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Effect of sunlight, ultraviolet irradiation and heat on proguanil

J.A. Owoyale and Z.S. Elmarakby

Department of Chemistry, University of Ilorin, Ilorin (Nigeria) and Department of Pharmaceutical Chemistry, Ahmadu Bello University, Zaria (Nigeria)

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A number of antimalarials are known to undergo photochemical reactions when exposed to ultraviolet light. These include chloroquine (Sams and Carroll, 1966; Owoyale and Elmarakby, 1982), hydroxychloroquine and quinacrine (Sams and Carroll, 1966). From the studies on chloroquine mentioned above, it was shown that heat had little or no effect on the "spectral shift" phenomenon of chloroquine at operating temperatures (< 37 °C). Accordingly in continuing our studies on the stability of antimalarials, we decided to examine initially the effect of sunlight and ultraviolet (UV) irradiation on proguanil.

Proguanil hydrochloride powder and proguanil hydrochloride tablets (100 mg) were obtained from the Pharmaceutical and Quality Control Unit of the Ahmadu Bello University, Zaria, Nigeria. Ultraviolet spectra were run on Pye Unicam SP8-100 spectrophotometer. Thin-layer chromatography (TLC) was performed on 20 × 10 cm glass plates coated with silica gel G containing fluorescence indicator (0.25 mm thick). The chromatograms were developed in strong ammonia–methanol (1.5 : 100), examined under a UV lamp (366 nm) and were later sprayed with Dragendorf reagent. The source of UV light was a Camag UV lamp Type 2900 Ger No. 850459 with fixed wavelengths at 254 nm and 366 nm.

Phosphate buffer (0.1 M) solutions (pH 5.8, 6.4, 7.4 and 8.0) were separately added to various aqueous solutions of proguanil hydrochloride (1 mg/ml) to obtain a final dilution of 10 μg/ml. Four ml of each solution in the different buffers was put in a quartz cell and exposed to June sunlight in Samaru (about 32 °C) for 8 h. Another set of 4 ml solutions was irradiated at 366 nm for 8 h while a third set of solutions was similarly irradiated at 254 nm with the UV lamp. The UV spectrum of each solution was run at 1, 3 and 8 h.

The UV spectra of proguanil hydrochloride were identical in the phosphate buffers at pH 5.8, 6.4, 7.4 and 8.0 and they resemble the spectrum for the control shown in Fig. 1 for pH 6.4. Accordingly pH 6.4 was used as a typical example for all the pHs throughout this discussion.

On irradiation with the UV lamp at 254 nm, proguanil hydrochloride showed only a slight increase in absorbance at 232 nm and 252 nm after 8 h. This is true for all the buffer solutions and such increases as typified by the absorption of proguanil hydrochloride in pH 6.4 buffer is shown in Fig. 1. Irradiation with the UV lamp at 366 nm gave identical spectra for all the buffer solutions. There was an initial slight increase in absorbance at 1 h of exposure to the UV lamp at 366 nm. Further increase after 1 h was negligible. Fig. 2

Correspondence: J.A. Owoyale, Department of Chemistry, University of Sokoto, Sokoto, Nigera.

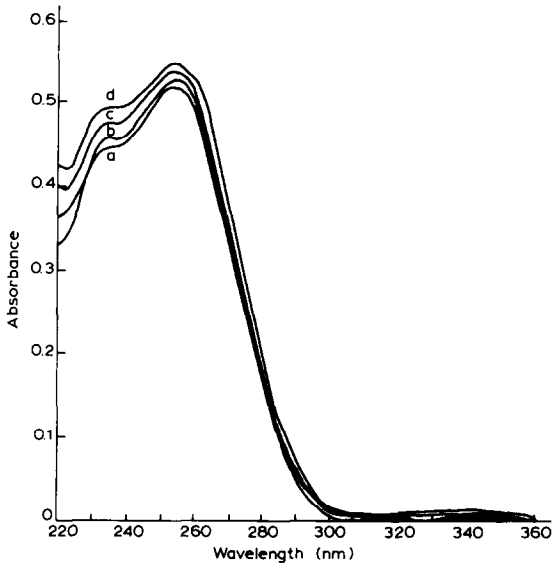

Fig. 1. Effect of irradiation of proguanil hydrochloride in phosphate buffer (pH 6.4) with a 254 nm UV lamp. Key: a = control; b = after 1 h; c = after 3 h; d = after 8 h.

