Photochemistry of Chlorpromazine [2-Chloro-*N*-(3-dimethylaminopropyl)phenothiazine] in Propan-2-ol Solution

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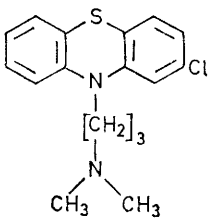
In oxygen-free propan-2-ol solution electronically excited chlorpromazine [2-chloro-*N*-(3-dimethylaminopropyl)phenothiazine] undergoes a carbon–chlorine bond fission to form free radicals which react with the solvent to produce promazine, isopropoxypromazine, hydrogen chloride, and acetone. In oxygen-saturated solution energy transfer occurs from excited chlorpromazine to molecular oxygen to produce excited singlet oxygen. Under these conditions chlorpromazine does not undergo any permanent photochemical change.

INTEREST in the photochemistry of the major tranquilliser chlorpromazine [2-chloro-*N*-(3-dimethylaminopropyl)phenothiazine] (I) was stimulated originally by the observation of photosensitivity in the form of skin rashes and occular changes in patients being treated with large doses of the drug.[1] Previous investigations of chlorpromazine photochemistry have been carried out mainly in aqueous solution [1–5] and in mixtures of water



(I)

and other solvents.[6] Absorption of light by air-saturated aqueous solutions of chlorpromazine results in the formation of brown and later violet colourations.[3] A fall in pH due to the formation of hydrochloric acid accompanies the change in colour.[1] Twelve products have been separated chromatographically but few have been identified.[3,4] In some studies very long periods of irradiation have been used [1,3] with the result that some of the products are very probably secondary in nature.

Differences in photochemistry have been found between air-saturated and air-free solutions. For example, chlorpromazine *N*-oxide [4] and chlorpromazine sulphoxide [2,4] have been identified in air-saturated aqueous solution. In nitrogen-saturated aqueous solution promazine and 2-hydroxypromazine have been isolated and the formation of a dimer, and polymeric materials has been reported.[1] Recent work [5] has shown that the formation of chlorpromazine sulphoxide in aqueous solution occurs *via* the cation radical, and that the oxygen atom of the sulphoxide originates from dissolved oxygen and not from water.

Grant and Greene [6] used mixtures of water and other solvents, including alcohols. They observed the formation of promazine, hydroxypromazine, and, with aqueous alcoholic solutions, the corresponding alkoxy-derivatives. These workers suggested a mechanism of reductive dechlorination leading to promazine coupled in some way with nucleophilic substitution possibly by excimer formation.

Except for the recent work of Iwaoka and Kondo on aqueous solutions of chlorpromazine containing oxygen,[5] little work has been done to establish unequivocally the reaction mechanisms involved. In this paper we report an investigation of the photochemistry of chlorpromazine in propan-2-ol solution. In this solvent the photochemistry is much simpler than that in aqueous solution, and we are able to present a complete mechanism for the reaction.

EXPERIMENTAL

Fluorescence and phosphorescence spectra, at room temperature and 77 K respectively, were measured with a Baird Atomic Fluorispec spectrofluorimeter.

Illumination for continuous photolysis experiments was provided by a 220 W medium pressure mercury lamp (Hanovia UVS 220). A Pyrex filter was employed to cut off light of wavelengths shorter than 300 nm.

Solutions of chlorpromazine hydrochloride (20 ml; 3×10^{-3}M) were irradiated in a Pyrex cell of diameter 33 mm and height 70 mm. The cell was fitted with an inlet tube through which the solution could be saturated with nitrogen or oxygen as desired. The gas stream, which also served to stir the solution during irradiation, was presaturated with propan-2-ol vapour before entering the cell. The temperature of the solutions was maintained at 25 ± 0.1° by carrying out the irradiation in a thermostatted water-bath. After photolysis the irradiated solution was diluted with water (20 ml) and chloride ion was titrated potentiometrically with silver nitrate solution (3×10^{-3}M) in a beaker (100 ml) containing a silver electrode. An ammonium nitrate bridge connected the solution in the beaker to a saturated calomel reference electrode. The mV range of a Pye Dynacap pH meter was used to record the change in the potential of the silver electrode. Hydrogen ion concentration was estimated in a similar way by potentiometric titration with sodium hydroxide solution (3×10^{-3}M) using a glass electrode in place of the silver electrode.

