International Journal of Pharmaceutics, 5 (1980) 273–286

IN VITRO STUDIES ON PHOTOSENSITIZATION BY PHENOTHIAZINES, SULPHONAMIDES AND TETRACYCLINES

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(Received January 29th, 1980)
(Modified version received March 21st, 1980)
(Accepted March 31st, 1980)

SUMMARY

Measurements have been made of the decreases that occur in the interfacial tensions of hydrocarbon oils when floating on water containing between 10^{-6} and 10^{-3} M of various phenothiazine, sulphonamide and tetracycline drugs and irradiated with UV light for up to 240 min. Photochemical reactions occur which follow fractional-order kinetics.

The reaction products that form in the oil and aqueous layers were identified by chemical analysis and reaction mechanisms are proposed. The results are discussed in relation to adverse photosensitization that these drugs may produce in vivo.

INTRODUCTION

A study of physicochemical reactions at oil/water interfaces can often provide insights into the mechanisms of more complex reactions which may be occurring in nature.

Moore et al. (1969) employed a butanol/water interface as a model for the transport of sugars into human erythrocytes. Rosano et al. (1961) measured the diffusion of salts through other oil/water interfaces representing model membranes. Other workers have used the oil/water interface to solve structural problems (Pilpel, 1956), to investigate the photolysis by sunlight of hydrocarbon mineral oils floating on the sea (Klein and Pilpel, 1974a and b), and to study photosensitization produced in patients when exposed to sunlight after having been treated with certain classes of drugs (Sanniez and Pilpel, 1980). High doses of phenothiazines can produce ocular opacity, tremors and deposition of melanin in the skin (Ayd, 1961; Zelickson and Zeller, 1964; Mathalone, 1965; Satanove, 1965; Ljunggren, 1977). Clinical symptoms associated with the use of sulphonamides and tetracyclines include oedema, dermatitis, rashes and general irritation of the skin (Sams, 1960; Wiebe and Moore, 1977).

Various mechanisms have been adduced to explain the photosensitizing action of these drugs. Sulphonamides in the body may be converted into activated species which combine with protein to form allergens. Phenothiazines and tetracyclines appear to yield both allergens and products which are toxic (Allison, 1966; Jarvick, 1970; Wiebe and Moore, 1977); but because of the difficulty of identifying and measuring the amounts of the photochemical reaction products from these drugs in vivo, the processes involved in photosensitization are still not well understood.

The present investigation re-examines some preliminary results that were obtained using sulphonamides and tetracyclines (Sanniez and Pilpel, 1980) and provides new data on phenothiazines. The drugs were dissolved in water at concentrations between 10^{-6} and 10^{-3} M (these are the approximate levels deduced to be present in the epidermal tissue of patients being treated with between 100 and 1000 mg of drug per day). A layer of a hydrocarbon oil – methyl-, isopropyl- or dodecyl-benzene – was floated on the aqueous surface and the systems were irradiated with UV light of two different wavelengths. By measuring the changes produced in the interfacial tensions and in the chemical compositions of the oil and the aqueous layers over periods of up to 240 min it was possible to establish the overall kinetics of photolysis of the drugs and to gain a better understanding of the mechanisms of photosensitization which may be responsible for adverse side-effects in patients.

MATERIALS AND METHODS

Methyl-benzene and isopropyl-benzene (A.R.) were further purified by passing them 3 times under pressure through a tightly packed bed of Fullers earth 2.5 cm thick, which was renewed after each passage. Commercial dodecyl-benzene (Dobane JN, Shell Chemicals) was purified by heating 3 times with 5% w/v of Fullers earth at 100°C for 30 min under nitrogen and then filtered.