shows the UV spectrum for pH 6.4 which, again, was similar for all the pHs. On exposure to sunlight, proguanil hydrochloride showed an increase in absorbance after 8 h and this is shown in Fig. 3 for the various pHs.

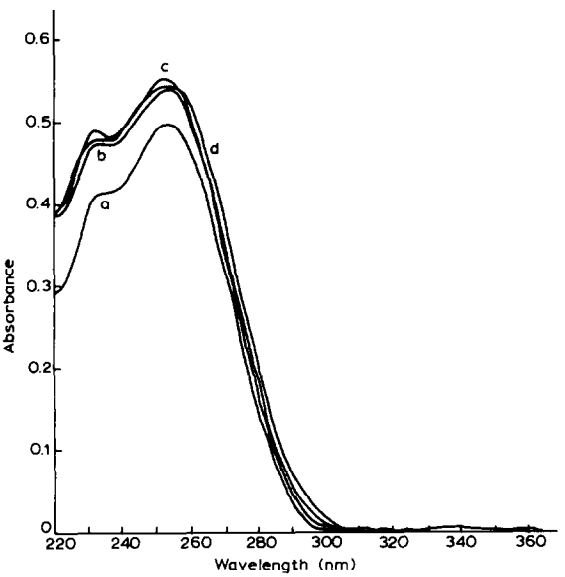

Fig. 2. Effect of irradiation of proguanil hydrochloride in phosphate buffer (pH 6.4) with a 366 nm UV lamp. Key: a = control; b = after 1h; c = after 3 h; d = after 8 h.

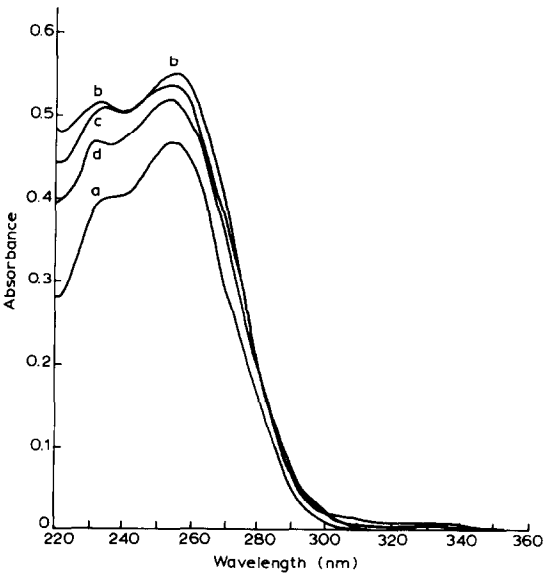

Fig. 3. Proguanil hydrochloride in phosphate buffer exposed to sunlight for 8 h. Key: a = control; b = pH 5.8; c = pH 6.4; d = pH 7.4.

When certain compounds that undergo photochemical reactions are exposed to UV light, they usually showed an increase in absorbance in their UV spectra followed by destruction of the characteristic peaks (Sams and Carroll, 1966; Owoyale and Elmarakby, 1982; Storck, 1965). However, in the case of proguanil, unlike chloroquine, there was only a slight increase in absorbance without any destruction of the characteristic peaks at 232 nm and 252 nm. It thus appears that proguanil does not readily undergo photochemical reactions.

