ISSN: 2395-7639

International Journal of Multidisciplinary Research in Science, Engineering, Technology & Management (IJMRSETM)

(A Monthly, Peer Reviewed Online Journal)

Visit: www.ijmrsetm.com

Volume 3, Issue 10, October 2016

Synthesis And Spectral Studies Of Phenothiazine Sulfones

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ABSTRACT: Phenothiazine, abbreviated PTZ, is an organic compound that has the formula $S(C_6H_4)_2NH$ and is related to the thiazine-class of heterocyclic compounds. Derivatives of phenothiazine are highly bioactive and have widespread use and rich history. The derivatives chlorpromazine and promethazine revolutionized the fields of psychiatry and allergy treatment, respectively. An earlier derivative, methylene blue, was one of the first antimalarial drugs, and derivatives are under investigation as possible anti-infective drugs. Phenothiazine is a prototypical pharmaceutical lead structure in medicinal chemistry. In organic chemistry, a sulfone is a organosulfur compound containing a sulfonyl ($R{-}S(=O)_2{-}R'$) functional group attached to two carbon atoms. The central hexavalent sulfur atom is double-bonded to each of two oxygen atoms and has a single bond to each of two carbon atoms, usually in two separate hydrocarbon substituents.

KEYWORDS: Phenothiazine, sulfones, heterocyclic, medicinal, organosulfur, hexavalent, sustituents, sulfur, thiazine

I.INTRODUCTION

In 1876, methylene blue, a derivative of phenothiazine, was synthesized by Heinrich Caro at BASF. The structure was deduced in 1885 by Heinrich August Bernthsen. Bernthsen synthesized phenothiazine in 1883.[4] In the mid 1880s, [1]Paul Ehrlich began to use methylene blue in his cell staining experiments that led to pioneering discoveries about different cell types. He was awarded a Nobel Prize based in part on that work. He became particularly interested in its use to stain bacteria and parasites such as Plasmodiidae – the genus that includes the malaria pathogen – and found that it could be stained with methylene blue. He thought methylene blue could possibly be used in the treatment of malaria, tested it clinically, and by the 1890s methylene blue was being used for that purpose.[4]

For the next several decades, research on derivatives lapsed until phenothiazine itself came to market as an insecticide and deworming drug. In the 1940s, chemists working with Paul Charpentier at Rhone-Poulenc Laboratories in Paris (a precursor company to Sanofi), began making derivatives. This work led to promethazine which had no activity against infective organisms, but did have good antihistamine activity, with a strong sedative effect. It went to market as a drug for allergies and for anesthesia. As of 2012 it was still on the market.[4] At the end of the 1940s the same lab produced[2] chlorpromazine which had an even stronger sedative and soothing effect, and Jean Delay and Pierre Deniker attempted to use it on their psychiatric patients, publishing their results in the early 1950s. The strong effects they found opened the door of the modern field of psychiatry and led to a proliferation of work on phenothiazine derivatives.[4] The systematic research conducted by chemists to explore phenothiazine derivatives and their activity was a pioneering example of medicinal chemistry; phenothiazine is often discussed as a prototypical example of a pharmaceutical lead structure.[4][5]

A number of phenothiazines other than methylene blue have been shown to have antimicrobial effects. In particular, thioridazine has been shown to make extensively drug-resistant tuberculosis (XDR-TB) drug-susceptible again[6][7] and make methicillin-resistant Staphylococcus aureus (MRSA) susceptible to beta-lactam antibiotics.[7][8] The major reason why thioridazine has not been utilized as an antimicrobial agent (it is a first-generation or "typical" antipsychotic medication) is due to its adverse effects on the central nervous system and cardiovascular system (particularly QT interval prolongation).[7]

