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Hexaamminecobalt(III)–Tricarbonatocobaltate(III) as a Redox Titrant for the Determination of Certain Thioxanthene Derivatives

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A simple titrimetric method is described for the determination of three thioxanthene derivatives, namely chlorprothixene, methixene, and thiothixene. The proposed method involves the use of hexaamminecobalt(III)–tricarbonatocobaltate(III) (HCTC) as a titrant. The detection of the endpoint is accomplished visually, using ferroin as indicator for chlorprothixene and thiothixene. Methixene, on the other hand, produces an orange color on addition of HCTC; the endpoint is marked by the complete disappearance of the orange color. The stoichiometric ratio of the reaction was assessed, and a proposal of the reaction pathway was suggested. The proposed method was applied to the determination of the studied compounds in dosage forms, and the results obtained were compared favorably to those given with the official methods.

INTRODUCTION

Thioxanthenes are widely prescribed central nervous system depressants. They have a more pronounced action than phenothiazines and have gradually replaced them. The literature contains many references for the determination of thioxanthenes, viz. gravimetric (*1*), titrimetric (*2–4*), spectrophotometric (*5–7*), fluorometric (*8*, *9*), polarographic (*10*), and chromatographic (*11–14*) methods. In this paper, a simple titrimetric method is described for the determination of three thioxanthene derivatives, namely, chlorprothixene, methixene, and thiothixene, either per se or in dosage forms.

The proposed method involves the use of hexaamminecobalt(III)–tricarbonatocobaltate(III) (HCTC) as an oxidimetric titrant. The latter was first described, evaluated, and used as an analytical reagent by Baur and Bricker (*15*) in 1965; since then, several articles have appeared reporting the use of HCTC for the determination of organic (*16*) and inorganic reducing compounds (*17–19*).

Work from our laboratory revealed the successful applications of HCTC in the field of pharmaceutical analysis. It was successfully utilized for the determination of phenothiazines (*20*), antimony(III) compounds (*21*), and reserpine (*22*). The purpose of the present investigation is to study the reaction of HCTC with some thioxanthenes in an attempt to develop a simple and accurate method for the determination of these compounds in bulk and dosage forms.

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EXPERIMENTAL

Reagents

1. HCTC: prepared as described by Baur and Bricker (*15*). Solution (5×10^{-3} *M*) is prepared by dissolving 3.0 g of the pure compound in 1 liter of water saturated with sodium bicarbonate by stirring for 2–3 hr. The solution is then filtered and standardized iodometrically.
2. Sodium thiosulfate: 5×10^{-3} *M* solution.
3. Potassium iodide: 10% solution.
4. Ferroin indicator: It is prepared by dissolving 0.7 g of ferrous sulfate in about 70 ml of water and adding 1.5 g of 1,10-phenanthiroline and sufficient water to produce 100 ml.

Materials

Pure drug samples were kindly provided by pharmaceutical companies: chlorprothixene (Hoffmann La-Roche, Switzerland), thiothixene (Pfizer, Brooklyn, NY), and methixene HCl (Wander, Berne, Switzerland).

Sample Preparation

Solutions (0.1% and 5×10^{-3} *M*) of the thioxanthene were prepared in 0.1 *N* HCl (chlorprothixene and thiothixene) or in distilled water (methixene HCl).

Procedure

A. Chlorprothixene and thiothixene. Transfer an accurately measured volume of the sample solution containing 2–15 mg of the analyte into a conical flask; add 25 ml of 10% H_2SO_4 (v/v) and two drops of ferroin indicator. Titrate slowly with 5×10^{-3} *M* HCTC solution, stirring the solution using a magnetic stirrer. The endpoint is the color change from red to pale blue. Carry out a blank experiment and deduce its value from the endpoint.

B. Methixene. Transfer an accurately measured volume of the sample solution containing 2–15 mg of methixene HCl into a conical flask; add 25 ml of 40% H_2SO_4 (v/v). Titrate slowly with 5×10^{-3} *M* solution of HCTC, stirring the solution with a magnetic stirrer. An orange color develops upon addition of the titrant. Continue the titration until the orange color completely vanishes.

Assay Procedure for Dosage Forms

Weigh and pulverize 20 tablets. Extract an amount of the powder equivalent to 100 mg of the active constituent with 3×30 ml of the appropriate solvent (as in sample preparation). Transfer to a 100-ml volumetric flask; complete to the mark with the same solvent. Apply procedure A or B.

Calculation

The nominal content of the drug is calculated using the formula

$$\text{Amount of the drug (mg)} = VMR/N,$$

where V is milliliters of HCTC used in the titration, M is the molecular weight of

the drug, R is the molarity of HCTC, and, N is the number of moles of HCTC per mole of the drug.

DISCUSSION

Table 1 shows the results for the determination of thioxanthenes using HCTC; the results are accurate and precise. Statistical analysis of the results obtained by both the proposed method and the official method, using the Student t test and the variance ratio F test, showed no significant difference with regard to accuracy and precision (*23*).

The proposed method is based on the oxidation of thioxanthenes with the Co(III) ion released from the latter half of the HCTC complex in acid medium. A proposal of the reaction pathway between thioxanthenes and HCTC is suggested in Fig. 1. The molar ratio of the reaction of HCTC with chlorprothixene and with thiothixene is 1:2; i.e., two Co(III) ions are consumed in the oxidation of each drug; the oxidation products are presumably the corresponding sulfoxides. The detection of the endpoint was accomplished using ferroin indicator. The titrant preferably oxidizes the substrates until the endpoint is reached; it oxidizes the indicator imparting a blue color to the solution.

