TITRATION OF MERCAPTANS AND SOME MERCAPTAN-BASED DRUGS WITH IODINE MONOBROMIDE IN NON-AQUEOUS DIMETHYL SULFOXIDE

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Mercaptans undergo smooth and quantitative oxidation to the corresponding disulfides with iodine monobromide in non-aqueous (dimethyl sulfoxide) medium, which has been made the basis of a simple, rapid and rugged method for the determination of mercaptan-based drugs *viz.* mercaptopurine and dimercaprol. The method has been thoroughly tested with a number of mercaptans before applying it to drugs. The salient features of the method are discussed.
Key words: Titration; Mercaptans; Iodine monobromide; Dimethyl sulfoxide.

Mercaptans are structurally the simplest organosulfur compounds of considerable biological, synthetic, pharmaceutical and commercial importance. This has prompted the appearance of many analytical methods for their determination[1–3]. The ease with which these compounds undergo oxidation to corresponding disulfides in aqueous media forms the basis of an important approach to their analysis.

$$2\ RSH \rightarrow RSSR + 2\ H^+ + 2\ e \qquad (A)$$

These methods, however, lack specificity and doubts have frequently been expressed about the stoichiometry of the oxidation[1–7]. With the hope that this problem can be overcome if non-aqueous oxidimetric methods are applied to the analysis of mercaptans, we found that in most of the organic solvents oxidation of mercaptans either did not proceed at all or was extremely slow. However, when dimethyl sulfoxide (DMSO) was used as the oxidation medium, the reaction proceeded quantitatively, thus affording an excellent method for their determination. This role of the solvent can be explained by the fact that DMSO is a stronger base as compared to water[8–10], and consequently it takes up the protons released in the oxidation step and drives the reaction to completion. The additional advantage of the solvent is its high dielectric constant, facilitating the solubility of a large number of organic compounds including mercaptans. In the present investigation, iodine monobromide has been found as a suitable oxidant for the

determination of mercaptans in DMSO medium. The method has been extended to the analysis of mercaptan-based drugs *viz*. mercaptopurine and dimercaprol.

EXPERIMENTAL

Chemicals

Dimethyl sulfoxide (AR grade) was dried over calcium oxide and distilled under reduced pressure[11]. Acetonitrile (Merck) was distilled twice over phosphorus pentoxide (5 g l^{-1}). Mercaptans: ethyl, propyl, butyl, hexyl, benzyl mercaptan (all Fluka), 1,2-dimercaptoethane, 2-mercaptoethanol (all Merck) were distilled before use. Pure mercaptopurine (Sigma) and dimercaprol (Merck) were used as received. Their purity was checked by IP method[12]. Iodine monobromide (0.02 mol l^{-1}) in acetonitrile was prepared by dissolving a little more than the calculated amount of the compound in acetonitrile and standardized iodometrically in aqueous-acidic medium[13].

Apparatus

Potentiometric titrations were performed with a Toshniwal (CLO6A) potentiometer using a bright platinum wire indicator electrode and modified calomel (saturated methanolic potassium chloride solution used instead of aqueous) reference electrode. Spectrophotometric measurements were carried out with Bausch and Lomb spectrophotometer Spectronic 20-D.

Procedures

Determination of Mercaptans

Visual and potentiometric titrations: Aliquots of solutions of pure compounds in DMSO were taken in titration vessels and volume made to 30 ml with the same solvent. Each solution was titrated at room temperature (*ca* 23 °C) visually and potentiometrically with standard (0.02 mol l^{-1}) iodine monobromide solution. The end point in visual titration was marked by the appearance of yellow colour (due to iodine). A sharp rise in potential of the order of 180–250 mV was observed with the addition of 0.05 ml of 0.02 mol l^{-1} oxidant solution at the equivalence point in each potentiometric titration. The results are given in Table I.

Photometric titrations: Aliquots of solutions in DMSO of each compounds were diluted to 5 ml with the same solvent and titrated photometrically at 380 nm with iodine monobromide solution at room temperature. A dilution correction was applied and titration curve plotted in the usual way. A typical titration curve with standard iodine monobromide is shown in Fig. 1. The results are summarized in Table II.

Drug Analysis

1. Mercaptopurine tablets: A known number of tablets (say 20) were weighed and finely ground. Stock solution was prepared by dissolving accurately weighed amount equivalent to 50 mg of active ingredient in dimethyl sulfoxide and filtered. The residue (if any) was washed 2–3 times with dimethyl sulfoxide. The filtrate and washings were diluted to a known volume with the same solvent. Aliquots were then taken for titrations. The visual, potentiometric and photometric titrations were performed in the same manner as described above. The results of analyses are given in Table III.

2. Dimercaprol injection: The stock solution was prepared by dissolving accurate volume of liquid dosage *i.e.* injection *ca* 50 mg ml^{-1} active ingredient in dimethyl sulfoxide and filtered. The residue

(if any) was washed 2–3 times with DMSO. The filtrate and washings were diluted to a known volume with the same solvent. Aliquots of this solution were taken for titrations and processed as described above. The results of analyses are given in Table III.

