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SHORT COMMUNICATION

Polarographic determination of microgramme quantities of chlorpromazine

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FEW polarographic procedures have been described for the determination of phenothiazine derivatives.

Kabasakalian & McGlotten (1959) reported anodic oxidation of about 1·5 mg quantities, while Blazek (1956) employed an amperometric method on 50 mg quantities. The method used by Chuen & Riedel (1961) is useful at the level of 350 μg.

A method sensitive at least to 2 μg of this class of compound was required, and initially chlorpromazine has been examined. Direct cathodic polarography of chlorpromazine solutions was not satisfactory, but treatment of a solution of the substance with bromine water produced a reducible solution with a well-marked polarographic wave. Bromine water was chosen as a suitable oxidant as excess bromine was readily removed by flushing with nitrogen.

Thin-layer chromatography of chlorpromazine after oxidation with bromine water showed no spot corresponding to unchanged starting material.

After examination of the effect of pH on the cathodic wave, 0·5N hydrochloric acid was chosen as a suitable electrolyte.

The determination is applicable to small quantities (0·002 to 0·1 ml) of chlorpromazine injection (25 mg/ml) and to corresponding amounts of chlorpromazine tablets and syrup.

EXPERIMENTAL AND RESULTS

Equipment. A Southern Analytical Ltd. K1000 cathode ray polarograph was used. Determinations were made at 25° using a mercury pool anode.

Calibration graph. Chlorpromazine base (50 mg) was dissolved in and made up to one litre with 0·5N hydrochloric acid. Quantities of 1, 2, 3, 4 and 5 ml of this solution were placed in each of 25 ml graduated flasks and diluted to the mark with 0·5N hydrochloric acid.

Each 25 ml of solution was treated with two drops of saturated bromine water, shaken, allowed to stand (1 min) and 1 ml transferred to a polarographic cell. After being flushed with nitrogen (3 min) the solution was polarographed using an initial potential of −0·5 V.

A clear, well formed wave resulted, with a peak potential of about −0·75 V, increasing in negativity with chlorpromazine concentration.

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Values of peak current and peak potential were recorded for each concentration (Table 1).

TABLE 1. PEAK CURRENTS AND PEAK POTENTIALS OF BROMINATED CHLORPROMAZINE TEST SOLUTIONS

Concentration of chlorpromazine (μg/ml)	Peak voltage (V)	Peak current (μA)
2	−0·740	0·31
4	−0·745	0·63
6	−0·750	0·96
8	−0·760	1·26
10	−0·775	1·60

The effect of pH was examined using Britton Robinson buffer solutions. An increase in pH resulted in more negative peak potentials and gave waves whose heights were difficult to read at the low concentrations employed because of the long slope imparted to the less negative side of the peak. 0·5N Hydrochloric acid, however, was satisfactory, giving a clearly defined wave at concentrations of chlorpromazine well below 0·5 μg/ml.

To assess the reproducibility of the method, 28 solutions of chlorpromazine in 0·5N hydrochloric acid were assayed as described above. The results, derived from the calibration graph, are summarised in Table 2.

TABLE 2. PEAK POTENTIALS AND ANALYSES OF BROMINATED CHLORPROMAZINE SOLUTIONS

Peak potential range V	Range of concentrations examined μg/ml	Standard deviation
−0·74 to −0·78	1 to 2	0·037
	2 to 4	0·037
	4 to 6	0·110
	6 to 8	0·085
	8 to 10	0·142

Assay of chlorpromazine injection, tablets and syrup. The sample (0·1 ml for liquid preparations, 0·2 g for tablets) was diluted or extracted with 0·5N hydrochloric acid to give 25 ml of a solution containing between 1 and 8 μg/ml of chlorpromazine. This solution was oxidised with bromine water and polarographed as described; the concentration was determined from the calibration graph. The mean of four assays on each type of preparation is shown in Table 3.

TABLE 3. RESULTS FOR POLAROGRAPHIC ASSAY OF CHLORPROMAZINE PREPARATIONS

Preparation	Concentration of chlorpromazine base in original preparation	
	Nominal	Found
Injection	22·4 mg/ml*	21·7 mg/ml*
Syrup	6·2 mg/ml	5·8 mg/ml
Tablets	11·8% w/w	11·3% w/w

* A fresh ampoule 25 mg/ml was used for each assay.

Method of standard addition applied to chlorpromazine injection. 25 ml of a solution containing about 2 μg of chlorpromazine per ml was prepared by diluting the injection with 0·5N hydrochloric acid. This was oxidised with bromine water, 1 ml pipetted out and flushed with nitrogen, polarographed and the peak current recorded.

25 ml of a solution in 0·5N hydrochloric acid, containing exactly 6 μg/ml of pure chlorpromazine was oxidised with bromine water and a few ml flushed with nitrogen. 1 ml of this standard was then added to the 1 ml of test already in the polarographic cell, nitrogen again passed to mix, and the peak current recorded.

The unknown concentration (C_1) is calculated from the formula

$$C_1 = \frac{i_1 \cdot v \cdot C_s}{i\,(V + v) + i_1 v}, \text{ where}$$

V = volume of unknown solution (ml); v = volume of standard added (ml); C_s = concentration of the standard (μg/ml); i = the increase in peak current (μA); i_1 = original peak current (μA).

DISCUSSION

The method described is rapid and simple. Compared to spectrophotometric methods it shows better sensitivity; it is also more specific. Preparation of a five point calibration graph takes about 30 min; a single determination takes about 6 min. The calibration is reproducible for any given capillary, and checks were made from time to time using two different standard solutions.

Using this method it has been possible to show directly the diminution in concentration of chlorpromazine in acid solutions on exposure to air and light. Such decomposition products as are formed have no effect on the characteristic wave.

The nature of the reaction product of bromine and chlorpromazine is unknown: it is not chlorpromazine sulphoxide.

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The paper was presented by THE AUTHOR.