The mean quantum yield of chloride ion formation for wavelengths of light between 300 and 400 nm was determined by potassium ferrioxalate actinometry [7] as follows. A

[1] C. L. Huang and F. L. Sands, *J. Pharm. Sci.*, 1967, **56**, 259.
[2] A. Felmeister and C. A. Discher, *J. Pharm. Sci.*, 1964, **53**, 756.
[3] A. Chodera, T. Dopierala, A. Mrozikiewicz, and E. Pawelczyk, *Bulletin de la Société des Amis des Sciences des Lettres des Poznan, Series C*, 1964, **13**, 69.
[4] C. L. Huang and F. L. Sands, *J. Chromatog.*, 1964, **13**, 246.
[5] T. Iwaoka and M. Kondo, *Bull. Chem. Soc. Japan*, 1974, **47**, 980.
[6] F. W. Grant and J. Greene, *Toxicology and Applied Pharmacology*, 1972, **23**, 71.
[7] C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc.*, 1956, *A*, **235**, 518.

two-compartment Pyrex cell 35 mm in diameter and 60 mm long was employed. In the first experiment propan-2-ol was placed in compartment (A) nearer to the lamp with the potassium ferrioxalate solution in compartment (B). The initial rate of ferrous ion formation was measured in the usual way.[7] In the second experiment, a deoxygenated solution of chlorpromazine was placed in compartment (A), and a fresh solution of potassium ferrioxalate in (B). The initial rate of chloride ion formation was determined by potentiometric titration and the initial rate of ferrous ion formation was determined as before.

The quantum yield of chloride ion formation was then calculated from expression (1) where α is the initial rate of

$$\phi Cl^- \ (300—400 \text{ nm}) = \alpha\phi Fe^{II}/(\beta_1 - \beta_2) \qquad (1)$$

chloride ion formation, β_1 and β_2 are the initial rates of iron(II) ion formation in the first and second experiments respectively, and ϕFe^{II} is the mean quantum yield of iron(II) ion formation for the ferrioxalate actinometer in the wavelength range 300—400 nm. Fortunately, ϕFe^{II} is almost constant in this range [7] and a value of 1.2 was used in the expression.

Detection of free radicals during irradiation was accomplished by measuring viscosity changes in solutions containing methyl methacrylate. For this purpose a viscometer was constructed which enabled measurements to be made in the absence of oxygen. Solutions were irradiated for 20 min and then the viscosity was determined at intervals of 10 min.

In certain experiments the absorption spectrum of the solution was measured after suitable periods of irradiation, using a Pye–Unicam SP 1800 spectrophotometer coupled to an AR 25 recorder. Solutions were irradiated in a circular quartz cell, 20 mm in diameter and of 10 mm path length, which fitted the spectrophotometer cell-housing. Prior to irradiation the solution was bubbled with oxygen or nitrogen as appropriate, and the cell stoppered.

The oxygen absorption apparatus was based on the design of Bolland and Cooper.[8] A description of the irradiation cell has been given elsewhere.[9]

The microsecond flash photolysis equipment has been described.[10] Solutions were flashed in a 200 mm long quartz cell having optically flat windows. Photoflash energies of 480 J were used. Spectra were recorded on Ilford HP3 plates and measurement of the spectra was carried out with a Joyce Lobel microdensitometer. The ns laser flash photolysis equipment has been described.[11]

Irradiated solutions were chromatographed on t.l.c. plates coated with alumina previously activated for 1 h at 110°. The solvent was methanol (28 ml)–benzene (12 ml)–ammonium hydroxide (0.2 ml). The separated components showed up clearly as coloured spots on spraying the chromatogram with 1 : 1 ethanol–50% aqueous sulphuric acid.[1]

For n.m.r. and mass spectrometric analysis, an air-free solution of chlorpromazine was irradiated until complete conversion to products had taken place. The product mixture was isolated by rotary evaporation (Buchi Rotavap R).

Acetone was measured with a Pye chromatograph (series 104) fitted with a Pye type 2 analyser. A column of 20% Carbowax 20 M on 8—100 mesh Gas Chrom CLA was employed. The column was maintained at 55° for 24 h before use. Calibration of the instrument for acetone was achieved by injecting samples of propan-2-ol containing known concentrations of acetone.