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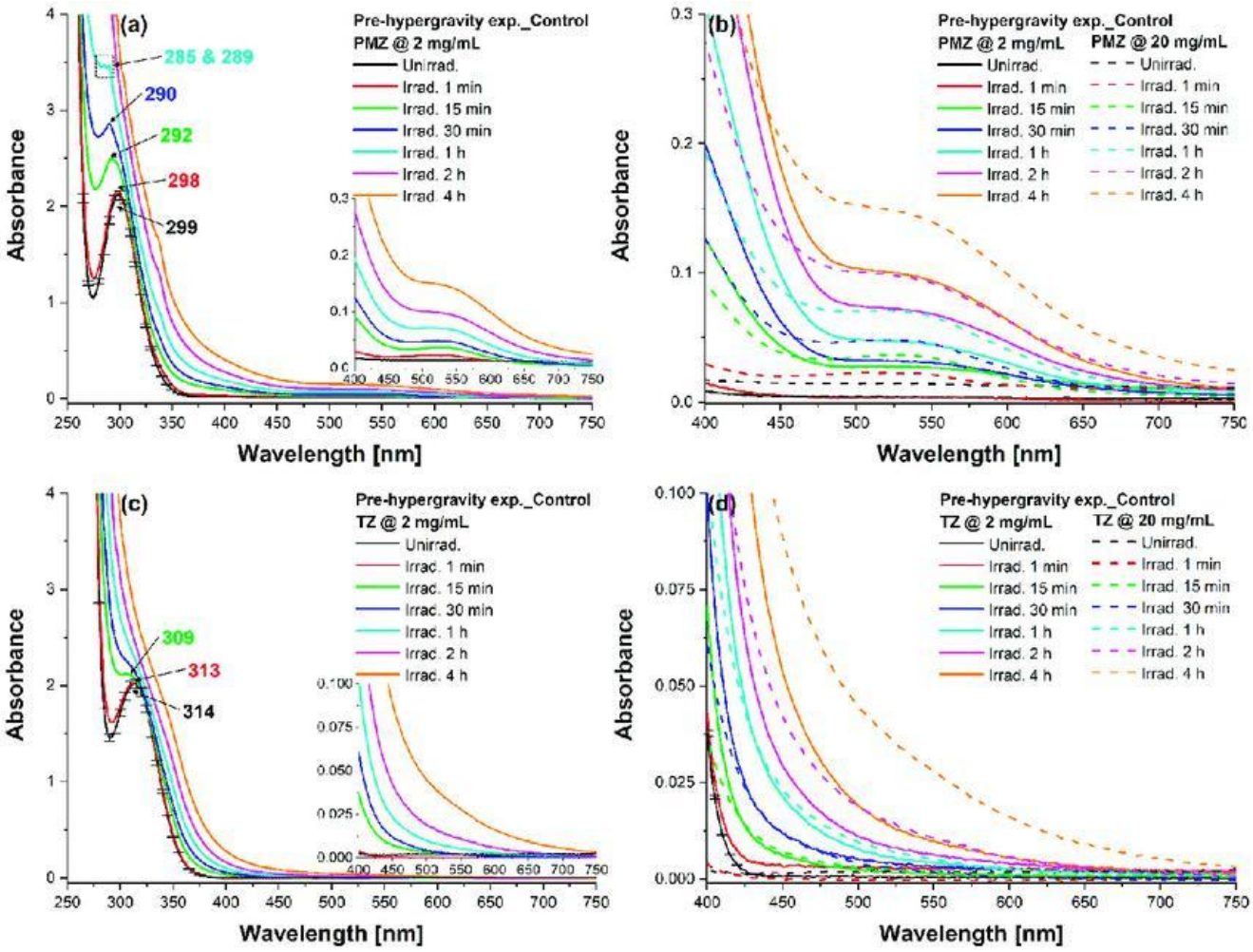

The term "phenothiazines" describes the largest of the five main classes of antipsychotic drugs. These drugs have antipsychotic and, often, antiemetic properties, although they may also cause severe side effects such as extrapyramidal symptoms (including akathisia and tardive dyskinesia), hyperprolactinaemia, and the rare but potentially fatal neuroleptic malignant syndrome, [3]as well as substantial weight gain.[4] Use of phenothiazines has been associated with antiphospholipid syndrome, [26]but no causal relationship has been established.[9]

Phenothiazine antipsychotics are classified into three groups that differ with respect to the substituent on nitrogen: the aliphatic compounds (bearing acyclic groups), the "piperidines" (bearing piperidine-derived groups), and the piperazine (bearing piperazine-derived substituents).[5]

The synthetic dye methylene blue, containing the structure, was described in 1876. Many water-soluble phenothiazine derivatives, such as methylene blue, methylene green, thionine, and others, can be electropolymerized into conductive polymers used as electrocatalysts for NADH oxidation in enzymatic biosensors and biofuel cells.[10][11][12]

