N-Bromohydantoins in Pharmaceutical Analysis I. Determination of Sulfonamides and Some Local Anesthetics with 1,3-Dibromo-5,5-dimethylhydantoin

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This communication reports the use of 1,3-dibromo-5,5-dimethylhydantoin in the quantitative determination of sulfanilamide, 3,4-dimethyl-5-sulfanilamidoisoxazole, 5-methoxy-2-sulfanilamidopyrimidine, ethyl aminobenzoate, and *p*-aminobenzoyldiethylaminoethanol hydrochloride in acid aqueous medium.

THE *N*-BROMOHYDANTOINS occupy a very important position in preparative organic chemistry because of their efficient bromating and oxidizing action. They are simply and economically prepared, stable, and the dibromated derivatives have a high positive bromine content. They have been successfully tested with a wide variety of organic compounds as shown in numerous publications (1).

Reactions with *N*-bromohydantoins take place under mild conditions and are highly selective. Halogenating experiments are usually carried out under the conditions recommended by Ziegler *et al.* (2) for other similar reagents, using nonpolar solvents, preferably carbon tetrachloride. The few examples studied with these reagents using polar solvents, such as acetic acid (3), indicate an exceptional reaction rate even at low temperatures (15–20°), nuclear halogenation being particularly favored (4).

N-Bromohydantoin has not yet been used for analytical purposes. In the present paper the application of a derivative, 1,3-dibromo-5,5-dimethylhydantoin (I) has been studied for the evaluation of some organic substances of pharmaceutical interest.

This stable halogenating reagent of high bromine content (55.9%), when tested in an aqueous acid medium under conditions similar to those used by Barakat *et al.* (5) for *N*-bromosuccinimide (II), proved to be an excellent brominating agent for several sulfonamides and some local anesthetics. This property made it useful for the volumetric determination of these drugs.

Under these conditions it reacts quantitatively with sulfanilamide (III), 3,4-dimethyl-5-sulfanilamidoiso xazole (sulfisoxazole) (IV), 5-methoxy-2-sulfanilamidopyrimidine (V), ethyl aminobenzoate (benzocaine) (VI), and *p*-aminobenzoyldiethylaminoethanol hydrochloride (procaine hydrochloride) (VII), with the reagent/substrate molar relationships of 1:1, 3:2, 1:1, 1:1, 1:1, respectively. The end point is directly visualized using methyl red as an indicator.

1,3-Dibromo-5,5-dimethylhydantoin decolorizes the indicator in an aqueous acidic medium, but halogenates preferentially the substrates; only when the halogenation has been total does a small excess of reactant decolorize the indicator. To achieve further accuracy a blank experiment is recommended with the indicator under the same conditions.

EXPERIMENTAL

Reagents—(*a*) 1,3-Dibromo-5,5-dimethylhydantoin[1] was prepared according to the method described by Orazi *et al.* (6) by means of bromine acting on an alkaline solution of 5,5-dimethylhydantoin. By means of repeated crystallizations in hot water (70–80°), the pure product is obtained with a 55.9% bromine content.

The positive quality of bromine in 1,3-dibromo-5,5-dimethylhydantoin permits the liberation of iodine from an acid solution of potassium iodide which makes it possible to carry out its quantitative determination by the iodometric method (7).

(*b*) Solution of 1,3-dibromo-5,5-dimethylhydantoin[2] at 0.1% w/v in distilled water: it is prepared by dissolving the pure substance in hot distilled water (70°), cooling it at once after the solution is obtained. Once the environmental temperature is reached, distilled water is added up to a total of 100 ml. The titer of the solution is iodometrically determined. The solution must be kept in a cool place and must be protected from light, controlling its factor every 3 days. Solutions prepared for more than 7 days should not be used.

(*c*) Solution 0.1%, of III, IV, V, VI, and VII in 10% hydrochloric acid.

(*d*) Hydrochloric acid solution, 10% w/v in distilled water.

(*e*) Methyl red solution (0.02%) in 50% ethanol.

(*f*) Acetic acid, glacial.

(*g*) *N*-Bromosuccinimide solution at 0.1% w/v in distilled water.

Procedure—A convenient volume of the substrate solution, accurately measured, *i.e.*, 5 ml. is poured into a conical flask, then 5 ml. of acetic acid and 2 drops of the indicator are added and titrated with the 0.1% titrant, shaking frequently until the indicator is decolorized. The volume required for the blank assay is deduced from the number of milliliters used.