Methixene, on the other hand, reacts with HCTC in a molar ratio of 1:4. The oxidation product is suggested to be the corresponding sulfone. Methixene is first

TABLE 1
Determination of Thioxanthenes with HCTC[a]

Compound	Milligrams taken	Found	% Found	Official method
1. Chlorprothixene	2.0	1.976	98.8	
	5.0	5.055	101.1	
	7.0	7.028	100.4	
	10.0	10.03	100.3	
	15.0	14.925	99.5	
X			100.02	99.0
(C.V.)[b]			(0.89)	(0.76)
2. Thiothixene	2.0	1.996	99.8	
	5.0	4.99	99.8	
	7.0	7.091	101.3	
	10.0	9.99	99.9	
	15.0	14.955	99.7	
X			100.1	100.8
(C.V.)			(0.67)	(1.2)
3. Methixene HCl	2.0	2.032	101.6	
	5.0	5.015	100.3	
	7.0	6.965	99.5	
	10.0	9.99	99.9	
	15.0	14.85	99.0	
X			100.1	100.4
(C.V.)			(0.99)	(1.12)

[a] Each result is the average of three separate determinations.
[b] C.V. is the coefficient of variation.

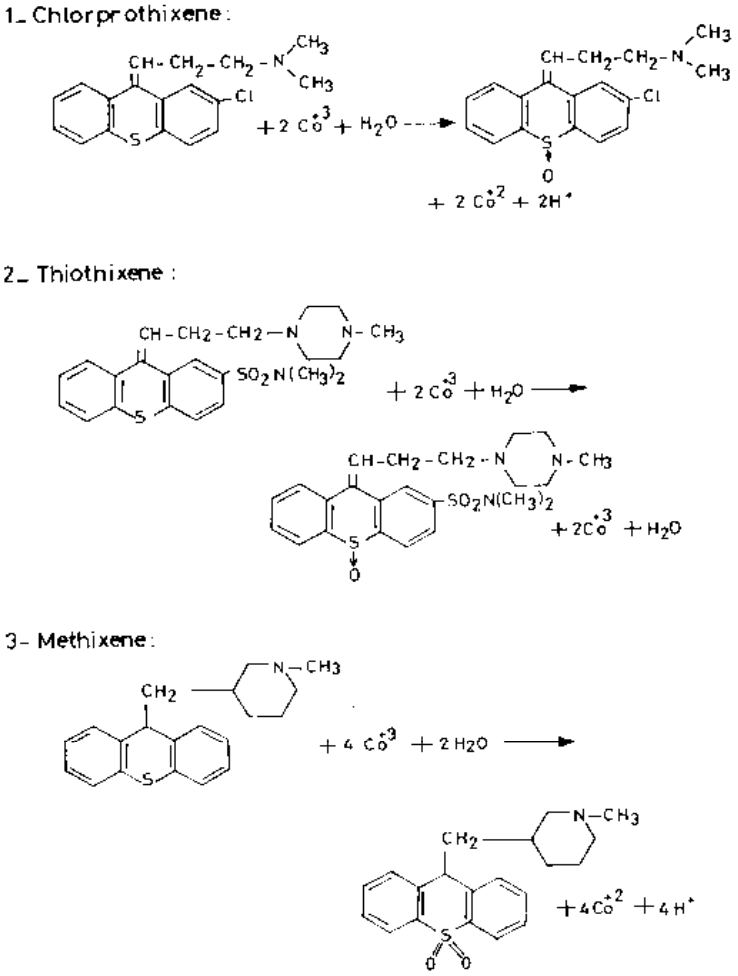

FIG. 1. Proposal of the reaction pathway between thioxanthenes and HCTC.

oxidized to the corresponding sulfoxide, thus imparting an orange color to the solution; further addition of the titrant causes the color to fade, and the endpoint is marked by the complete disappearance of the orange color. The titration of methixene was carried out in strong acid medium (40% H_2SO_4). Lower concentrations of the acid causes the color to fade earlier, the high acidity is suggested to prevent the disproportionation of the free radical formed as an intermediate stage in the oxidation of methixene.

Once the proposed method was established, it was applied to the determination of the studied compounds in certain dosage forms. The results in Table 2 show that the results are in accordance with those given with the official methods with regard to accuracy and precision.

The proposed method is characterized by its simplicity compared with the official methods. The USP (*2*) recommends an HPLC method for thiothixene and its preparations, an expensive apparatus that might not be available in a control laboratory. The method described for chlorprothixene in dosage forms is very tedious, requiring successive extractions and a lengthy procedure. Compared with

TABLE 2
Application of the Proposed Method to the Determination of Thioxanthenes in Dosage Forms[a]

Preparation	% Recovery[b]	
	Proposed method	Official method
1. Taractan tablets[c]	100.8	100.1
(5 mg chlorprothixene HCl/tablet)	(0.47)	(0.96)
2. Taractan tablets[c]	101.1	100.1
(15 mg chlorprothixene HCl/tablet)	(0.81)	(0.91)
3. Navane tablets[d]	100.3	99.7
(10 mg thiothixene/tablets)	(0.64)	(1.3)
4. Tremaril tablets[e]	95.1	95.0
(5 mg methixene HCl/tablet)	(0.64)	(0.34)

[a] Each result is the average of four separate determinations.
[b] The figures in parentheses are the coefficients of variation.
[c] Product of Hofmann-La-Roche, Switzerland.
[d] Product of Pfizer, Inc., Brooklyn, New York.
[e] Product of Wander, Berne, Switzerland.

the published titrimetric methods, the method is characterized by simplicity; neither special skill nor any instrumentation is required. The most striking feature of the reagent is its stability; in the dry form, it is stable for years, and in suitably buffered solution, it is stable for about 1 month (*24*) and is thus recommended for routine analysis in control laboratories.

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