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Oxidation Behaviour of Phenothiazine

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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.

KEYWORDS: Phenothiazine, organic compound, heterocyclic, psychiatry, allergy, methylene blue, antimalarial, medicinal

I.INTRODUCTION

Phenothiazine itself is only of theoretical interest, but its derivatives revolutionized psychiatry, other fields of medicine, and pest management. Other derivatives have been studied for possible use in advanced batteries and fuel cells.[4] 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, Paul Ehrlich began to use methylene blue in his cell staining experiments that led to pioneering discoveries about different cell types.[1] 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.[2] 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[3]. In the 1940s, chemists working with Paul Charpentier at Rhone-Poulenc Laboratories in Paris (a precursor company to Sanofi), began making derivatives. [4]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 chlorpromazine which had an even stronger sedative and soothing effect, and Jean Delay and Pierre Deniker[5] 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 [6] 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[7] 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[8] on the central nervous system and cardiovascular system (particularly QT interval prolongation).[7]

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[9] (including akathisia and tardive dyskinesia), hyperprolactinaemia, and the rare but potentially fatal neuroleptic malignant syndrome, as well as substantial weight gain.[4] Use of phenothiazines has been associated with antiphospholipid syndrome,[10] 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)[11], and the piperazine (bearing piperazine-derived substituents).[5]

II.DISCUSSION

Group	Anticholinergic	Example	Sedation	Extrapyramidal side effects
Aliphatic compounds	moderate	Chlorpromazine (marketed as Thorazine, Aminazine, Chlor-PZ, Klorazine, Promachlor, Promapar, Sonazine, Chlorprom, Chlor-Promanyl, Largactil)	strong	moderate
		Promazine (trade name Sparine, Propazine)	moderate	moderate
		Trifluprom azine (trade names Clinazine, Novaflurazine, Pentazine, Terfluzine, Triflurin, Vesprin)	strong	moderate/strong
		Levomepromazine in Germany, Russia, most American countries (e.g., Brazil) and methotrimeprazine in USA (trade names Nozinan, Levoprome, Tisercin)	extremely strong	low
Piperidines	strong	Mesoridazine (trade name Serentil)	strong	weak
		Thioridazine (trade names Mellaril, Novoridazine, Thioril, Sonapax)	strong	weak
Piperazines	weak	Fluphenazine (trade names Prolixin, Permitil, Modecate, Moditen)	weak/moderate	strong
		Perphenazine (sold as Trilafon, Etrafon, Triavil, Phenazine, Etaperazin)	weak/moderate	strong
		Prochlorperazine (trade names Compazine, Stemetil)		
		Trifluoperazine (trade name Stelazine, Triphtazine)	moderate	strong

Nondrug application

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]

Like many commercially significant compounds, phenothiazine has numerous trade names, including AFI-Tiazin, Agrazine, Antiverm, Biverm, Dibenzothiazine, Orimon, Lethelmin, Souframine, Nemazene, Vermitin, Padophene, Fenoverm, Fentiazine, Contaverm, Fenothiazine, Phenovarm, Ieeno, ENT 38, Helmetina, Helmetine, Penthazine, XL-50, Wurm-thional, Phenegic, Phenovis, Phenoxur, and Reconox.[14] 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.[12]

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] 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[13] same mode of action.[21] Uses for this purpose in the US are still described[22] but it has "virtually disappeared from the market."[23]:369

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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,[14] 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.[15]

The oxidation of phenothiazine in dilute solutions of sulphuric acid leads to the corresponding cation radical. Using a potentiometric technique, a pK, value of 5.72 ? 0.05 was determined for phenothiazine. The kinetics has been studied and participation of both protonated and unprotonated oxidant in the oxidation reaction has been confirmed.[16] Using a voltammetric technique with a rotating disk electrode, the anodic oxidation of phenothiazine was shown to be a oneelectron diffusion-controlled process. A quantum chemical explanation was found for the direction of phenothiazine protonation and the absence of a dimerization stage of oxidation.[17]