Blank Experiment—The same procedure is followed using, instead of the substrate solution, an equivalent volume of 10% hydrochloric acid solution (in the given sample, 5 ml.).

The results obtained in the tested samples are indicated in Tables I, II, and III. Each value represents the average of three parallel determinations.

The range of applicability of I and other similar titrants is currently under study in this laboratory.

CONCLUSIONS

The results in Tables I and II indicate that 1,3-dibromo-5,5-dimethylhydantoin is a suitable analytical reagent for the quantitative determination of some sulfonamides and local anesthetics; the reaction takes place rapidly and quantitatively at room temperature, experimental errors range about 1% and, moreover, quantities as small as 1 mg. can be determined.

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[1] Commercial products are supplied by the K E K Laboratories, Inc., New York, and Fluka A. G. Chemische Fabrik, Schweiz.

[2] Solubility in water at 75°, 8.5 mg./ml., and solubility at 25°, 1.75 mg./ml.

TABLE I—DETERMINATION OF SULFONAMIDES WITH 1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN (I)

Substrate	Soln. Used, ml.	Soln. I,[a] ml.	Content, mg.	Found, mg.	Error, %
Sulfanilamide (III)	1	1.68	1.00	1.01	1
	2	3.36	2.00	2.02	1
	3	5.02	3.00	3.02	0.6
	4	6.63	4.00	3.99	0.25
	5	8.29	5.00	4.99	0.20
3,4-Dimethyl-5-sulfanilamidoisoxazole (IV)	5	8.00	5.00	4.98	0.4
	6	9.58	6.00	5.97	0.6
	7	11.30	7.00	7.04	0.57
	8	12.79	8.00	7.97	0.37
	9	14.59	9.00	9.09	1
	10	16.09	10.00	10.02	0.2
5-Methoxy-2-sulfanilamidopyrimidine (V)	1	1.02	1.00	1.00	0
	2	2.06	2.00	2.02	1
	3	3.04	3.00	2.98	0.67
	4	4.02	4.00	3.99	0.25
	5	5.05	5.00	4.95	1

[a] One milliliter of a 0.1% solution of I = 0.602 mg. of III, 0.623 mg. of IV, and 0.980 mg. of V.

TABLE II—DETERMINATION OF LOCAL ANESTHETICS WITH 1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN (I)

Substrate	Soln. Used, ml.	Soln. I,[a] ml.	Content, mg.	Found, mg.	Error, %
Ethyl aminobenzoate (VI)	1	1.74	1.00	1.01	1
	2	3.49	2.00	2.02	1
	3	5.24	3.00	3.03	1
	4	6.95	4.00	4.02	0.50
	5	8.74	5.00	5.05	1
p-Aminobenzoyl diethylaminoethanol hydrochloride (VII)	1	1.06	1.00	1.01	1
	2	2.11	2.00	2.01	0.50
	3	3.18	3.00	3.03	1
	4	4.24	4.00	4.04	1
	5	5.23	5.00	4.99	0.2

[a] One milliliter of solution 0.1% of I = 0.578 mg. of VI and 0.954 mg. of VII.

TABLE III—DETERMINATION OF SULFONAMIDES WITH 1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN (I) AND *N*-BROMOSUCCINIMIDE (II)

Substrate	Soln. Used, ml.	Soln., ml. I[a]	Soln., ml. II[b]	Content, mg.	Found, mg. I	Found, mg. II	Error, % I	Error, % II
Sulfanilamide (III)	5	8.29	10.42	5.00	4.99	5.03	0.20	0.60
3,4-Dimethyl-5-sulfanilamidoisoxazole	5	8.00	10.05	5.00	4.98	5.03	0.40	0.60

[a] One milliliter of solution 0.1% = 0.602 mg. of III and 0.623 mg. of IV. [b] One milliliter of solution 0.1% of II = 0.483 of III and 0.501 mg. of IV.

Comparative studies with *N*-bromosuccinimide (11) against sulfanilamide and 3,4-dimethyl-5-sulfanilamidoisoxazole show that the results obtained with both reactants are similar; however, the hydantoin derivatives offer the advantage of their better stability (8).

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