressed to research professionals, research scientists (chemists, physicists, pharmaceutics, biochemists, chemical technologists), engineers, and "physicians—especially those dealing with oncology". This book can be used as a textbook for postdoctorals and graduate students in chemistry, biochemistry, medical pharmacology, agricultural bioapplications, and for all who want to get acquainted with the chemistry and structure of nitroazoles.

The book may be of interest for the specialists dealing with the production of high-energy compounds (gas generators for air-bags, explosives, propellants, and pyrotechnics), nanomaterials, polymers, fibers, superelectrophiles, nonlinear optical materials, dyes (including fluorescent and cyanine dyes), and inhibitors of metal corrosion. It is also useful for people working in pharmaceutical industry.

We hope that it will be an invaluable reference for professionals in the field of heterocyclic chemistry, and that this book will initiate new investigations in this area.

The recent nature of the material and a large number of references (~2,200) make the book interesting for a wide range of specialists.

The authors would greatly appreciate receiving from readers any suggestions, comments, and recommendations.

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Contents

Introduction

Vigorous development of the chemistry of nitro compounds can be explained in terms of the practical and theoretical significance of these compounds. It can be said with assurance that the chemistry of nitro compounds has transformed into an independent area of organic chemistry. Many nitro compounds are used as explosives, ignition mixtures, and rocket fuels. Nitro aromatics serve as initial compounds for numerous dyers and pharmaceutical preparations. Nitro group-containing substances are constituents of many medicines. There are known nitro-containing pesticides and anticorrosion additives, technical solvents, etc.

From the theoretical viewpoint, compounds containing the nitro group are of interest due to their peculiar reactivity. They are very convenient in the investigation of structure–composition relationships. The reaction of electrophilic nitration is one of the most important and popular directions in organic chemistry.

Nitro compounds were the objective of much research. Certain aspects of this field of organic chemistry are discussed in many monographs and reviews. Well known treatise is a monograph on the chemistry of nitro and nitroso groups edited by Feuer [1]. The chemistry and technology of aromatic nitro compounds is considered in monographs [2–4]. Much attention has been given to unsaturated [5], aliphatic and alicyclic nitro compounds [6].

A great number of publications deal with the reaction of nitration [7–20]. At the same time, volumes literature on nitro heterocycles has not been systematized until the present time. Direct nitration of some five-membered heterocycles such as pyrroles, furans, thiophenes, pyrazoles, imidazoles, and thiazoles has been discussed by Katritzky [21, 22]. Some synthetic routes to nitrated six-membered nitrogen-containing aromatic heterocycles [23], as well as the nitration of oxo-pyrimidines and -imidazoles [24], and quantum-chemical studies of the nitration of benzazoles [25] have been reported.

The present monograph is devoted to the chemistry of a fascinating class of heterocyclic compounds, that of nitroazoles. The presence of the nitro group in the heterocyclic ring containing two or more hetero atoms points to a unique character of this cycle.

Some little data on the nitroazoles have been published in monographs and reviews dealing with the derivatives of pyrazole [26, 27], oxazole [28], thiazole [29], 1,2,4-triazole [30], 1,2,3-triazole [31], tetrazoles [32], benzimidazole [33], and benzotriazole [34]. Some representatives of nitroazoles are described in a comprehensive and excellent book on heterocycles by Katritzky and Pozharskii [35] and in reviews on five-membered ring systems with two and more heteroatoms [36–39]. Recently Elguero and colleagues have surveyed some problems on tautomerism investigation of azoles [40]. Special monographs and reviews are dedicated to the chemistry, biological properties, and clinical application of nitroimidazoles [41–43]. In a monograph devoted to nitroazoles [44], only five-membered heterocycles with *N*- and *N*,*O*-endocyclic heteroatoms have been considered, whereas thia- and selenazoles, *N*-nitroazoles (a new class of the oxide nitrogen generator [45]), and all the nitrobenzoazoles were ignored. We have published some reviews on the synthesis of five-membered nitroazoles [46, 47] and their fused analogs [48, 49], on NMR spectroscopy [50] and mass spectrometry of nitroazoles [51], and on electronic substituent effects in five-membered, nitrogen-containing aromatic heterocycles [52].

Thus, azoles represent five-membered heteroaromatic compounds and they're benzanalogs with two or more heteroatoms of which at least one is nitrogen. According to Albert's classification subdividing all heteroaromatic compounds into π-rich and π-deficient ones, the azoles occupy an intermediate position, as they do not show clearly expressed π-donating or π-deficient properties [53]. It should be noted that this classification reflects the π-electron density distribution in the ground state of a molecule. Though reactivity is determined by the difference in energy of the ground and the transition state of the reaction, in practice a correlation of π-sufficiency change and the facility of electrophilic substitution is frequently observed. Really, as the number of "pyridine" nitrogen atoms increases the π-donating properties of azoles decrease and thus their reactivity in electrophilic substitution reactions is reduced [54]. However, this is not the case sometimes. Thus, 1*H*-imidazo[1,2]benzimidazole, for example, is less active than its 9*H*-isomer in the reactions of this type, though the donating ability of the latter is lower [55].

Nitroazoles possess a very broad array of practical applications. They can be used as anticancer preparations, antiseptics, radiosensitizers, herbicides, fungicides, dyes, ionic liquids, etc. The significant number of applications of nitroazoles makes them rather promising for research and requires deep understanding of their peculiar electronic structure, spectral properties, and chemical and tautomeric transformations [56, 57].

All this provoked us to write a monograph considering from unified positions all the literature available and our own data concerning the methods of synthesis, structure, properties, and application of *C*- and *N*-nitroderivatives of azoles and their condensed analogs.

An extensive volume of literature related to the question under consideration made us exclude a number of references to earlier publications and patents cited in the aforementioned monographs and reviews as well as in later publications.

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