Pure samples of chlorpromazine and promazine (as hydrochlorides) were kindly donated by May and Baker Ltd. and John Wyeth and Brother Ltd., respectively. 2,5-Dimethylfuran (Fluka) was used without further purification. 1,4-Diazabicyclo[2.2.2]octane was a gift from Imperial Chemical Industries. Water was distilled. Propan-2-ol was purified by refluxing with 2,4-dinitrophenylhydrazine to remove carbonyl impurities followed by fractional distillation. The purity of the propan-2-ol was checked by u.v. spectrophotometry.

RESULTS

The fluorescence spectrum of chlorpromazine hydrochloride (ClP) in oxygen-free propan-2-ol solution at 25° consisted of a broad featureless band, $\lambda_{max.}$ 456 nm. The fluorescence intensity was reduced by *ca.* 30% when the solution was saturated with oxygen at 1 atm.

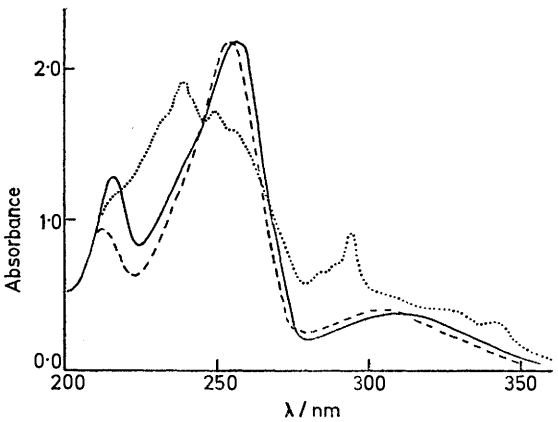


FIGURE 1 Spectral changes observed on irradiation of 7×10^{-5}M-ClP in oxygen-free propan-2-ol: before photolysis (——); after photolysis through a Pyrex filter (– – – –); after photolysis without Pyrex filter (· · · ·)

In propan-2-ol glass at 77 K ClP phosphoresces with $\lambda_{max.}$ 500 nm, corresponding to a first excited triplet state energy of 239 kJ mol^{-1}.

Irradiation of a 7×10^{-5}M solution of ClP in oxygen-free propan-2-ol through a Pyrex filter produced the absorption spectrum shown as a dashed line in Figure 1. Precise isosbestic points were not obtained suggesting the formation of more than one product, although the final absorption spectrum resembles that of promazine. Further irradiation beyond 15 min produced only an extremely slow change. However, on repeating the experiment without the Pyrex filter, the initial spectral change was followed by a further slower change to produce a completely different absorption spectrum, shown as a dotted line in Figure 1. This new absorption spectrum was also obtained when promazine was irradiated under the same conditions.

Irradiation of an oxygen-saturated solution of ClP through the Pyrex filter produced no measurable spectral changes even after 2 h.

[8] J. L. Bolland and H. R. Cooper, *Proc. Roy. Soc.*, 1954, *A*, **225**, 405.

[9] G. O. Phillips, A. K. Davies, and J. F. McKellar, *Lab. Practice*, 1971, **19**, 1037.

[10] J. H. Allen and J. F. McKellar, *Lab. Practice*, 1967, **16**, 991.

[11] G. A. Gee, G. O. Phillips, and J. T. Richards, *J. Soc. Dyers and Colourists*, 1973, **89**, 285.

T.l.c. of solutions, following photolysis through the Pyrex filter for 30 min, gave the results shown in the Table.

T.l.c. of irradiated solutions of ClP compared with authentic samples of ClP and promazine

Solution	Colour of spots	R_F Value
Irradiated nitrogen-saturated ClP solution	(1) Pale orange	0.43
	(2) Purple	0.49
Irradiated oxygen-saturated ClP solution	Rose	0.5
Authentic ClP	Rose	0.5
Authentic promazine	Pale orange	0.43

One of the products (pale orange spot) was shown to be promazine by comparison of its R_F value with that of an authentic sample (Table). Mass spectrometry of the product mixture showed *m/e* 342, consistent with isopropoxypromazine. A second peak, *m/e* 299, corresponding to the loss of an isopropyl group, confirms this assignment. Further confirmation that the product is isopropoxypromazine was obtained from n.m.r. spectroscopy, τ 8.8 (d, J 6 Hz). This is indicative of an isopropyl group in which the signal of the methyl group protons is split into a doublet by the adjacent proton.

