A NOTE ON THE IDENTIFICATION OF THIOURACIL AND ITS CLINICALLY IMPORTANT HOMOLOGUES

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In the routine analytical control of medicinal products it is frequently necessary to apply rapid identity tests to distinguish between two or more chemically similar substances. The introduction of thiouracil, methylthiouracil and propylthiouracil to the range of chemotherapeutic substances thus makes it desirable that a simple and reliable means of differentiation of these homologues should be available. A survey of identity tests already recommended in official monographs for these compounds shows that attention has been directed chiefly to:—

(*a*) *The melting point.* Thiouracil and methylthiouracil melt with decomposition and at temperatures too high for convenient manipulation; propylthiouracil, however, can be identified by its lower melting point (218 to 221° C.) and this is included in the B.P. monograph (Addendum 1951).

(*b*) *The formation of* 2:4-*dichloropyrimidine.* This is described in the monograph (B.P. 1948) for thiouracil but it has been found in these laboratories that the test is not suitable for routine use since the procedure is time-consuming and the yield is extremely small. No corresponding test for methylthiouracil and propylthiouracil is specified in the Pharmacopœia (Addendum 1951) probably because of the rather unsatisfactory nature of the reaction.

(*c*) *Colour reactions* (*hydroxylamine hydrochloride and sodium nitroprusside*) *and precipitation reactions* (*bromine-water and baryta*). These depend essentially on the $-N = C(SH) - N<$ grouping and give virtually identical results with all three compounds. They are specified in the Addendum 1951 for both methylthiouracil and propylthiouracil but are not mentioned in connection with thiouracil.

Bucher[1] has described conditions for the preparation of the benzylthioethers of the thiouracils, these derivatives being quoted as having characteristic melting points. Work carried out here prior to the publication of his paper confirms Bucher's findings but nevertheless it was considered desirable to find, if possible, a more rapid means of differentiation and, in addition, in view of the relatively high cost of these compounds, a method using small quantities would be advantageous. Simple colorimetric and precipitation reactions were rejected as showing little promise and attention was directed to microscopical examination of crystal formations obtained by solvent evaporation and precipitation by acid from alkaline solutions using conditions similar to those described by Turfitt.[2] This line of approach gave promising results at the outset and conditions

were devised whereby satisfactory differentiation would be effected. The following two methods are recommended:—

1. Dissolve a few crystals of the material to be identified in a drop of 0·1N sodium hydroxide placed on a microscope slide, acidify by allowing a drop of 10 per cent. sulphuric acid to coalesce gradually with the solution. Gently rock the slide to obtain adequate mixing and examine microscopically the crystal formations obtained using a suitable magnification and compare with the crystals similarly obtained from an authentic sample.

2. Prepare a clear saturated solution of the substance in ethanol (75 per cent.) maintained at approximately 70° C. and quickly smear one drop of the solution as nearly as possible over the whole surface of a clean microscope slide by means of a small glass rod. Allow the solution to evaporate at room temperature and examine the crystal formations microscopically using suitable magnification and compare with the crystals similarly obtained from an authentic sample.

The individual appearances of the crystal formations obtained as above are shown in the accompanying photomicrographs (Figs. 1–6, magnification × 77 diameters). The methods have been successfully applied to tablets of the three compounds, insoluble tablet excipients being removed by filtration of the solution prior to crystallisation. These methods are recommended only as a means of differentiating between the three compounds and do not in themselves provide conclusive evidence of identification: the tests should always be supplemented by other tests (e.g., those of the British Pharmacopœia) which will characterise the compounds as a class.

The author wishes to express thanks to Mr. E. Young for the photomicrographs.

References

1. Bucher, *Pharm. Acta. Helvet.*, 1951, **26**, 145.
2. Turfitt, *Quart. J. Pharm. Pharmacol.*, 1948, **21**, 1.

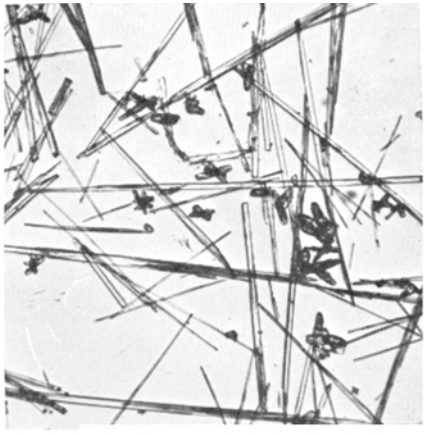

FIG. 1.
Thiouracil. Method 1.

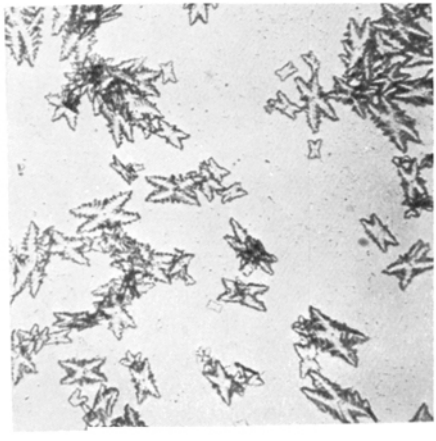

FIG. 2.
Methylthiouracil. Method 1.

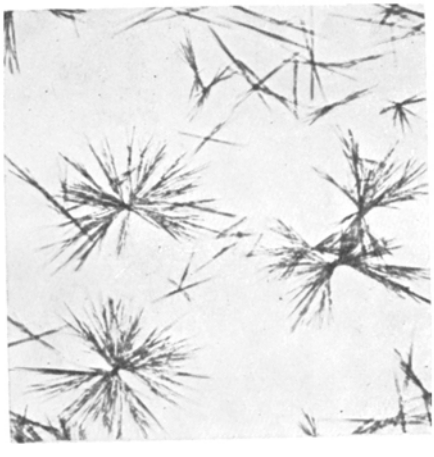

FIG. 3.
Propylthiouracil. Method 1.

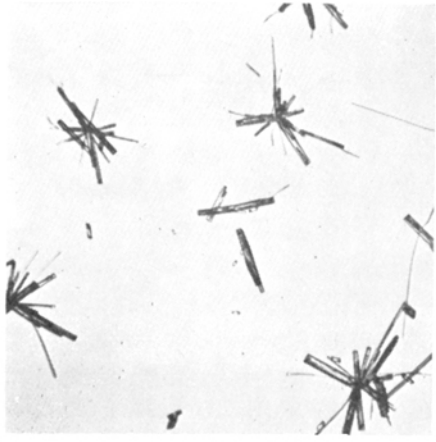

FIG. 4.
Thiouracil. Method 2.

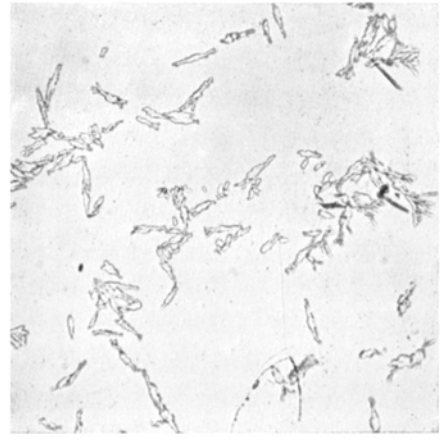

FIG. 5.
Methylthiouracil. Method 2.

FIG. 6.
Propylthiouracil. Method 2.