The best available grades of chlorpromazine hydrochloride (cpz, m.p. 196°C, May and Baker), thiopropazate dihydrochloride (tpp, Searles), triflupromazine hydrochloride (tpz, m.p. 174°C, Squibb) and of tetracycline hydrochloride tc, chlortetracycline hydrochloride ctc, demethylchlortetracycline hydrochloride dmctc (Lederle), oxytetracycline dihydrate otc, (I.C.I.) and β-deoxytetracycline (Pfizer) were checked for purity by UV spectroscopy and were used without further purification. Reference standards of chlorpromazine sulphoxide, thiopropazate sulphoxide, triflupromazine sulphoxide, 2 hydroxyproma-

TABLE 1

PHYSICAL PROPERTIES OF HYDROCARBONS (AFTER PURIFICATION)

	d_4^{20}	n_D^{20}	Surface tension at 20°C mN m^{-1}	Interfacial tension at 20°C mN m^{-1}
Methyl-benzene	0.8625	1.4968	29.9	34.9
Isopropyl-benzene	0.8623	1.4917	30.1	38.8
Dodecyl-benzene	0.8781	1.4860	32.2	46.2

zine, and of the epi- and anhydro- derivatives of the tetracyclines were also obtained from the manufacturers and from the World Health Organization. Sulphanilamide (sa, m.p. 165°C), sulphathiazole (st, m.p. 202°C from B.D.H.) and sulphapyridine (sp, m.p. 191°C, Lederle) were recrystallized 3 times from boiling water. Triple-distilled water (surface tension 72 mN m^{-1} at 21°C, specific conductivity 1.4×10^{-6} Ω^{-1} cm^{-1} at 21°, pH 5.7) was used throughout.

Apparatus and procedure

Dilute aqueous solutions of the drugs were prepared in the concentration range 10^{-6}–10^{-3} M and 20 cm^3 was placed in a 5 cm diameter glass vessel. Twelve cm^3 of hydrocarbon oil was floated on the surface of the aqueous solution to form a layer 0.6 cm deep. The vessel was suspended in a water bath at 22 ± 1°C in a light-proof cabinet which was fitted with a Vent-Axia exhaust fan to assist in the temperature control. Each sample was irradiated with UV light produced by a 125 W Philips MB/u arc. This was positioned 20 cm above the sample under a reflector and was fitted with silica and perspex filters by means of which the wavelength of the light reaching the sample could be selected at 250–325 nm (designated 'short-wave') or 290–325 nm (designated 'long-wave'). With this arrangement oxygen was freely available at the oil/water interface. The light intensity, as measured by actinometry (Hatchard and Parker, 1956) was about 2×10^{-9} einstein sec^{-1} cm^{-2} ('short-wave') or about 1×10^{-9} einstein sec^{-1} cm^{-2} ('long-wave'). These levels are of the same order of magnitude as that of the UV component of sunlight on a clear day in temperate latitudes (Freegarde et al., 1971). The intensity of the light was uniform over the surface of the sample.

A du Noüy tensiometer with a platinum ring was used to measure the equilibrium interfacial tension at 20°C (attained after standing for 10 min in the dark) before and after irradiation for specified periods of time. The accuracy of the technique was confirmed by the interfacial tensions of the pure oils.

At the end of the 240 min irradiation period the reaction products formed in the oil and aqueous layers were separately analyzed using GLC and TLC in conjunction with UV, IR, NMR and mass spectrometry. Peroxides formed in the oil layer were determined by iodometric titration (Lea, 1946).

RESULTS

Interfacial tensions

With the exception of sulphapyridine, all the drugs employed were substantially more soluble in water than in the hydrocarbon oils and they partitioned preferentially in the aqueous phase. Typical graphs showing their effects at different concentrations, c, on the interfacial tensions of the 3 oils are plotted in Fig. 1. The slope of each curve $d\gamma/d \log c$ remained practically constant at a value of about −1.2 mN m^{-1} for drug concentrations between 10^{-6} and 10^{-5} M and at about −2.0 mN m^{-1} for drug concentrations between 10^{-5} and 10^{-4} M. The shapes of the curves were as expected if the drugs were being adsorbed according to the Gibbs' equation:

$$\Gamma = -\frac{1}{2.303RT} \cdot \frac{d\gamma}{d \log c} \qquad (1)$$

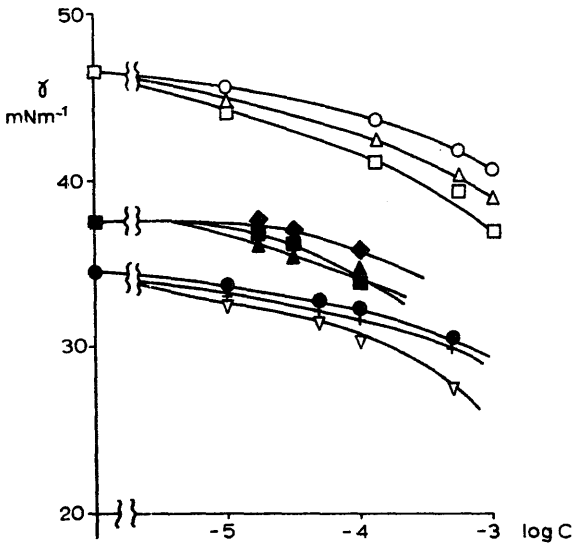

Fig. 1. Interfacial tension vs log drug concentration. ○, tc; □, ctc; △, dmctc; in dodecyl-benzene. ▲, sa; ◆, sp; ■, st; in isopropyl-benzene. ●, cpz; ▽, tpp; +, tpz; in methyl-benzene.

and typical values of the surface excess, Γ, are listed in Table 2.

The surface excesses at different concentrations were converted to areas, A, per drug molecule at the interface using the expression:

$$A = \frac{1.667}{\Gamma} \text{ nm}^2 \text{ molecule}^{-1} \quad (2)$$

the corresponding surface pressure, Π mN m^{-1}, being obtained from the difference between the interfacial tension of the pure oil and that of the sample.

Typical force–area (Π–A) curves are shown in Fig. 2. On this basis all the drugs were being similarly adsorbed at the oil/water interface to form highly expanded gaseous films (Pilpel, 1956).

Graphs showing the effects of irradiation on the interfacial tensions of tpp in methyl-benzene are plotted in Fig. 3A and B. Similar graphs were obtained with the other systems (Sanniez and Pilpel, 1980). In the 240 min period of irradiation, the interfacial tensions of the oils decreased slightly when floating on pure water but more markedly when floating on aqueous solutions of the drugs. The higher the drug concentration the greater the decrease. At any particular concentration the effects of the different drugs on the interfacial tensions of the different oils were compared by means of their photosensitive index (P.I.) defined (cf. with Felmeister and Schaubman, 1969) by:

$$\text{P.I.} = \frac{\gamma_1 - \gamma_{240}}{\gamma_0 - \gamma_{240}} \times 100 \quad (3)$$

where γ is the interfacial tension and the subscripts, 0, 1 and 240, refer, respectively, to

TABLE 2

SURFACE EXCESSES *

Oil	Drug	Conc. range (M)	Γ (μ mol m^{-2})	Conc. range (M)	Γ (μ mol)
Methyl-benzene	cpz		0.18		0.23
	tpp	10^{-6}–10^{-5}	0.25	10^{-5}–10^{-4}	0.40
	tpz		0.20		0.28
Isopropyl-benzene	sa		0.10		0.38
	st	10^{-6}–10^{-5}	0.18	10^{-5}–10^{-4}	0.42
	sp		0.18		0.46
Dodecyl-benzene	tc		0.20		0.28
	ctc	10^{-6}–10^{-5}	0.30	10^{-5}–10^{-4}	0.48
	dmctc		0.25		0.40

Similar values of Γ were obtained for the other oil/drug systems at these concentrations.

* At a concentration of 10^{-4} M the error in Γ resulting from the use of Eqn. 1 is <0.1%. At concentrations $>10^{-2}$ it is advisable to apply a correction to allow for partitioning of the drug in the oil phase (Pilpel, 1956).

the initial value for the pure hydrocarbon, the initial value for the hydrocarbon plus drug and the final value for the hydrocarbon plus drug after 240 min irradiation.

Values for systems containing 10^{-4} M of drug are listed in Table 3. The P.I. values increased with drug concentration, those for the tetracyclines (except otc) were higher than those for the sulphonamides which were higher than those for the phenothiazines.