That isopropoxypromazine is a primary product of ClP photolysis, and is not a secondary product derived from promazine, was shown by irradiating promazine in oxygen-free propan-2-ol. This did not produce any isopropoxypromazine. Neither promazine nor isopropoxypromazine were produced on irradiating oxygen-saturated ClP solutions.

Figure 2 shows the increase in chloride and hydrogen ion concentration which accompanied the formation of promazine and isopropoxypromazine in oxygen-free solution. One mole of hydrogen chloride was formed per mole of ClP photolysed. The mean quantum yield of chloride ion formation for wavelengths of light between 300 and 400 nm was 0.12. No hydrogen chloride was formed when an oxygen-saturated ClP solution was irradiated.

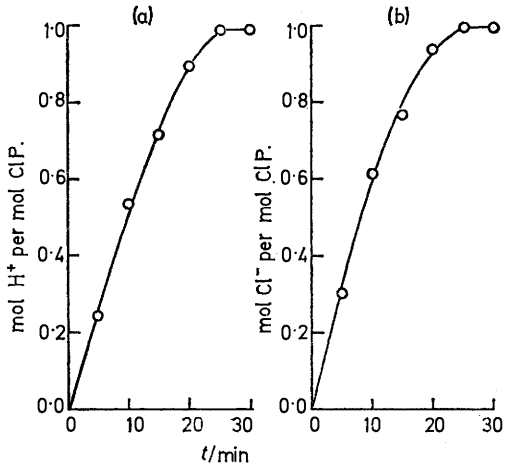


FIGURE 2 (a) Increase in hydrogen ion concentration and (b) increase in chloride ion concentration during the photolysis of a 3×10^{-3}M solution of ClP in oxygen-free propan-2-ol

Evidence for the formation of free radicals on photolysis of ClP was obtained by irradiating an air-free solution of the compound in methyl methacrylate. This experiment was carried out in a viscometer so that the flow-time could be measured at suitable time intervals. A Corning 5850 filter was used to prevent direct absorption of light by methyl methacrylate. Indeed when air-free methyl methacrylate

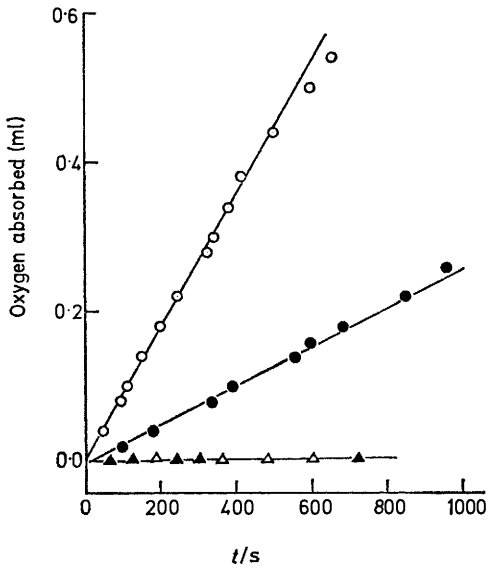


FIGURE 3 Oxygen absorbed during the irradiation in propan-2-ol of 1.25×10^{-3}M-ClP alone (▲); 1.25×10^{-3}M-ClP + 1×10^{-3}M-2,5-dimethylfuran (○); 1.25×10^{-3}M-ClP + 1×10^{-3}M-2,5-dimethylfuran + 1.5×10^{-1}M-DABCO (●); and 1.25×10^{-3}M-ClP + 1.5×10^{-1}M-DABCO (△)

was exposed to filtered light for 20 min in the absence of ClP no change in flow time occurred during or after the irradiation period. However, when an air-free 3×10^{-3}M solution of ClP in methyl methacrylate was irradiated in the same way, the flow time increased from 19 to 42 s during photolysis. In the subsequent dark period the flow time continued to increase and after 40 min it was 105 s.

