CLXI. THE CONVERSION OF COLCHICINE INTO COLCHICEINE

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COLCHICINE is readily converted into the corresponding hydroxymethylene derivative, colchiceine, by hydrolysis of the methoxymethylene group in dilute acid solution. Colchiceine has only a fraction ($\frac{1}{40}$ to $\frac{1}{200}$) of the biological action of colchicine [Brues & Cohen, 1936; Ludford, 1936; Boyland & Boyland, 1937]. Hence the activity of orally administered colchicine might be partially destroyed by conversion into colchiceine by the action of the acid in the gastric juice.

EXPERIMENTAL

Method of estimation

Colchiceine gives a green colour with FeCl_3 in chloroform; colchicine and hexahydrocolchicine [Bursian, 1938] give no colour under the same conditions. The test can be used as a qualitative test for the detection of colchiceine in samples of colchicine. The method described below has been developed for the colorimetric estimation of colchiceine. As the colour reaction is given with trimethylcolchicinic acid, this and other hydroxymethylene ketones would be estimated by this method.

The solution containing colchicine and colchiceine is extracted by shaking with three separate lots of 3 ml. chloroform. The combined extracts are placed in a 15 ml. graduated flask, and 4 ml. absolute alcohol and 0.8 ml. of a 0.2% solution of FeCl_3 in chloroform added. The total volume is brought to 15 ml. by addition of chloroform. Standards for comparison are made by dissolving known amounts of pure colchiceine in chloroform. Such standard solutions are unstable and must be freshly made. The colours developed by the unknown and an appropriate standard are compared in a colorimeter, using a red screen if the amount is less than 1 mg. The depths of colour obtained are easily compared without a screen if the amount of colchiceine present is 1–4 mg.

The greatest error in the method lies in the extraction of colchiceine from the aqueous solution with chloroform. Extractions of pure colchiceine showed that between 90 and 95% with an average of 93% was extracted. Allowance is made for this error in the calculation of results.

Hydrolysis of colchicine

Colchicine $\text{C}_{22}\text{H}_{25}\text{O}_6\text{N}$, 1.5 H_2O should theoretically yield 92% of its weight of colchiceine $\text{C}_{21}\text{H}_{22}\text{O}_6\text{N}$, 0.5 H_2O . Colchicine, on heating in $N/10$ HCl at 100° for 1 hr., gives only 93% of the theoretical amount of colchiceine (see Fig. 1), even after allowing for the loss in the extraction. By carrying out the hydrolysis for 1 hr. and then estimating colchiceine the original colchicine content of a solution can be determined. Hydrolysis in stronger acid such as N HCl gives lower yields

(see Fig. 1) owing to further decomposition and a similar decomposition occurs even in weaker acid.

Solutions containing 1 mg. colchicine per ml. were incubated with *N* HCl, *N*/50 HCl and with normal human gastric juice at 37°. Samples of the incubated solutions were taken and colchicine estimated by the method described. The hydrolysis curves obtained are shown in Fig. 2.

Fig. 1.

Fig. 2.

The amount of colchicine hydrolysed in *N*/50 HCl or by gastric juice during the time that orally administered colchicine would be expected to remain in the stomach is small. If colchicine is absorbed from the gut oral administration would be expected to be as effective as injection.

SUMMARY

A method for the colorimetric estimation of colchicine and colchicine is described. The rates of acid hydrolysis of colchicine at 37° and 100° have been measured.

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