Phenothiazine is used as an anaerobic inhibitor for acrylic acid polymerization, often used as an in-process inhibitor during the purification of acrylic acid.[13]

II.DISCUSSION

Phenothiazine was formerly used as an insecticide and as a drug to treat infections with parasitic worms (anthelminthic) in livestock and people, but its use for those purposes has been superseded by other chemicals.[25]

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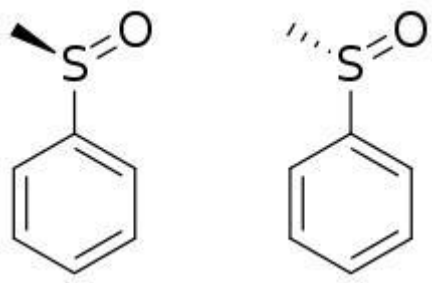
Phenothiazine was introduced by DuPont as an insecticide in 1935.[15] About 3,500,000 pounds were sold in the US in 1944.[16] However, because it was degraded by sunlight and air, it was difficult to determine how much to use in the field, and its use waned in the 1940s with the arrival of new pesticides like DDT that were more durable.[17]:161–162 As of July 2015 it is not registered for pesticide use in the US, Europe,[18] or Australia.[19]

It was introduced as anthelminthic in livestock in 1940 and is considered, with thiabendazole, to be the first modern anthelminthic.[20] The first instances of resistance were noted in 1961.[20] Among anthelmintics, Blizzard et al. 1990 found only paraherquamide to have similar activity to phenothiazine. It is possible that they share the same mode of action.[21] Uses for this purpose in the US are still described[22] but it has "virtually disappeared from the market.[24]"In the 1940s it also was introduced as antihelminthic for humans; since it was often given to children, the drug was often sold in chocolate, leading to the popular name, "worm chocolate." Phenothiazine was superseded by other drugs in the 1950s.[4] The central C_4SN ring is folded in phenothiazines.[24]

The compound was originally prepared by Bernthsen in 1883 via the reaction of diphenylamine with sulfur, but more recent syntheses rely on the cyclization of 2-substituted diphenyl sulfides. Few pharmaceutically significant phenothiazines are prepared from phenothiazine,[25] although some of them are.[26]

Phenothiazines are electron donors, forming charge-transfer salts with many acceptors.[4]



In organic chemistry, a sulfonanilide group is a functional group found in certain organosulfur compounds. It possesses the chemical structure $R{-}S(=O)_2{-}N(-C_6H_5){-}R'$, and consists of a sulfonamide [5] group ($R{-}S(=O)_2{-}NR'R''$) where one of the two nitrogen substituents (R' or R") is a phenyl group (C_6H_5). It can be viewed as a derivative of aniline ($C_6H_5NH_2$).[1]

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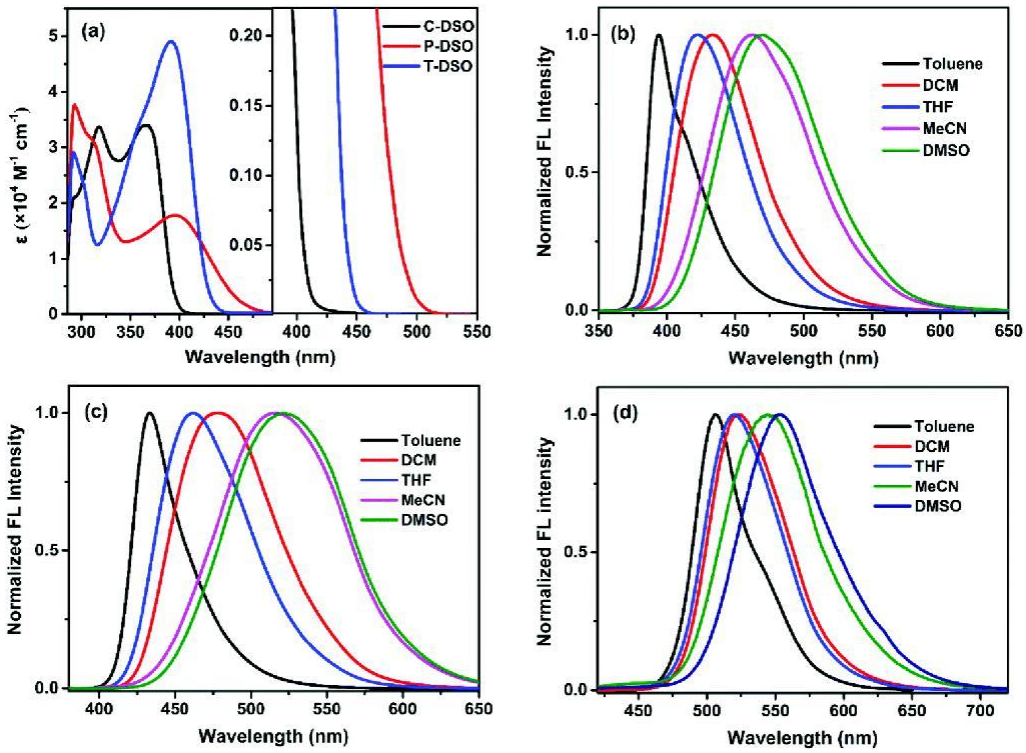

