THE STABILITY OF SOLUTIONS OF SODIUM PHENOBARBITONE

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It is well known that sodium phenobarbitone decomposes slowly in aqueous solution at ordinary temperatures to give phenylethylacetylurea. Nielsen[1] found that the rate and extent of the decomposition depended mainly on temperature and also on the *p*H of the solution. The method of analysis used however, depended upon the measurement of the amount of carbon dioxide evolved in the reaction, and extraction of the ureide with chloroform from alkaline solutions of the phenobarbitone.

The use of non-ionic solvents for the estimation of barbiturates gives a new approach to this problem, provided that solvents can be found in which the phenobarbitone alone can be estimated as an acid, without interference from phenylethylacetylurea. We have found that the method using pyridine and sodium methoxide[2] fulfils these requirements and has enabled us to study the stability of sodium phenobarbitone solutions of different strengths, at temperatures ranging from 4 to 30° C.

Method. A volume of solution calculated to give about 0·4 g. of sodium phenobarbitone was pipetted into a separating funnel, diluted to 30 ml. with water and then treated according to the method of the British Pharmacopœia for soluble barbitone. The residue in the flask was partially dried by gentle heat under reduced pressure (water pump) and finally dried in an oven at 110° C. The residue was then dissolved in 10 ml. of pyridine and titrated with sodium methoxide solution using phenolphthalein as indicator.

Reagents. The pyridine was dried over sodium hydroxide and distilled. The sodium methoxide was prepared by dissolving 6 g. of clean sodium in 100 ml. of dry methanol, then adding a further 150 ml. of dry methanol and 1500 ml. of dry benzene. The sodium methoxide solution was kept in a burette system fitted with calcium chloride and soda lime tubes and standardised frequently against pure benzoic acid dissolved in dry pyridine. The phenolphthalein indicator used was a 0·2 per cent. solution in dry methanol.

Results

Recovery experiments. The accuracy of the method was tested by analysing sodium phenobarbitone solutions by the Pharmacopœial method, and after weighing the dry residue of phenobarbitone, dissolving it in pyridine and titrating. The results given in Table I indicate that recovery is complete.

Estimation of phenobarbitone in the presence of phenylethylacetylurea. A sample of phenylethylacetylurea was prepared by boiling a solution of

sodium phenobarbitone for 30 minutes. The ureide crystallised on cooling and was purified by recrystallisation from water and then from ethanol (70 per cent.). The product was dried in a vacuum desiccator and the m.pt. 148° C. agreed with that given in the literature[3]. Phenobarbitone and phenylethylacetylurea were mixed in varying amounts,

TABLE I

Sodium phenobarbitone g.	Phenobarbitone recovered (calculated as sodium phenobarbitone)			
	Gravimetric g.	Percentage recovery	Titration g.	Percentage recovery
0·439	0·438	99·8	0·43	98·0
0·349	0·356	102·0	0·35	100·3
0·604	0·602	99·7	0·60	99·4
0·534	0·533	99·8	0·53	99·3

dissolved in pyridine and titrated. The results in Table II indicate that phenylethylacetylurea does not behave as an acid in pyridine solution and therefore does not interfere with phenobarbitone estimations under these conditions.

TABLE II

Phenobarbitone g.	Phenylethylacetylurea g.	Phenobarbitone by titration g.	Percentage recovered
0·40	0·2	0·397	99·2
0·30	0·1	0·301	100·3
0·54	0·4	0·502	100·4

Sodium phenobarbitone solutions. Solutions of sodium phenobarbitone 5, 10 and 20 per cent. w/v were prepared in freshly boiled and cooled water. The solutions, when first prepared, had *p*H 9·4, 9·5 and 9·4 respectively. Each solution was divided into 3 parts, placed in tightly corked flasks and stored:—(*a*) in a refrigerator 4° to 7° C., (*b*) at room temperature 14° to 17° C. (maintained by immersion in a large water bath), and (*c*) in an incubator at 30° C. At intervals, suitable amounts of the solutions were pipetted and assayed. The results were calculated as percentage loss of sodium phenobarbitone and are shown in Table III.

TABLE III

PERCENTAGE LOSS IN SODIUM PHENOBARBITONE SOLUTIONS AFTER STORAGE

Original solution per cent. w/v	5			10			20		
Temperature	5° C.	15° C.	30° C.	5° C.	15° C.	30° C.	5° C.	15° C.	30° C.
Time in days 2	0	0	0	0	0	0	0	0	0
3	0	0	1·6	0	0	2·6*	0	0·2	1·5
4	0	0	3·0	0	0	5·2	0	0·4	3·0
5	0	0	4·8*	0	0·2	5·8	0·2	0·6	4·4*
10	0	0	9·0	1·4	1·8	8·8	1·1	1·5	8·2
15	0	0·4	11·0	3·0	3·3	11·8	2·0	2·4	10·0†
25	0	2·0	14·0†	5·9	6·4	17·8	3·6	4·1	13·0
30	0	2·7	—	7·4	7·9	—	4·3	4·9†	—
35	0	3·4	—	8·4	9·4†	—	5·1†	6·0	—

* Precipitation of phenobarbitone occurred.
† Crystals appeared which were mainly phenylethylacetylurea.

Discussion

Nielsen[1], using 10 per cent. solution of sodium phenobarbitone found that 1 per cent. loss occurred in 60 days at 1° C. and in 20 days at 20° C. Our results indicate that 7·4 per cent. decomposed in 30 days at 4° C. and 6·4 per cent. decomposed in 25 days at 15° C. It appears therefore that the rate of decomposition of sodium phenobarbitone in solution is more rapid than was formerly thought and we think that the difference in these results can be explained by the more accurate method of analysis made possible by the use of non-ionic solvents.

Summary

1. The estimation of phenobarbitone by titration in anhydrous pyridine solution with sodium methylate is not affected by phenylethylacetylurea.

2. The rate and extent of decomposition of sodium phenobarbitone in different strength aqueous solutions at various temperatures has been followed for periods up to 35 days.

3. The results indicate a more rapid rate of decomposition than has been found previously, and confirm the necessity for avoiding the storage of phenobarbitone solutions for long periods at room temperature.

References

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