TABLE I
Visual and potentiometric determination of mercaptans with iodine monobromide[a]

Compound	Amount found[b], mg		Amount found[c], mg	
	visual	potentiometric	visual	potentiometric
Ethyl mercaptan	3.03 ± 0.025	3.01 ± 0.022	12.08 ± 0.044	11.90 ± 0.040
Propyl mercaptan	3.01 ± 0.020	2.98 ± 0.020	11.92 ± 0.052	11.88 ± 0.042
Butyl mercaptan	2.97 ± 0.030	2.99 ± 0.022	11.89 ± 0.062	12.05 ± 0.042
Hexyl mercaptan	2.98 ± 0.028	3.01 ± 0.025	12.10 ± 0.048	11.92 ± 0.050
Benzyl mercaptan	3.02 ± 0.025	2.98 ± 0.020	12.06 ± 0.052	11.90 ± 0.048
1,2-Dimercaptoethane	3.01 ± 0.020	2.97 ± 0.018	11.88 ± 0.044	12.08 ± 0.042
2-Mercaptoethanol	3.01 ± 0.030	2.99 ± 0.026	11.90 ± 0.052	11.94 ± 0.038
Mercaptopurine	2.97 ± 0.025	2.98 ± 0.030	11.92 ± 0.048	12.10 ± 0.045
2,3-Dimercaptopropanol	2.98 ± 0.022	3.01 ± 0.022	11.89 ± 0.050	11.94 ± 0.042

[a] Mean of 10 determinations with standard deviations given; [b] amount taken, 3 mg; [c] amount taken, 12 mg.

TABLE II
Photometric titrimetric determination of mercaptans with iodine monobromide[a]

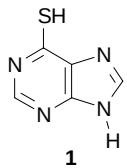
Compound	Found[b], mg	Found[c], mg
Ethyl mercaptan	0.297 ± 0.002	0.903 ± 0.005
Propyl mercaptan	0.301 ± 0.001	0.896 ± 0.006
Butyl mercaptan	0.303 ± 0.002	0.897 ± 0.006
Hexyl mercaptan	0.298 ± 0.002	0.905 ± 0.005
Benzyl mercaptan	0.296 ± 0.001	0.903 ± 0.007
1,2-Dimercaptoethane	0.301 ± 0.002	0.898 ± 0.007
2-Mercaptoethanol	0.302 ± 0.001	0.898 ± 0.005
Mercaptopurine	0.298 ± 0.002	0.903 ± 0.006
2,3-Dimercaptopropanol	0.297 ± 0.002	0.898 ± 0.005

[a] Mean of 10 determinations with standard deviations given; [b] given 0.30 mg; [c] given 0.90 mg.

RESULTS AND DISCUSSION

The present method has primarily been developed for the analysis of mercaptan-based drugs with mercapto group present in them serving as the basis of analysis. In order to establish the generality and versatility of the method, it was thought advisable to standardize the method with a number of mercaptans to give the user of this method confidence in extending it to other mercaptan-based drugs if available on the market or in the process of being marketed. The results shown in Table I indicate that each of the listed mercaptans in the range of 3–12 mg could be determined both visually and potentiometrically with the maximum relative standard deviation (RSD) of 1.0%. These compounds in the range of 0.3–0.9 mg have also been determined using photometric titrations with the maximum RSD of 0.7% (Table II).

The excellent performance of the reagent for determining mercaptans prompted us to extend its use to the analysis of some commercially important drugs based on mercaptans, *viz*. mercaptopurine (**1**) and dimercaprol (**2**) to ensure the quality of the marketed products. The drug formulations when analyzed for their active ingredient gave recoveries in the range of 98.8–99.5% with RSD's in the range of 0.4–0.6% (Table III). The results agreed with the IP method[12]. The proposed methods, besides being simple



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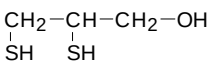

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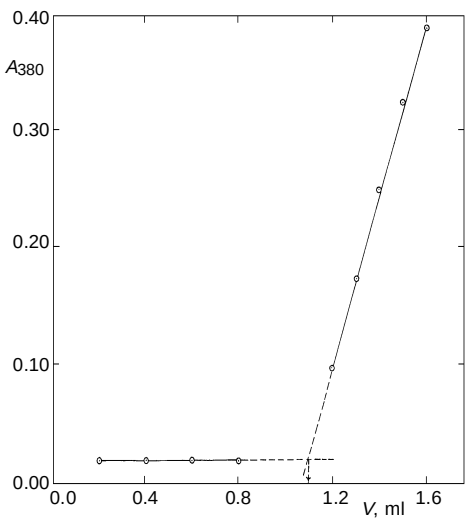

FIG. 1
Photometric titration of benzyl mercaptan with iodine monobromide. Corrected absorbance given

and rapid, give results of acceptable precision and accuracy and hence are recommended for the routine assay of mercaptans and commercial drugs based on them.

TABLE III
Assay of pharmaceutical preparations of mercaptopurine and dimercaprol with iodine monobromide

Drug	Labelled amount	Recovery of drug[a], %			
		visual	potentiometric titration	photometric	comparison method[12]
Mercaptopurine tablets	50 mg/tablet	98.8 ± 0.6	99.0 ± 0.5	99.2 ± 0.5	98.2 ± 0.6
Dimercaprol injection	50 mg/ml	99.0 ± 0.5	99.2 ± 0.4	99.5 ± 0.3	100.6 ± 0.6

[a] Values are mean of 5 determinations with standard deviation.

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