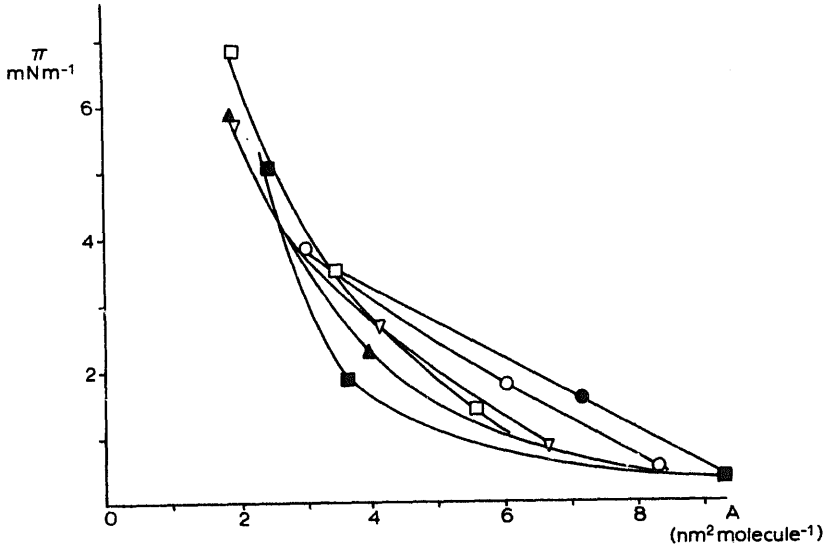

Fig. 2. Force–area curves. ●, cpz; ▽, tpp; in methyl-benzene. ▲, sa; ■, st; in isopropyl-benzene. ○, tc; □, ctc; in dodecyl-benzene.

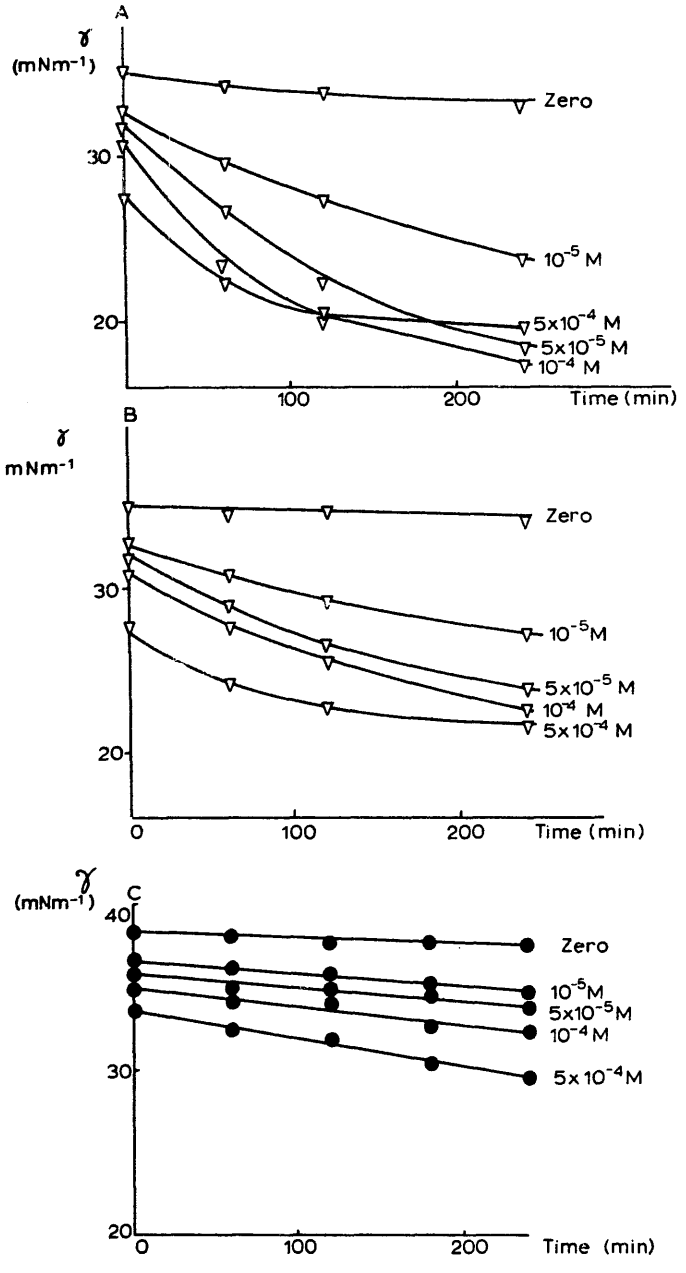

Fig. 3. Effect of UV irradiation on interfacial tension. A: ▽, tpp in methyl-benzene (short wave). B: ▽, tpp in methyl-benzene (long wave). C: ●, cpz in isopropyl-benzene (long wave).

