A NEW METHOD FOR THE DETERMINATION OF BROMINE IN THE α-BROMOACYLCARBAMIDES, CARBROMAL AND BROMVALETONE

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Introduction

The methods in general use for estimating bromine in α-bromoacylcarbamides are based on the Volhard method. Many foreign pharmacopœias include this method in their specifications, e.g., the Danish Pharmacopœia for bromisovalerylurea, carbromal and acetylcarbromal, the Swedish and German Pharmacopœias for bromisovalerylurea, and the Finnish Pharmacopœia for carbromal. The British Pharmaceutical Codex 1949, in its monographs on bromvaletone and carbromal, does not call for a quantitative assay, but here also the Volhard procedure is generally accepted whenever a bromine assay is required to determine the purity of such substances. The general procedure involves hydrolysis of the test sample with hot aqueous alkali, acidification of the solution with nitric acid, and estimation of bromide by the normal Volhard procedure. The Swedish Pharmacopœia XI and the German Pharmacopœia VI specify that the initial alkaline hydrolysis is carried out by boiling; the Danish Pharmacopœia 1948 requires heating on a steam-bath for 15 minutes. Detailed study of these variations has led us to conclude that the results obtained by these methods tend to be inaccurate and erratic.

When applied to the α-bromoacylcarbamides, the method appears to be liable to some specific sources of error, in addition to those which are generally known to be associated with this method, viz., the usual disadvantages inherent in the use of back titrations, the effect of traces of nitrous acid present in the nitric acid used, the risk of decomposition of the thiocyanate solution to give cyanate, difficulties in attaining adsorption equilibrium, etc. (cf. Kolthoff and Lingane,[1] and others). It was, therefore, considered desirable to develop a simple alternative method, which is at once more rapid and more accurate.

Alternative Methods

We investigated various direct titration procedures, using an adsorption indicator. It was at first thought that, for this purpose, titration would have to be performed in a strongly acid solution, and the procedure developed by Lang and Messinger[2] was therefore tried, using oxidised diphenylamine as adsorption indicator. However, when applying this method, difficulties were experienced, due to fading of the indicator.

Attention was next turned to a procedure involving alkaline hydrolysis, followed by acidification with acetic acid, and silver nitrate titration with eosin as indicator. The use of eosin as indicator for the estimation of bromine generally has been described by Kolthoff and Van Berk.[3] Its application to bromine estimation in carbromal was described by Hök.[4]

It was found that the end-point obtained with this method was somewhat indefinite. This was thought to be due to interference by some material produced during the hydrolysis, and an attempt was, therefore, made to apply the alkaline ashing procedure of Francis and Harvey[5] to the product obtained after alkaline hydrolysis. Unsatisfactory results were at first obtained, again owing to a somewhat doubtful end-point. The cause of this was traced to the formation of cyanide in the ashing, the presence of which was confirmed qualitatively. In view of this finding, the product obtained from the alkaline ashing procedure was dissolved in water and subjected to oxidation by means of hydrogen peroxide (100 vols.).[6] The solution, after boiling to destroy excess of peroxide, was then titrated as before, using eosin as indicator, and very sharp end-points were obtained. This method, though giving reproducible and accurate results, suffers from one serious drawback. It involves a very lengthy procedure, one estimation requiring between 3 and 4 hours for completion.

The next method to be examined was based on an alkaline hydrolysis of the test sample, followed by oxidation of the resulting bromide to bromate, by means of sodium hypochlorite in a phosphate buffer (Kolthoff and Yutzy[7]), and iodimetric determination of the bromate. However, it was found that the oxidation of bromide to bromate was incomplete, owing to the presence of organic matter which would have to be destroyed completely before this procedure might be applied with success.

Since cyanide was known to be one of the hydrolytic products of carbromal (Newbery[8]), attention was redirected to an alkaline hydrolysis procedure, followed by oxidation with hydrogen peroxide (100 vols.) to destroy the cyanide[6] and, after removal of excess of hydrogen peroxide by boiling, acidification with acetic acid and subsequent titration with silver nitrate solution, using eosin as indicator. It is essential to destroy any cyanide produced on hydrolysis, since its presence is known to interfere with the end-point in titrations using eosin. This method gave a sharp and reproducible end-point and was ultimately adopted as our method of choice.

