STABILITY OF CHLORPROGUANIL IN SOLUTION

R.B. Taylor and A.S. Low.
Robert Gordon's Institute of Technology, Aberdeen. Scotland.

Following the resurgence of interest in the biguanides as malaria prophylactics several reports of assay methods and pharmacokinetic studies have appeared mainly concerned with proguanil. The aqueous stability of these drugs is also of interest particularly in the context of blood samples collected at sites remote from the laboratory. A recent publication (Taylor et al 1987) has outlined the stability characteristics of proguanil but no information has appeared in the literature concerning the stability of the dichloro analogue, chlorproguanil (See Figure 1).

The decomposition of chlorproguanil was monitored by HPLC assay of the chlorproguanil after storing aqueous solutions of the drug hydrochloride under different conditions of pH and temperature and also after high intensity UV irradiation. The major hydrolysis product was determined as 3,4-dichloroaniline.

The hydrolysis reaction was determined to be first order by assay of 3,4-dichloroaniline and application of the intial rate method.

First order rate constants were determined as a function of pH at a temperature of 83°C and the resultant log k - pH profile showed increased rate constants in both acid and basic solution. Minimum values of the rate constant were obtained in the region of pH 7.

The temperature variation of reaction rate was studied at pH 10 over a temperature range from 37 - 83°C. The results showed good agreement with the Arrhenius equation and yielded an activation energy of 46.9 $kJmol^{-1}$.

These results are shown in Table 1.

TEMP/°C	pH	$k/h^{-1} \times 10^{3}$	SD $\times 10^{4}$
83	2.0	3.17	8.6
83	3.0	2.65	2.2
83	5.9	1.73	1.8
83	7.0	0.64	0.8
83	9.0	3.40	0.5
37	10.0	0.46	0.9
55	10.0	0.90	1.4
65	10.0	1.90	2.0
83	10.0	4.49	3.2

Table 1. Showing first order rate constants for chlorproguanil hydrolysis at various temperatures and pH values.

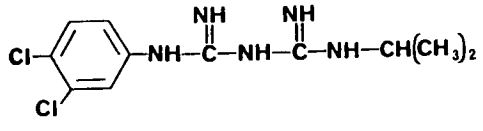

Figure 1. Showing the structure of Chlorproguanil.

Decomposition under ultraviolet radiation (254nm) in a photochemical reactor resulted in the production of several components one of which was 3,4-dichloroaniline. The chromatogram of the decomposition reaction, showing two additional as yet unidentified products, appears to parallel that observed for proguanil.

The rate constant under the conditions used was 0.35 h^{-1} which is considerably higher than the hydrolysis decomposition rate constants measured.

Extrapolation of the data obtained on temperature and pH dependence produces a rate constant of 2.1×10^{-4} h^{-1} at pH 7 and 25°C. The corresponding t_{90} value of about 1 year indicates that chlorproguanil like its monochloro analogue is a relatively stable compound requiring severe conditions of hydrolysis to cause appreciable rates of decomposition. It appears from these results that samples in plasma should be adequately stable for transfer if not exposed to appreciable ultraviolet radiation.

Taylor, R. B. et al (1987) Chromatographia. 24. 560-564