III.RESULTS

The reaction kinetics of phenothiazine oxidation by ammonium vanadate and potassium dichromate was studied in the sulphuric acid medium. The reaction with both oxidizing agents was shown to be first order in substrate (phenothkine) [18]and first order in oxidant. Furthermore, the reaction rate depends upon the concentration of the acidic component. For explanation of the latter, let us consider the following two reaction schemes of substrate with oxidant, assuming the participation of protonated phenothiazine pH+ in the redox process. [19]The species PH' interacts with protonated oxidant. Since PH' predominates in solution at pH 1-3, no proton transfer occurs before reaction with Ox. If V - [H+] at pH 1-3,[20] it means that another proton transfer occurs before the electron transfers. This may be protonation of the anions of the oxidants: pK, values for HV03 and HCr, 0,- are 3.8 and 0.7, respectively. To compare with the homogeneous oxidation, electrooxidation of 1 mM phenothiazine was investigated in sulphuric acid solutions containing 50% ethanol and using 0.3 M LiCl[21] as supporting electrolyte. Using a glassy-carbon rotating disk electrode. an anodic wave was obtained with limiting current controlled by diffusion. This was proved by linear dependence of ili,, on w"~. The half-wave potential (Ell, = 0.51 V vs. saturated silver,[22] silver chloride electrode in 26.47% KC1 solution) is independent of the sulphuric acid concentration between 0.65 and 6.8 mM acid. Independence of Ell, from pH indicates that the species predominating in the bulk of solution undergoes electrooxidation. [23] Because in all instances the conjugate base of a substrate is oxidized more readily than the acid, the observed independence also means that the dissociation of PH' under the conditions used is slow when compared with rate of oxidation.[24] The number of oxidations on rotating disk electrodes accompanied by acid-base equilibria reported in the literature is limited and hence no estimate of the rate of dissociation of PH' can be offered. Decay curves of the limiting current with time at the potential 0.80 V[25] vs. saturated silver, silver chloride electrode (26.47% KC1) were measured. A linear dependence of ili, on t1'2 (t is time) at the end part of the decay curve provides evidence for mixed control conditions of the anodic reaction in the corresponding time interval.[26]

In the present work, the formation of diphenothiazinyls was not detected. At the same time, oxidational dimerization via the cation radical step under identical or similar conditions (oxidation by vanadate or dichromate in sulphuric acid medium) is characteristic for structurally similar diarylamines [20].Using the INDO method, we found spin density distribution in the cation radical. An excess of this spin density value features the following atoms: nitrogen (-0.468), sulphur (-0.323), carbon in positions 1 (-0.029) and 3 (-0.071) of the cycle. The most probable centre of recombination is the nitrogen atom. However, N,N-coupling is hindered by the lability of the N-N bond in acidic media .Also, S,S-coupling is impossible, since it would lead to the formation of an S-S bond between positively charged sulphur atoms. Dimerization of the C,S-type cannot be realized either:[21] the formation of sulphonium salts is known to occur only in heterolytic alkylation (but not arylation) reactions of sulphides .Coupling involving the C-3 and C-1 carbon atoms may occur, the latter to a lesser degree owing to both a lesser density of the uncoupled electron and the steric factor[22] (which has been proved for diphenylamine derivatives . From the viewpoint of spin density, the formation of 3,101- and 1,lO'-diphenothiazinyls as well as their relative quantities is explained. At the same time, following from the present work , oxidational dimerization for phenothiazine is characteristic to a lesser degree than for diarylamines, the reason being a smaller value of spin density at the nitrogen and C-3 atoms in the phenothiazine cation radical, as compared to the cation radicals of diphenylamines .[23]

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IV.CONCLUSIONS

The reaction kinetics of phenothiazine oxidation by ammonium vanadate and potassium dichromate was studied in the sulphuric acid medium. [25]The reaction with both oxidizing agents was shown to be first order in substrate (phenothkine) and first order in oxidant. Furthermore, the reaction rate depends upon the concentration of the acidic component. [26]

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