Method Recommended

Reagents. (i) 0·1N silver nitrate; (ii) 0·5 per cent. eosin solution (sodium salt in water); (iii) 5N acetic acid; (iv) sodium hydroxide (pellets); (v) hydrogen peroxide (100 vol.); (vi) phenolphthalein, 0·2 per cent. solution in 60 per cent. ethanol.

Procedure. About 0·5 g., accurately weighed, is washed into a 250-ml. conical flask with about 50 to 100 ml. of water. About 0·2 g. of solid sodium hydroxide (1 pellet) is added and the mixture is boiled on an electric hot plate for 10 minutes under reflux (e.g., "cold finger" inserted in the mouth of the flask). The flask is removed from the hot plate, allowed to cool slightly, and 5 to 10 ml. of hydrogen peroxide (100 vol.) is then added and the mixture is again boiled gently to destroy excess of peroxide. After cooling to room temperature, 1 drop of phenolphthalein indicator solution is added, and the contents are acidified with acetic acid. A further 10 ml. of acetic acid is then added, followed by 10 drops

of eosin indicator, and the solution is titrated with 0·1N silver nitrate, as quickly as possible and with vigorous shaking. Just before the end-point is reached the solution assumes a rose-pink colour, and thin strings of precipitate may appear on the surface and on the sides of the flask. The titration is now completed very carefully and with vigorous shaking until, at the end-point, the precipitate coagulates and turns intensely red.

1 ml. of 0·1N silver nitrate = 7·992 mg. of Br; 22·31 mg. of $C_6H_{11}O_2N_2Br$ (bromisovalerylurea); 23·71 mg. of $C_7H_{13}O_2N_2Br$ (carbromal); 27·92 mg. of $C_9H_{15}O_3N_2Br$ (acetylcarbromal).

The tables which follow will serve to illustrate the types of results that have been obtained in our laboratories over the past 12 months.

Results

Table I shows typical results obtained with highly purified samples of bromisovalerylurea and carbromal. The values were obtained for separate weighings and illustrate the high degree of accuracy which is attained by the new method of assay. In Tables II and III, typical results obtained by the new method are compared with those given by the Swedish and Danish Pharmacopœia modifications of the Volhard method. Commercial samples of bromisovalerylurea and carbromal were used in this series of experiments.

For the repeat determinations shown in Tables II and III for samples No. 1, 2, 6 and 7, each determination has been carried out on a freshly weighed sample of material. The "average deviation" shown in these cases refers to average deviation of a single result.

TABLE I

DETERMINATION OF BROMINE IN PURE BROMISOVALERYLUREA AND CARBROMAL, BY THE PEROXIDE/EOSIN METHOD

Bromisovalerylurea, m.pt. 152° to 153° C. (Theoretical Br-content: 35·82 per cent.)			*Carbromal*, m.pt. 118° to 119° C. (Theoretical Br-content: 33·70 per cent.)		
Assay	Bromine per cent.	$C_6H_{11}O_2N_2Br$. per cent.	Assay	Bromine per cent.	$C_7H_{13}O_2N_2Br$. per cent.
1	35·84	100·06	4	33·71	100·03
2	35·82	100·00	5	33·74	100·12
3	35·84	100·06	6	33·74	100·12
Average value ..	35·83	100·04	Average value	33·73	100·09

The new procedure has also been used successfully for assaying acetylcarbromal and can be applied also to other bromoacylcarbamide derivatives. The results of some typical assays of acetylcarbromal are shown in Table IV.

TABLE IV

DETERMINATION OF BROMINE IN ACETYLCARBROMAL BY THE PEROXIDE/EOSIN METHOD (28·63 PER CENT. OF BR. = 100 PER CENT.)