Photosensitive indices in isopropyl-benzene tended to be higher than those in methyl-benzene or dodecyl-benzene (presumably because of the well-known susceptibility of tertiary C–H bonds to oxidation) (Gollnick and Schenck, 1964); the photosensitive indices at long wavelength UV were lower than those at short wavelengths because of the lower intensity of the light being employed due to the use of the extra filter.

TABLE 3

PHOTOSENSITIVE INDICES AT 10^{-4} M

Oil	Methyl-benzene		Isopropyl-benzene		Dodecyl-benzene
UV wavelength Drug	Short	Long	Short	Long	Long
cpz	82.4	60.0	74.6	50.0	–
tpp	77.1	69.0	77.7	66.9	–
tpz	61.6	39.8	67.1	46.6	–
sa	–	–	–	66.9	63.3
st	–	–	–	62.7	58.4
sp	–	–	–	68.6	56.6
tc	–	–	–	87.6	64.0
ctc	–	–	–	87.0	60.9
dmctc	–	–	–	91.7	75.9
otc	–	–	–	65.4	45.5

Reaction products

Oil phase. After irradiation the oil phases from all the systems were found to contain peroxides/hydroperoxides which were measured by iodometric titration (Lea, 1946). Typical results for systems containing 5×10^{-4} M of drug are listed in Fig. 4 (cf. Sanniez and Pilpel, 1980). With methyl-benzene at both long and short wavelengths the presence of cpz and tpp in the aqueous phase caused an increase, and of tpz a decrease, in peroxide formation, but with isopropyl-benzene the 3 phenothiazines caused a decrease, this being most noticeable with tpz. With isopropyl- and dodecyl-benzenes the presence of tc, ctc and dmctc in the aqueous phase accelerated the formation of peroxide and this coincided with a gradual migration of yellow colour from the aqueous phase to the oil phase. otc and the sulphonamide drugs, which produced a purple-blue colour in isopropyl- and dodecyl-benzene, hardly affected their peroxide contents.

The other reaction products formed by the phenothiazines and the tetracyclines in the oil phases were separated by tlc using benzene–ethanol–ammonia (80 : 20 : 1) and ethyl acetate respectively. Their R_f values and UV absorption spectra were compared with those of prepared standards and the results for the phenothiazines are given in Table 4.

The tetracyclines yielded anhydrotetracycline, anhydrochlortetracycline and anhydro-demethyl-chlortetracycline with R_f values of 0.88, 0.82 and 0.87, respectively, but the systems containing otc and the 3 sulphonamide drugs did not yield any other products in the oil phases besides peroxides/hydroperoxides.

Aqueous phase. Examination of the aqueous phases from the various systems showed that after irradiation for 240 min the pH values of 10^{-4} M solutions of cpz, tpp and tpz decreased from 5.8, 4.1 and 5.2 to 4.5, 3.9 and 4.1, respectively (under short-wave irradiation the decrease was greater to 4.2, 3.7 and 3.5, respectively); the pH values of the sa, sp and st systems decreased from 5.4, 5.8 and 5.8 to 3.8, 4.1 and 4.4, respectively, but those of the tc, ctc, dmctc and otc systems remained constant at 4.4, 4.6, 4.6 and 6.1, respectively. In the same period, UV spectroscopy showed that between 25% and 12% of the respective phenothiazines, between 40% and 20% of the respective sulphonamides and

