IODOMETRIC DETERMINATION OF CYSTAMINE DIHYDROCHLORIDE IN TABLET FORMULATIONS USING DIPEROXYADIPIC ACID

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Cystamine dihydrochloride (cystamine hydrochloride RS-1) is an emergency radioprotection from the group of sulfur-containing drugs. Increases the body's resistance to ionizing radiation. The action is based on the ability to reduce the number of radicals, ionized and excited molecules formed in the tissues during irradiation, as well as the ability of the drug to interact with certain enzymes and to impart resistance to ionizing radiation. Contained in the first-aid kit (AI-2) - two plastic pencil boxes for 6 tablets (0.2 grams) of cystamine dihydrochloride in each.

Cystamine dihydrochloride was determinated coulonometrically with electrogenerated bromine. Potentiometric titration of this compound after its reduction using silver nitrate as titrant and sulfide-selective indicator electrode was also elaborated. Cystamine dihydrochloride in pure form, tablets and biological media have been determined by a number of methods including separation by thin-layer chromatography. The analytical methods used for it determination in substance included alkalimetric titration in non-aqueous medium, direct spectrophotometry or based on the reaction of cystamine with p-nitrophenyl-diazonium to form a red-colored diazoamino compound and subsequent photometric analysis at the wavelength of 510 nm, and also using HPLC method with coulometric detection.

Like all other disulfides, Cystamine is interesting substrate for oxidation reactions as it may undergo either electrophilic or nucleophilic oxidation. The mode of oxidation is controlled largely by the by the pH of the reaction mixture, whereas solvent effects are minimal. Thus, stepwise oxidation of Cystamine dihydrochloride with m-Chlorperbenzoic acid first gives 2-amonoethyl 2-amonoethanethiolsulfinate dihydrochloride and then the corresponding thiolsulfonate. In acidic or neutral solution, the oxidation follows the same mechanism as that described for the oxidation of sulfide to sulfoxide. In basic solution, however, a nucleophilic attack of the peroxy anion takes place at the sulfur atom. However, no kinetic studies have been carried out to probe the analytical aspects of the oxidation of Cystamine dihydrochloride with aliphatic Diperoxyadipic acid in aqueous buffer solutions.

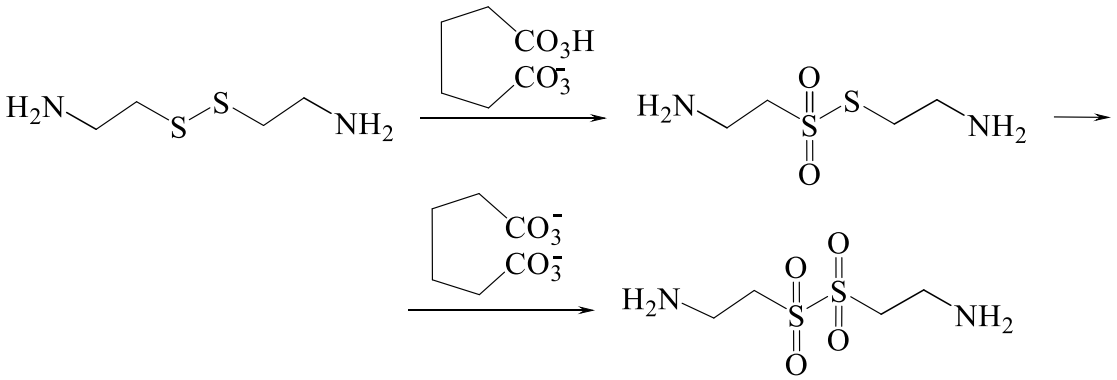
The present communication reports the use of Diperoxyadipic acid (DPAA) for the indirect titrimetric determination of Cystamine. The proposed method is based on the smooth stoichiometric and quantitative oxidation of Cystamine with the oxidant in aqueous solutions at the pH 7.5-8.0 to the corresponding Cystamine disulfone $CyS(=O)_2S(=O)_2Cy$. The excess DPAA was iodometry titrated applying either visual end-point detection.

As oxidant was used Diperoxyadipic acid (hexanebis (peroxoic acid), T mp. + 114 ºC (with decom.), the content of active oxygen species (AOC) 17,4%; DPAA was prepared according to the method described in this article : Parker W. E., Witnauer L. P., Swern D. Peroxides. IV. 2 Aliphatic Diperacids. J. Am. Chem. Soc. 1957,79 (8), 1929-1931. Cystamine dihydrochloride (2,2′-Diaminodiethyl disulfide

dihydrochloride; $C_4H_{14}C_{l2}N_2S_2$, M = 225.2 g/mol) pharma grade (Sigma-Aldrich-02712, CAS Number 56-17-7) ≥98.0% and Plastic pencil boxes for 6 tablets (0.2 grams) of cystamine in each from first-aid kit (AI-2) were objects of research.

Kinetic studies were carried out in buffer solutions under second-order conditions with diperoxy adipic acid (DPAA) in the temperature 293 K and over pH range 2.9 to 9.2. The reaction was followed by estimating the unreacted DPAA as a function of time by using the iodometric method. From the titre values, plots of 1/c *vs* time were made and from the slope of such plots, the second order rate constants, k_{obs} (L mol^{-1} min^{-1}) were obtained; c - current molar concentration of DPAA (for time t, min), mol/L.

It was found that one mole of Cystamine dihydrochloride react with two moles of diperoxyadipic acid. The optimum for the Cystamine dihydrochloride determination was pH 7.5 - 8.0 (time of quantitative interaction is 7-10 min). *pH effects on the kinetics of the Cystamine-diperoxyadipic acid reaction was shown.* The observed rate constant k_{obs} is reasonably constant over the first half of oxidation corresponding to the conversion of Cystamine to the corresponding disulfoxide Cystamine CyS(=O)-S(=O)Cy and/or S-dioxocystamine CyS(=O)$_2$SCy), but later the reaction slows down, implying that the later stages of formation of the corresponding of disulfone Cystamine CyS(=O)$_2$S(=O)$_2$Cy) by means diperoxy acid mono- and dianions are slower or more complex. A suitable mechanism scheme based on these observations is proposed and given in the following equations (Scheme):



This, in particular, points to a linear dependence of the observed reaction rate constant on the mole fraction of the sum of the mono- and dianions of the diperoxy acid.

The possibility of application of DPAA as reagent in the oxidimetric determination of Cystamine dihydrochloride was investigated. With this proposed method, 1.0-4.0 mg of Cystamine dihydrochloride can be accurately and precisely analyzed (RSD<1.61%, $\left|\bar{x}\text{-}\mu\right| \leq \frac{tS}{\sqrt{n}}$). The advantages of the applied analytical techniques in the determination of Cystamine dihydrochloride acid in tablets «Cystamine 0.2 g» has been presented. The recovery of this analyte was 102.55±1.50%. Statistical analysis of the results obtained by the proposed and the official methods reveals no significant differences between them in accuracy and precision as concluded from Student's *t* test and the variance ratio.