

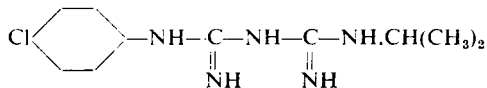
# THE DETERMINATION OF PROGUANIL

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PROGUANIL (Paludrine), introduced as an antimalarial drug in 1946, has the constitution  $N_1$ -*p*-chlorophenyl- $N_5$ -isopropylbiguanide.



It is a strongly basic substance which is administered orally as tablets containing the monohydrochloride and by injection as a 5 per cent. solution of the lactate.

Methods for the determination of traces in biological fluids have been described by Spinks and Tottey<sup>1</sup> and Gage and Rose<sup>2</sup>. Spinks and Tottey employ hydrolysis with N/4 hydrochloric acid in a sealed tube at 100°C. followed by diazotisation of the *p*-chloroaniline, coupling with N-β sulphatoethyl-*m*-toluidine and colorimetric determination of the azo dye which is formed. Gage and Rose's method depends on formation and extraction of the copper-complex  $(C_{11}H_{13}N_3Cl)_2Cu$  (see page 392) with benzene and determination of the copper in the extracted complex by the well-known dithiocarbamate method.

Neither method, however, is of sufficient accuracy to be satisfactory for the determination of major amounts, either in the bulk product or in pharmaceutical preparations, and the methods which have been developed for these purposes are described herein.

## METHODS OF ANALYSIS

1. VOLUMETRIC DETERMINATION IN THE HYDROCHLORIDE BY TITRATION WITH ACID. The drug is in reality a diacidic base, and although the form in which it is mainly encountered (the monohydrochloride) is neutral in aqueous solution, this salt can be dissolved in glacial acetic acid and the second basic group can be titrated with a standard solution of perchloric acid in glacial acetic acid in the manner described by Bandel and Blumrich for the titration of weak bases with strong acids<sup>3</sup>. The indicator is  $\alpha$ -naphthol benzein, which changes from yellow to green at the end-point.

This method has the advantage of rapidity and the results are not affected by normal tablet excipients (e.g. starches, gums, sugars, etc.); it can, therefore, be used for the direct determination of the content of tablets.

*Reagents required:* 1. Acetic acid, glacial, analytical reagent quality.

2. N/10 solution of perchloric acid in glacial acetic acid: dissolve the equivalent of 10.05 g. of perchloric acid (calculated from the acid content

of the 60 per cent. aqueous solution) in 50 ml. of acetic acid; add this mixture, a drop at a time, to an amount of freshly distilled acetic anhydride (boiling point 137° to 139°C.) which is exactly sufficient to combine with the water present in the perchloric acid, cooling the mixing vessel in ice during the addition. Dilute with acetic acid to 1 litre.

3. Standard solution of sodium acetate in acetic acid: cautiously dissolve 1.325 g. of sodium carbonate, previously dried for 5 hours at 300°C., in 50 ml. of acetic acid, transfer to a 250-ml. measuring flask and make up to volume with acetic acid.

4.  $\alpha$ -Naphthol benzein indicator: dissolve 0.2 g. of  $\alpha$ -naphthol benzein in 100 ml. of acetic acid.

*Determination.* Standardise the perchloric acid (reagent 2) by titrating 50.0 ml. of the standard solution of sodium acetate (reagent 3) and 1 ml. of the indicator (reagent 4) until the colour changes from brown to green. The temperature of the perchloric and sodium acetate solutions should be kept as near to 20°C. as possible for all measurements of volume in order to minimise errors due to the large coefficient of expansion of acetic acid.

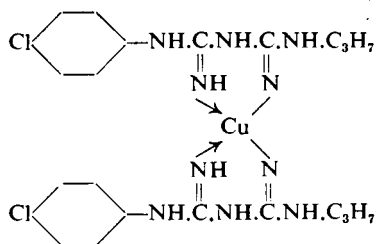
Experience has shown that the normality of this solution remains constant, under ordinary conditions of storage in a stoppered bottle, for at least 3 months.