The lack of any permanent photochemical change in oxygen-saturated ClP solutions indicates very efficient quenching of the excited state by oxygen. Confirmation that this is the case was obtained from oxygen absorption measurements. No oxygen was absorbed when ClP was irradiated in propan-2-ol. However, when 2,5-dimethylfuran, an efficient acceptor of excited singlet oxygen,[12] was added a pronounced uptake of oxygen ensued on irradiation (Figure 3).

We conclude, therefore, that in oxygen-saturated solution, ClP, probably in its first excited triplet state, is quenched by molecular oxygen to form excited singlet oxygen. This was confirmed by adding 1,4-diazabicyclo[2.2.2]octane (DABCO) which markedly reduced the rate of oxygen absorption. DABCO is a recognised quencher of excited singlet oxygen.[13]

The results of conventional and laser flash photolysis experiments are shown in Figures 4 and 5. In oxygen-free propan-2-ol solution, ClP produced two transients, one of which had $\lambda_{max.}$ 460 nm and decayed by first-order kinetics ($t_{\frac{1}{2}}$ 3.2 μs). The other, longer lived transient, had $\lambda_{max.}$ 510 nm. The transients were strongly quenched by oxygen. Flash photolysis of promazine gave only one transient ($\lambda_{max.}$

[12] K. Gollnick, T. Franken, G. Schade, and G. Dörhöfer, *Ann. New York Acad. Sci.*, 1970, **171**, 89.

[13] R. H. Young and R. L. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 5183.

465 nm) which decayed by first-order kinetics ($t_{\frac{1}{2}}$ 22.8 μs). The transient was strongly quenched by oxygen.

DISCUSSION

It follows from the fact that the fluorescence intensity of ClP in propan-2-ol is only partially reduced by saturation of the solution with oxygen, while, at the same time,

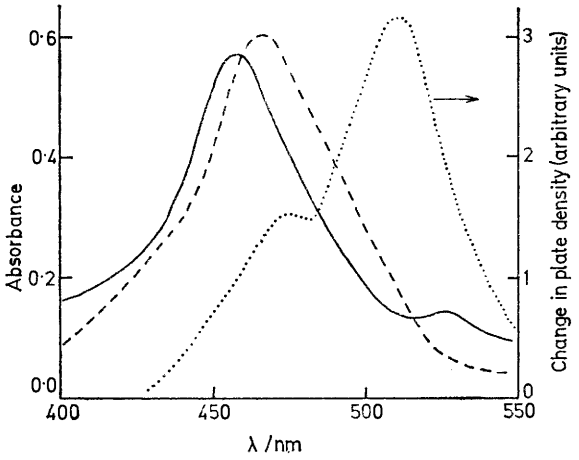


FIGURE 4 Transients observed on flash photolysis of ClP (—— and ····), and promazine (– – – –) in oxygen-free propan-2-ol

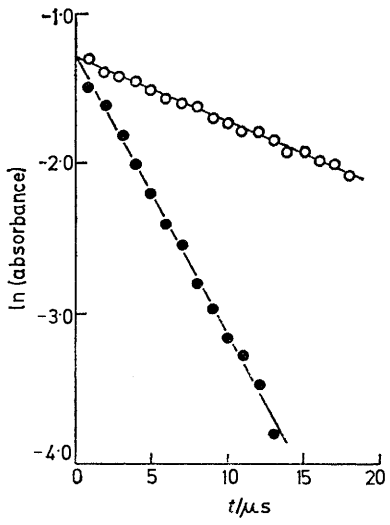


FIGURE 5 First-order decay plots for the ClP transient having $\lambda_{max.}$ 460 nm (●), and the promazine transient with $\lambda_{max.}$ 465 nm (○), observed in oxygen-free propan-2-ol, by ns laser flash photolysis

the photoreaction is completely quenched, that the reactive state cannot be the first excited singlet. We conclude, therefore, that the photoreaction of ClP almost certainly occurs *via* the first excited triplet state. The

$$ClP \xrightarrow{h\nu} {}^1ClP^* \qquad (2)$$

initial process of light absorption (2) must thus be followed by intersystem crossing (3) to the triplet state.

$$^1ClP^* \longrightarrow {}^3ClP^* \qquad (3)$$

The phosphorescence observed in rigid glass shows that the triplet state is indeed populated in propan-2-ol solution. In oxygen-saturated solution, process (4)

$$^3ClP^* + {}^3O_2 \longrightarrow ClP + {}^1O_2^* \qquad (4)$$

occurs. Reaction (4) must be very efficient and is responsible for the complete absence of any measurable photochemical change in oxygen-saturated solution. Excited singlet oxygen is evidently incapable of oxidising ClP, a result which confirms the conclusions of Iwaoka and Kondo.[5]