Sulfoxides feature relatively short S–O distances. In DMSO, the S–O distance is 1.531 Å. The sulfur center is pyramidal; the sum of the angles at sulfur is about 306°.[3] Sulfoxides are generally represented with the structural formula R−S(=O)−R', where R and R' are organic groups. The bond between the sulfur and oxygen atoms is intermediate of a dative bond and a polarized double bond.[4] The double-bond resonance form implies 10 electrons around sulfur (10-S-3 in N-X-L notation). The double-bond character of the S−O bond may be accounted for by donation of electron density into C−S antibonding orbitals ("no-bond" resonance forms in valence-bond language)[6]. Nevertheless, due to its simplicity and lack of ambiguity, the IUPAC recommends use of the expanded octet double-bond structure to depict sulfoxides,[22] rather than the dipolar structure or structures that invoke "no-bond" resonance contributors.[5] The S–O interaction has an electrostatic aspect, resulting in significant dipolar character, with negative charge centered on oxygen.[7]

A lone pair of electrons resides on the sulfur atom, giving it tetrahedral electron-pair geometry and trigonal pyramidal shape (steric number 4 with one lone pair; see VSEPR theory). When the two organic residues are dissimilar, the sulfur is a chiral center, for example, in methyl phenyl sulfoxide. The energy barrier required to invert
this stereocenter is sufficiently high that sulfoxides are optically stable near room temperature. That is, the rate of racemization is slow at room temperature. The enthalpy of activation for racemization is in the range 35 - 42 kcal/mol and the corresponding entropy of activation is -8 - +4 cal/mol-K. The barriers are lower for allylic and benzylic substituents.[6]

DMSO is a widely used solvent.[8]

The sulfoxide functional group occurs in several drugs. Notable is esomeprazole, the optically pure form of the proton-pump inhibitor omeprazole. Another commercially important sulfoxides include armodafinil.[21]

Methionine sulfoxide forms from the amino acid methionine and its accumulation is associated with aging. The enzyme DMSO reductase catalyzes the interconversion of DMSO and dimethylsulfide.

Naturally-occurring chiral sulfoxides include alliin and ajoene.[9]

In organic chemistry, sulfonic acid (or sulphonic acid) refers to a member of the class of organosulfur compounds with the general formula $R{-}S(=O)_2{-}OH$, where R is an organic alkyl or aryl group and the $S(=O)_2(OH)$ group

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a sulfonyl hydroxide.[1] As a substituent, it is known as a sulfo group. A sulfonic acid can be thought of as sulfuric acid with one hydroxyl group replaced by an organic substituent. The parent compound (with the organic substituent replaced by hydrogen) is the parent sulfonic acid, $HS(=O)_2(OH)$, a tautomer of sulfurous acid, $S(=O)(OH)_2$.[a] Salts or esters of sulfonic acids are called sulfonates.[10]

III.RESULTS

Sulfonic acids are strong acids. They are commonly cited as being around a million times stronger than the corresponding carboxylic acid[20]. For example, p-Toluenesulfonic acid and methanesulfonic acid have pK_a values of −2.8 and −1.9, respectively, while those of benzoic acid and acetic acid are 4.20 and 4.76, respectively. However, as a consequence of their strong acidity, their pK_a values cannot be measured directly, and values commonly quoted should be regarded as indirect estimates with significant uncertainties. For instance, various sources have reported the pK_a of methanesulfonic acid to be as high as −0.6[3] or as low as −6.5.[4] Sulfonic acids are known to react with solid sodium chloride (salt) to form the sodium sulfonate and hydrogen chloride.[5] This property implies an acidity within two or three orders of magnitude of that of $HCl_{(g)}$, whose pK_a was recently accurately determined ($pK_a^{aq} = -5.9$).[11]