Weigh about 0.8 g. of the sample, or its equivalent in tablet form, into a dry conical flask and dissolve in 30 ml. of acetic acid, warming to a temperature not exceeding 80°C. Cool to room temperature, add 0.5 ml. of indicator solution and titrate with the perchloric acid solution until the colour of the titration matches that obtained in the standardisation.

If B = vol. of N/10 perchloric acid required

$$\frac{2.90B}{\text{wt. of sample}} = \text{per cent. calculated as hydrochloride, mol. wt. 290}$$

2. GRAVIMETRIC DETERMINATION IN THE HYDROCHLORIDE OR LACTATE BY PRECIPITATION OF THE COPPER COMPLEX. When an excess of ammoniacal cupric chloride solution is added to a cold aqueous solution of the hydrochloride or lactate, the base is precipitated as a copper complex containing ten atoms of nitrogen for each atom of copper. There is little doubt that this precipitate is an inner complex having the formula:



and it has been found to be suitable for gravimetric determination, being easily washed free from the excess of reagent and dried at 130°C.

## DETERMINATION OF PROGUANIL

*Reagent required.* 5. Ammoniacal cupric chloride solution: dissolve 22.5 g. of cupric chloride,  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ , in 200 ml. of water and add 100 ml. of ammonia solution (880).

*Determination.* Weigh 0.5 to 0.7 g. of sample into a 250-ml. beaker, and dissolve in 50 ml. of water by gentle warming. Cool in an ice bath to  $5^\circ$  to  $10^\circ\text{C}$ . and add ammoniacal cupric chloride solution (reagent 5), with stirring, until the solution remains a deep blue colour. Allow to stand at room temperature for at least 1 hour and then filter on a sintered glass crucible, porosity 3—preferably one having a large filtering surface—fitted with an asbestos pad and previously dried at  $130^\circ\text{C}$ . to constant weight. Wash the precipitate with 100 ml. of dilute ammonia and then with cold water until the washings are quite colourless. Dry at  $130^\circ\text{C}$ . ( $\pm 5^\circ$ ) to constant weight.

$$\frac{\text{Wt. of precipitate} \times 1.020}{\text{Wt. of sample}} = \text{per cent. calculated as hydrochloride, mol. wt. } 290$$

### DISCUSSION

The colour change which occurs at the end-point of the volumetric method extends over a range of about 0.5 ml. of titrant in a titre of 25 ml., and the averages of duplicate tests by two operators upon the same sample often differ by 1.5 per cent. The method has, however, the advantage of rapidity and is, therefore, of special value where large numbers of determinations have to be carried out, as, for example, in the routine examination of tablets.

The precision of the gravimetric method is considerably higher than that of the volumetric method, and the averages of duplicate tests by two operators upon the same sample usually agree within 0.5 per cent. Recovery from specially purified hydrochloride has not been determined; this was not considered to be necessary, since the technical hydrochloride (i.e., the material which is normally manufactured for use in pharmaceutical preparations) is itself a very pure product, and the sum of the determined constituents—active agent, *p*-chloroaniline, moisture and ash—in technical samples is normally over 99.0 per cent.

Analysis of a typical sample of technical proguanil hydrochloride is given below:—

content, by gravimetric method, calc. as hydrochloride, mol. wt. 290 .....	99.5 per cent.
<i>p</i> -Chloroaniline .....	Less than 0.01 per cent.
Moisture (by loss of weight on heating at $100^\circ\text{C}$ .) .....	0.1 per cent.
Sulphated ash .....	0.05 per cent.
Total .....	99.6 per cent.

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SUMMARY

1. Two methods are described for the determination of proguanil hydrochloride: one method depends upon titration with perchloric acid in glacial acetic acid solution, and the other upon gravimetric determination of the copper-complex precipitated from cold aqueous solution by ammoniacal cupric chloride.
2. The volumetric method is rapid and is applicable to the determination in tablets, but is less precise than the gravimetric method.
3. The gravimetric method is applicable also to the lactate.

REFERENCES

1. Spinks and Tottey, *Ann. trop. Med. Parasit.*, 1946, **40**, 101.
2. Gage and Rose, *ibid.*, 1946, **40**, 333.
3. Bandel and Blumrich, *Angew. Chem.*, 1941, 374.