The ClP-photosensitised polymerisation of methyl methacrylate suggests that free radicals are formed during photolysis. We therefore postulate the intramolecular reaction (5). Reaction (5) is consistent with

$$^3ClP^* \longrightarrow P^\cdot + Cl^\cdot \qquad (5)$$

the flash photolysis results. On the basis of its first-order decay and sensitivity to oxygen, we attribute the transient absorption having $\lambda_{max.}$ 460 nm to the triplet state of ClP. Further evidence for the formation of the triplet state of chlorpromazine in propan-2-ol solution was provided by energy transfer experiments using β-carotene. Consistent with its very low singlet–triplet crossover efficiency,[14] β-carotene (2×10^{-5}M) showed no triplet absorption when flashed alone in air-free propan-2-ol. However, in the presence of chlorpromazine (2×10^{-4}M), the growth ($t_{\frac{1}{2}}$ 750 ns) and decay ($t_{\frac{1}{2}}$ *ca.* 10 μs) of the β-carotene triplet were clearly observed at 520 nm. Similar results were obtained with promazine. Due to the intense absorption of β-carotene in the same wavelength region (460 nm) as the transient which we attribute to the ClP triplet, it was not possible to monitor the decay of this species in solutions containing β-carotene. However the sensitisation of the β-carotene triplet, observed in these experiments, proves conclusively that the triplet states of both chlorpromazine and promazine are formed in propan-2-ol solution under our experimental conditions.

We assign the chlorpromazine transient with $\lambda_{max.}$ 510 nm to the radical P$^\cdot$ formed in reaction (5). This assignment is supported by the fact that promazine, which cannot undergo reaction (5), produces only a shorter wavelength transient which we attribute to the triplet state (Figure 4). Reaction (5) also explains the shorter half-life of the ClP triplet state compared with that of promazine (Figure 5).

The formation of one mole of hydrogen chloride per mole of ClP photolysed, is consistent with reaction (6).

$$Cl^\cdot + (CH_3)_2CHOH \longrightarrow HCl + (CH_3)_2\dot{C}OH \qquad (6)$$

The formation of promazine (PH) and acetone may then be explained by reaction (7) while reaction (8) explains

$$P^\cdot + (CH_3)_2\dot{C}OH \longrightarrow PH + (CH_3)_2CO \qquad (7)$$

$$P^\cdot + (CH_3)_2\dot{C}OH \longrightarrow POCH(CH_3)_2 \qquad (8)$$

the formation of isopropoxypromazine. Reactions (7) and (8) are more probable than other possible radical–

[14] R. Bensasson, C. Chachaty, E. J. Land, and C. Salet, *Photochem. and Photobiol.*, 1972, **16**, 27.

radical reactions because radicals P$^{\bullet}$ and $(CH_3)_2\dot{C}OH$ would be formed, in close proximity, in the same solvent cage.

The absorption spectrum shown by the dotted line in Figure 1 was also recently reported by Iwaoka and Kondo [5] who were unable to explain it. It is clear from our results that the formation of this product only occurs to a measurable extent with light of wavelengths shorter than 300 nm. Furthermore the product is formed subsequent to reactions (5)—(7) in a photochemical reaction of promazine. A study of this interesting reaction will be the subject of another publication.

The full implications of this work to the understanding of drug photosensitivity will be discussed elsewhere. However, it is useful here to recall that ClP is known to have both phototoxic and photoallergic properties. The ClP-sensitised formation of excited singlet oxygen, which we have demonstrated, may be one factor which contributes to the phototoxicity of this drug. Furthermore reactions (9) and (10) which are analogous to reactions

$$Cl^{\bullet} + \text{Protein—H} \longrightarrow HCl + \text{Protein}^{\bullet} \quad (9)$$

$$\text{Protein}^{\bullet} + P^{\bullet} \longrightarrow \text{Protein—P} \quad (10)$$

(6) and (8) would give rise to an antigen molecule (Protein-P), thus stimulating an antigen–antibody reaction culminating in photoallergy.

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