A NEW METHOD FOR THE DETERMINATION OF BARBITURATES

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THE use of complexometric analysis for the determination of metal ions has suggested that this could usefully be applied to the assay of barbiturates. The method depends on precipitation of the barbiturate with excess of a metallic salt, followed by estimation of this excess complexometrically.

In earlier methods (Budde, 1934; Chavanne and Marie, 1953; Danielson, 1951; Kalinowski, 1935; Schulek and Rozsa, 1938; Stanier, Lapiere and De Tiege-Robinet, 1956) the barbiturates are precipitated as the silver salts, and excess silver nitrate determined by Volhard's method. In the modification of Mangouri and Milad (1947) precipitation is carried out in a sodium acetate buffer and the liberated acetic acid is neutralised with calcium carbonate before titration of the excess silver nitrate. When examined in our laboratory this method gave results which varied according to the amount of calcium carbonate used.

Another approach to the assay involves precipitation of the barbiturates as the mercuric salt with mercuric perchlorate. Excess reagent is again determined by Volhard's method (Pedley, 1950). Repetition showed that this method was reproducible only within 1 per cent when applied to barbitone and barbitone sodium: the end point moreover was found to be indistinct and easily over-stepped. Complexometric titration of the excess mercuric perchlorate was therefore investigated. After precipitating the barbiturate as described by Pedley the filtrate was treated with a known excess of standard magnesium complexonate

TABLE I

APPLICATION OF THE Hg AND Zn METHODS TO SOME BARBITURATES

Substance	Indicator	Results
Hg method—		
Barbitone	E[1]	99·4; 99·2; 98·8
	Cu P[2]	98·8; 99·3; 99·3
Barbitone sodium	E	99·5; 99·3; 99·3
	Cu P	98·1; 99·5; 98·9
Phenobarbitone	E	99·4; 99·1; 99·2
	Cu P	98·9; 99·6; 99·3
Phenobarbitone sodium	E	98·9; 98·5; 98·6
	Cu P	98·8; 98·6; 98·4
Zinc method—		
Barbitone sodium	E	99·4; 99·3; 98·7
Phenobarbitone sodium	E	99·2; 99·1; 98·7[3]
Amylobarbitone sodium	E	98·3; 99·0; 98·7
Pentobarbitone sodium	E	100·6; 100·4; 100·6

[1] Eriochrome black T.
[2] Cu [1-(2-Pyridylazo)-2-naphthol] complex.
[3] Result calculated on the assumption that the precipitate is 8 molecules phenobarbitone to 3 atoms Zn.

solution, buffered to pH 10, warmed to about 50° and titrated with standard EDTA using Eriochrome black T as indicator. Alternatively, the solution was buffered to pH 5 and the copper-PAN indicator used (Flaschka and Abdine, 1956abc). Reproducible results were obtained, and the end points were sharp. The results are shown in Table I.

Attempts were then made to use zinc as the precipitating ion instead of mercury. Zinc is much easier to titrate complexometrically as far as the pH of the titration, the interfering ions, and the available indicators are concerned (Schwarzenbach, 1955). Barbituric acid derivatives were quantitatively precipitated by zinc sulphate at pH 6, more acid solutions

TABLE II

RESULTS OF ASSAY OF A SAMPLE OF BARBITONE SODIUM BY DIFFERENT METHODS

B.P. method	Ag method	Hg method (*a*) Volhard	Hg method (*b*) complex (E.T.)	Hg method (*c*) complex (PAN)	Zn method
99·8	98·3	99·8	99·3	99·1	99·4
99·8	100·7	99·0	99·5	99·6	99·3
99·8	103·5	99·2	99·3	98·9	98·7
—	103·8	—	—	—	—
—	106·9	—	—	—	—
Mean 99·8	—	99·3	99·4	99·2	99·1

caused dissociation of the precipitate, while more alkaline solutions caused co-precipitation of basic zinc salts. The following procedure is recommended.

Weigh accurately about 0·4 g. of the sodium salt of the barbiturate, dissolve in water (about 100 ml.) and add boric acid buffer solution pH 6 (10 ml.), and heat nearly to boiling. Add 0·10M zinc solution (20 ml.) slowly with stirring, and keep at about 100° for 15 min. Cool and transfer to a 250 ml. volumetric flask, adjust to the mark and filter. Take 100 ml. of the filtrate, add buffer solution, pH 10 (10 ml.) and titrate with 0·02M EDTA solution using Eriochrome black T as indicator. Carry out a blank experiment omitting the barbiturate.

The results, shown in Table I, are calculated on the assumption that the complex is composed of one zinc atom and two molecules of the barbiturate. Table II compares the results of assay of a sample of barbitone sodium by the different methods.

Reagents

0·10M EDTA *disodium salt:* B.P. 1958. 0·10N *standard zinc solution:* Metallic zinc A.R. (6·538 g.) is dissolved by the aid of heat in the minimum amount of sulphuric acid A.R. The solution is cooled and made up to one litre with distilled water.

Buffer solutions. Borax buffer pH 6; Ammonium chloride-ammonium hydroxide buffer pH 10.

Indicators. Eriochrome black T (0·1 g.) is mixed with sodium chloride A.R. (20 g.). PAN (1-(2-pyridylazo)-2-naphthol) (0·1 per cent) in methanol.

Copper-EDTA : Mix equal volumes of 0·10M copper sulphate solution, and 0·10M EDTA.

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