THE BROMINATION OF *p*-AMINOSALICYLIC ACID, SODIUM *p*-AMINOSALICYLATE AND *m*-AMINOPHENOL

By D. SIMMONITE

From the Research Department, Herts. Pharmaceuticals Ltd.

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THE quantitative bromination of phenols by acid bromide/bromate solution, first described by Koppeschaar[1] in 1876 is based upon the general assumption that aqueous nascent bromine will substitute quantitatively only in the *ortho* and *para* positions of phenols. The presence of certain groups other than hydrogen in these positions has been found to give anomalous results. Ruderman[2] showed that certain alkylated phenols brominate quantitatively regardless of the bromine excess used while others overbrominate to an extent which varies with the magnitude of the bromine excess. Day and Taggart[3] found that Koppeschaar's method was unsatisfactory for materials like *o*- and *p*-cresol but satisfactory for *m*-cresol, phenol and a number of salicylates. Sprung[4] found that phenols substituted in the *meta* position brominate quantitatively. The present paper was undertaken to study the behaviour of *p*-aminosalicylic acid and *m*-aminophenol on bromination with the object of developing an assay method for these compounds.

EXPERIMENTAL

The *p*-aminosalicylic acid used was purified by two crystallisations from methyl alcohol. A melting-point is not quoted since the material is known to decompose on heating at temperatures over 110°C., the melting-point being variable according to the rate of heating[5]. The sodium *p*-aminosalicylate was purified by recrystallisation from hot 90 per cent. aqueous alcohol. The product contained two molecules of water of crystallisation. The *m*-aminophenol was recrystallised from boiling water; m.pt. 122° to 123°C.

Procedure.—An accurately weighed quantity of the material was dissolved in distilled water using sufficient sodium hydroxide in the case of *p*-aminosalicylic acid and *m*-aminophenol to effect solution and made up to 1 l. A 25 ml. aliquot of the solution was transferred to a 250 ml. iodine flask, to which were added varying volumes of N/10 potassium bromate/bromide solution, together with a volume of distilled water to ensure that the total volume of bromate/bromide solution and diluent water was 50 ml. 5 ml. of concentrated hydrochloric acid was then added, the flask was immediately stoppered and allowed to stand for 5 minutes, being shaken intermittently during this time. 5 ml. of a 20 per cent. w/v solution of potassium iodide was then added, the flask quickly stoppered and allowed to stand for a further 5 minutes. The stopper and sides of the flask were then washed down with water and the excess of iodine estimated by titration with N/10 sodium thiosulphate, using starch solution as indicator. A blank was run using an additional 25 ml. of distilled water in place of the test solution.

The number of reactive positions R in the molecule of *p*-aminosalicylic acid, sodium *p*-aminosalicylate or *m*-aminophenol was calculated from the formula $R = \frac{EM}{50C}$ where E is the number of milli-equivalents of bromine absorbed, M is the molecular weight of the compound and C is the concentration of the test sample in g./l.

Results and Discussion

The results of a series of titrations on the three materials is set out in Tables I, II and III. It appears that the materials examined brominate quantitatively under the conditions used and the reaction could be made the basis of an assay process.

TABLE I

THE BROMINATION OF *p*-AMINOSALICYLIC ACID
(ASSAY BY ALKALI TITRATION 99·74 PER CENT. W/W)
CONCENTRATION OF SOLUTION 1·200 G./L.

Bromine added milli-equivalents	$Na_2S_2O_3$ required milli-equivalents	Bromine absorbed milli-equivalents	No. of reactive positions found	Percentage w/w of $C_6H_3COOH.OH.NH_2$
1·500	·330	1·170	2·99	99·5
2·000	·822	1·178	3·01	100·2
2·000	·828	1·172	2·99	99·7
2·500	1·320	1·180	3·01	100·3
2·500	1·323	1·177	3·00	100·1
2·500	1·323	1·177	3·00	100·1
2·500	1·325	1·175	3·00	99·9
2·500	1·324	1·176	3·00	100·0
2·500	1·328	1·172	2·99	99·7
3·000	1·828	1·172	2·99	99·7
3·500	2·330	1·170	2·99	99·5
3·500	2·326	1·174	2·99	99·8
4·000	2·822	1·178	3·01	100·2
5·000	3·820	1·180	3·01	100·3

TABLE II

THE BROMINATION OF SODIUM *p*-AMINOSALICYLATE DIHYDRATE
(CONTAINS 82·9 PER CENT. W/W OF $C_6H_3COONaOH.NH_2$)
CONCENTRATION OF SOLUTION 1·600 G./L.