Sample	M.pt. °C.	Bromine per cent.	$C_9H_{15}O_3N_2Br$. per cent.
11	109 to 110	28·69	100·20
12	108 to 110	28·25	98·65
13	110 to 112	28·69	100·20
14	109 to 110	28·67	100·10

TABLE II

DETERMINATION OF BROMINE IN BROMISOVALERYLUREA
COMPARISON OF RESULTS OBTAINED BY THREE DIFFERENT METHODS OF ASSAY

Sample	M.pt.	Peroxide/Eosin Method		Volhard (Swedish Pharmacopœia)		Volhard (Danish Pharmacopœia)	
		Bromine per cent.	$C_8H_{11}O_2N_2Br$. per cent.	Bromine per cent.	$C_8H_{11}O_2N_2Br$. per cent.	Bromine per cent.	$C_8H_{11}O_2N_2Br$. per cent.
1	147° to 148° C. (A)	35·24	98·37	34·18	95·43	34·58	96·54
	(B)	35·24	98·37	34·13	95·30	31·35	87·52
	(C)	35·23	98·35	34·50	96·32	33·78	94·30
	(D)	35·25	98·40	34·45	96·18	32·28	90·14
	Average value	35·24	98·37	34·32	95·83	33·00	92·12
	„ deviation	0·005	0·013	0·16	0·44	1·18	3·30
2	153·5° to 154° C. (A)	35·88	100·19	36·13	100·90	35·84	100·06
	(B)	35·90	100·20	36·35	101·50	35·69	99·63
	(C)	35·88	100·19	35·46	99·00	35·88	100·19
	Average value	35·89	100·2	35·98	100·50	35·80	99·95
	„ deviation	0·01	0·007	0·44	0·97	0·08	0·22
3	147° to 148° C.	35·39	98·81	34·47	96·25	34·45	96·18
4	148° to 149° C.	34·89	97·40	33·90	94·64	35·33	98·65
5	149° to 150° C.	34·98	97·66	34·65	96·74	35·02	97·77

TABLE III

DETERMINATION OF BROMINE IN CARBROMAL
COMPARISON OF RESULTS OBTAINED BY THREE DIFFERENT METHODS OF ASSAY

Sample	M.pt.	Peroxide/Eosin Method		Volhard (Swedish Pharmacopœia)		Volhard (Danish Pharmacopœia)	
		Bromine per cent.	$C_7H_{13}O_2N_2Br$. per cent.	Bromine per cent.	$C_7H_{13}O_2N_2Br$. per cent.	Bromine per cent.	$C_7H_{13}O_2N_2Br$. per cent.
6	117° to 119° C. (A)	33·81	100·32	33·71	100·03	30·64	90·93
	(B)	33·82	100·36	31·28	92·83	32·60	96·74
	(C)	33·80	100·30	33·72	100·06	32·64	96·85
	(D)	33·81	100·32	30·32	89·97	30·74	91·22
	Average value	33·81	100·32	32·26	95·72	31·66	93·96
	„ deviation	0·005	0·015	1·46	4·32	0·97	2·86
7	118° to 118·5° C. (A)	33·40	99·10	33·19	98·49	33·11	98·24
	(B)	33·40	99·10	33·43	99·19	33·13	98·31
	(C)	33·42	99·17	33·12	98·28	33·11	98·24
	Average value	33·41	99·13	33·25	98·65	33·12	98·28
	„ deviation	0·01	0·03	0·12	0·36	0·01	0·04
8	118° to 119° C.	33·40	99·10	32·59	96·72	33·59	99·68
9	118° to 119° C.	32·72	97·09	31·60	93·78	31·73	94·17
10	117° to 119° C.	33·30	98·81	32·26	96·03	32·25	95·72

Summary

1. In the determination of bromine in bromoacylcarbamides the values obtainable by the Volhard method are unreliable and inconsistent. Of the two modifications which have been examined, and which differ from each other only by the method of hydrolysis to which the test sample is subjected, neither has been found to give consistently high or low results, although more often both are inclined to be low.

2. There was a tendency for both Volhard modifications to be rather more reliable with extremely pure samples of the bromocarbamides, e.g., Nos. 2 and 7. These samples had been purified by repeated recrystallisations and were of a much higher degree of purity than that demanded by any of the official specifications in this country or abroad.

3. An adsorption indicator method, using eosin, has been found to give accurate and consistent results.

4. The advantages of the method may be summarised as follows: (*a*) It requires only one standard solution, instead of the two required by the Volhard procedures; (*b*) it is rapid and much simpler than the Volhard method; (*c*) it gives results of a degree of accuracy far superior to the old Volhard procedures which, in our experience, tend to be inaccurate and unreliable when applied to this class of substances. These difficulties are entirely eliminated by the new procedure.

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