Because of their polarity, sulfonic acids tend to be crystalline solids or viscous, high-boiling liquids. They are also usually colourless and nonoxidizing,[6] which makes them suitable for use as acid catalysts in organic reactions. Their polarity, in conjunction with their high acidity, renders short-chain sulfonic acids water-soluble, while longer-chain ones exhibit detergent-like properties.[12]

The structure of sulfonic acids is illustrated by the prototype, methanesulfonic acid. The sulfonic acid group, RSO_2OH features a tetrahedral sulfur centre, meaning that sulfur is at the center of four atoms: three oxygens and one carbon. The overall geometry of the sulfur centre is reminiscent of the shape of sulfuric acid.

Although both alkyl and aryl sulfonic acids are known,[19] most of the applications are associated with the aromatic derivatives.[13]

Detergents and surfactants

Detergents and surfactants are molecules that combine highly nonpolar and highly polar groups. Traditionally, soaps are the popular surfactants[18], being derived from fatty acids. Since the mid-20th century, the usage of sulfonic acids has surpassed soap in advanced societies. For example, an estimated 2 billion kilograms of alkylbenzenesulfonates are produced annually for diverse purposes. Lignin sulfonates, produced by sulfonation of lignin are components of drilling fluids and additives in certain kinds of concrete.[7]

Dyes

Many if not most of the anthraquinone dyes are produced or processed via sulfonation.[8] Sulfonic acids tend to bind tightly to proteins and carbohydrates. Most "washable" dyes are sulfonic acids (or have the functional sulfonyl group in them) for this reason. p-Cresidinesulfonic acid is used to make food dyes.

Acid catalysts

Being strong acids, sulfonic acids are also used as catalysts. The simplest examples are methanesulfonic acid, CH_3SO_2OH and p-toluenesulfonic acid, which are regularly used in organic chemistry as acids that are lipophilic (soluble in organic solvents). Polymeric sulfonic acids are also useful. Dowex resin are sulfonic acid derivatives of polystyrene and is used as catalysts and for ion exchange (water softening). Nafion, a fluorinated polymeric sulfonic acid is a component of proton exchange membranes in fuel cells.[9]

Drugs

Sulfa drugs, a class of antibacterials, are produced from sulfonic acids.[17]

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IV.CONCLUSIONS

Esterification

Sulfonic acids can be converted to esters. This class of organic compounds has the general formula $R{-}SO_2{-}OR$. Sulfonic esters such as methyl triflate are considered good alkylating agents in organic synthesis. Such sulfonate esters are often prepared by alcoholysis of the sulfonyl chlorides:

$$RSO_2Cl + R'OH \rightarrow RSO_2OR' + HCl$$ [14]

Halogenation

Sulfonyl halide groups occur when a sulfonyl functional group is singly bonded to a halogen atom. They have the general formula $R{-}SO_2{-}X$ where X is a halide, almost invariably chloride. They are produced by chlorination of sulfonic acids using thionyl chloride and related reagents.[15]

Displacement by hydroxide

Although strong, the $(aryl)C{-}SO_3^-$ bond can be broken by nucleophilic reagents. Of historic and continuing significance is the α-sulfonation of anthroquinone followed by displacement of the sulfonate group by other nucleophiles, which cannot be installed directly.[8] An early method for producing phenol involved the base hydrolysis of sodium benzenesulfonate, which can be generated readily from benzene.[11]

$$C_6H_5SO_3Na + NaOH \rightarrow C_6H_5OH + Na_2SO_3$$

The conditions for this reaction are harsh, however, requiring 'fused alkali' or molten sodium hydroxide at 350 °C for benzenesulfonic acid itself.[12] Unlike the mechanism for the fused alkali hydrolysis of chlorobenzene, which proceeds through elimination-addition (benzyne mechanism), benzenesulfonic acid undergoes the analogous conversion by an S_NAr mechanism, as revealed by a ^{14}C labeling, despite the lack of stabilizing substituents.[13] Sulfonic acids with electron-withdrawing groups (e.g., with NO_2 or CN substituents) undergo this transformation much more readily.[16]

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