Bromine added milli-equivalents	$Na_2S_2O_3$ required milli-equivalents	Bromine absorbed milli-equivalents	*No. of reactive positions found	Percentage w/w of $C_6H_3COONaOH.NH_2$
1·500	·365	1·135	2·48	82·8
2·000	·866	1·134	2·48	82·7
2·500	1·360	1·140	2·49	83·2
2·500	1·365	1·135	2·48	82·8
3·000	1·865	1·135	2·48	82·8
3·500	2·360	1·140	2·49	83·2
4·000	2·860	1·140	2·49	83·2
5·000	3·867	1·133	2·48	82·6
5·000	3·866	1·134	2·48	82·7

* Theoretical figure equivalent to three bromine atoms when calculated for the anhydrous salt.

The results on *m*-aminophenol substantiate the results of Sprung[4] while the results on *p*-aminosalicylic acid and its sodium salt would appear to agree with Day and Taggart's[3] conclusions regarding a number of salicylates. The analyses suggest that three atoms of bromine are absorbed per molecule of the compounds studied. Although their point of reaction is a matter for conjecture it is interesting to note from Allen's Commercial Organic Analysis (4th Ed., 1910, Vol. III) that salicylic acid

brominates with loss of the carboxyl group and the formation of 2:4:6 tribromphenol.

From the present work it would appear that pure specimens of *p*-aminosalicylic acid and its sodium salt brominate quantitatively regardless of the excess of bromine used. It is interesting to notice, however,

TABLE III

THE BROMINATION OF *m*-AMINOPHENOL
CONCENTRATION OF SOLUTION 0·8000 G./L.

Bromine added milli-equivalents	$Na_2S_2O_3$ required milli-equivalents	Bromine absorbed milli-equivalents	No. of reactive positions found	Percentage w/w of $C_6H_4OH.NH_2$
1·500	·403	1·097	2·99	99·7
1·500	·407	1·093	2·98	99·3
1·500	·405	1·095	2·98	99·5
1·500	·400	1·100	3·00	99·9
2·500	1·394	1·106	3·15	100·4
3·000	1·896	1·104	3·01	100·3
3·000	1·897	1·103	3·01	100·2
3·500	2·400	1·100	3·00	99·9
3·500	2·395	1·105	3·01	100·4
4·000	2·910	1·090	2·97	99·0
4·000	2·903	1·097	2·99	99·7
4·500	3·398	1·102	3·00	100·1
5·000	3·900	1·100	3·00	99·9
5·000	3·890	1·110	3·02	100·8
5·000	3·895	1·105	3·01	100·4

that as mentioned in an earlier communication[5], less pure material shows a slight variation in bromine absorption which does depend upon the available bromine. Accordingly, a direct bromination method using an external indicator has been suggested for assay purposes, although the present method is more convenient where the degree of purity of the material warrants its application.

SUMMARY

1. The bromination of *p*-aminosalicylic acid, sodium *p*-aminosalicylate and *m*-aminophenol has been studied using a variable excess of bromide/bromate solution.

2. *p*-Aminosalicylic acid, sodium *p*-aminosalicylate and *m*-amino phenol brominate quantitatively regardless of the excess of bromide/bromate solution used.

3. The basis for an assay process for *p*-aminosalicylic acid, sodium *p*-aminosalicylate and *m*-aminophenol has been described.

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REFERENCES

1. Koppeschaar, *Z. anal. Chem.*, 1876, 15, 233.
2. Ruderman, *Ind. Engng. Chem. Anal., Ed.* 1946, 18, 753.
3. Day and Taggart, *Ind. Engng. Chem.*, 1928, 20, 545.
4. Sprung, *Ind. Engng. Chem. Anal., Ed.* 1941, 13, 35.
5. Oberweger, Seymour and Simmonite, *Quart. J. Pharm. Pharmacol,* 1948, **21,** 292.