Temperatures in the quartz cells used for irradiation often go up as high as 37 °C but they do not appear to have any noticeable effect on the spectra. Since the concentration of proguanil hydrochloride in irradiated samples was too low for the isolation of the proguanil base, it was decided to study the effect of heat on the proguanil hydrochloride tablets. A temperature of 45 °C was chosen to represent the hottest weather in Nigeria (e.g. Sokoto in the far north with a Saharan temperature of 43 °C).

A number of tablets of proguanil hydrochloride was kept in the oven at 45 °C for up to 6 weeks with two tablets being withdrawn weekly for TLC and UV spectral analyses. The data thus obtained

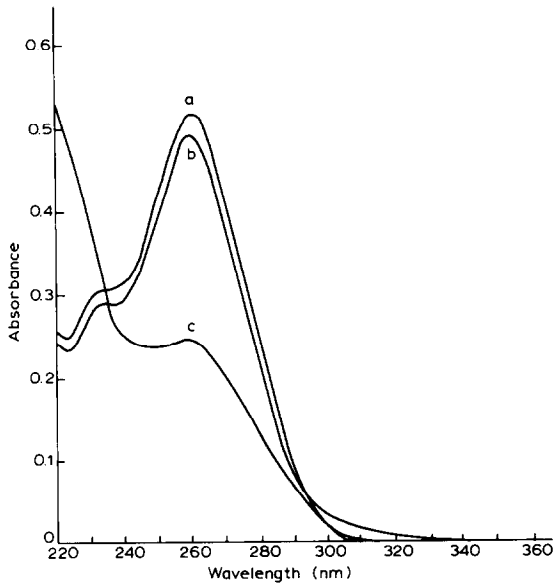

Fig. 4. Effect of heat on proguanil hydrochloride (UV spectra of extracted proguanil in ethanol). Key: a = control; b = heated sample; c = new compound isolated.

were compared with those of unheated tablets (control). The UV spectral study was done by separately dissolving in water 2 heated and 2 unheated tablets (1 mg/ml) and filtering the resulting suspension. 0.1 M phosphate buffer (pH 7.4) was added to each filtrate to obtain a final dilution of 10 μg/ml. Similarly, aqueous solutions of heated and unheated tablets were basified with ammonia and extracted into chloroform. The UV spectra in the latter case were run in ethanol. The UV spectra of the heated tablets and the control in phosphate buffer (pH 7.4) were found to be identical with the control in Fig. 1 and this remained the case even after 5 months in the oven at 45 °C. The spectra of the extracted proguanil base in ethanol for both heated tablets and the control were found to be identical to that shown for the control in Fig. 4. This suggested that proguanil hydrochloride was stable to heat at 45 °C.

However, when the TLC of the heated tablets were run, a very small but new fluorescent spot ($R_f = 0.32$) which turned pink with Dragendorf reagent was observed as early as two weeks. This was not observed for the control. The proguanil base in the heated tablets and the control were extracted as described above and preparative TLC was run to isolate the fluorescent spot and the unchanged proguanil. Ultraviolet spectra were run for the fluorescent spot (less than 5%), the unchanged proguanil and the control in ethanol. Proguanil had two absorption peaks at 258 nm and 235 nm whereas the fluorescent compound (a breakdown product) had an absorption at 258 nm (Fig. 4). The presence of this fluorescent compound could obviously not have been detected from the UV spectrum of the unchromatographed heated sample since both absorb at 258 nm.

Though proguanil does not appear to enter into photochemical reactions, it is nevertheless unstable to heat at 45 °C as shown by the small amount of breakdown product formed. Interestingly, the TLC of proguanil hydrochloride tablets stored at an average room temperature of 25 °C and an average relative humidity of 43% at the Pharmaceutical and Quality Control Unit, Zaria (where they were manufactured) for 1 to 6 years was found not to show any breakdown product. A full kinetic study on the effect of heat on the stability of proguanil may thus prove interesting.

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