TABLE 4

REACTION PRODUCTS AND R_f VALUES FROM OIL PHASE

Spot System	1	2	3	4	5
Isopropyl benzene	Acetophenone (0.75)	–	–	–	–
Isopropyl benzene + cpz	Acetophenone (0.75)	cpz (0.50)	cpz sulphoxide (0.31)	2 hydroxy cpz (0.20)	–
Isopropyl benzene + tpp	Acetophenone (0.75)	tpp (0.60)	tpp sulphoxide (0.29)	2 hydroxy tpp (0.38)	–
Isopropyl benzene + tpz	Acetophenone (0.75)	tpz (0.52)	tpz sulphoxide (0.25)	–	–
Methyl benzene	Benzylalcohol (0.87)	–	–	–	Benzaldehyde (0.77)
Methyl benzene + cpz	Benzylalcohol (0.87)	cpz (0.50)	cpz sulphoxide (0.31)	2 hydroxy cpz (0.20)	Benzaldehyde (0.77)
Methyl benzene + tpp	Benzylalcohol (0.87)	tpp (0.60)	tpp sulphoxide (0.29)	2 hydroxy tpp (0.38)	Benzaldehyde (0.77)
Methyl benzene + tpz	Benzylalcohol (0.87)	tpz (0.52)	tpz sulphoxide (0.25)	–	Benzaldehyde (0.77)

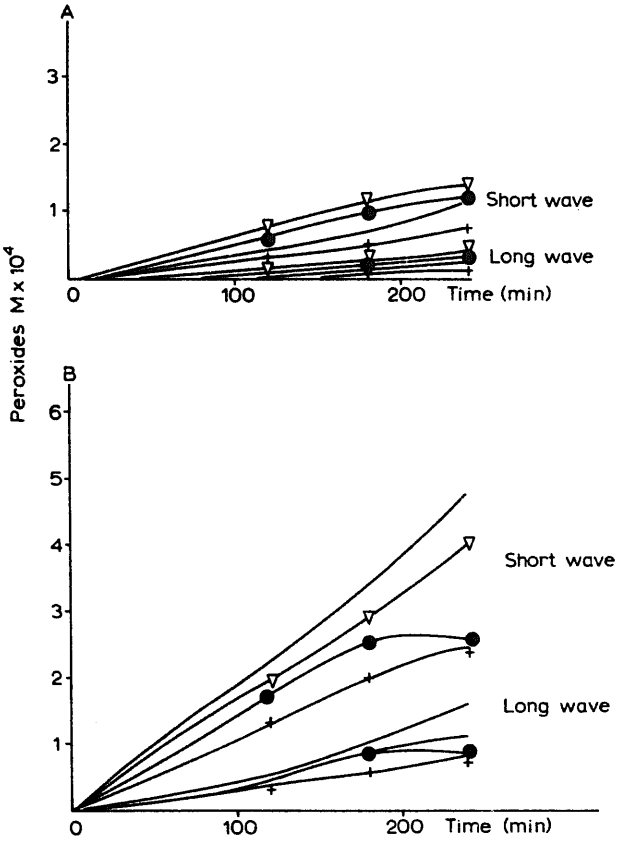

Fig. 4. Peroxide formation druing irradiation. A: 5×10^{-4} M •, cpz; ▽, tpp; +, tpz in methyl-benzene; (———), methyl-benzene alone. B: 5×10^{-4} M •, cpz; ▽, tpp; +, tpz in isopropyl-benzene; (———), isopropyl benzene alone.

TABLE 5

REACTION PRODUCTS FROM AQUEOUS PHASE

System	Products	Quantum efficiency moles product/ einstein
cpz	cpz sulphoxide; 2 hydroxy-cpz	–
tpp	tpp sulphoxide; 2 hydroxy-tpp	–
tpz	tpz sulphoxide; 2 hydroxy-tpz	–
sa	2,4 hydroxylamino benzene sulphonamide	3.7
sp	2,4 hydroxylamino benzene sulphonamido pyridine	2.9
st	2,4 hydroxylamino benzene sulphonamido thiazole	1.2
tc	tc epimer	2.0
ctc	ctc epimer	1.6
dmctc	dmctc epimer	2.9
otc	β-deoxytetracycline	–

about 30% of each tetracycline were decomposed, the percentage being smaller the higher the initial concentration in solution. The drugs were therefore acting as photosensitizers and not as photocatalysts (Calvert and Pitts, 1966). Further analysis of the various aqueous substrates after 240 min irradiation using tlc, UV and mass spectrometry revealed the products shown in Table 5.

DISCUSSION

The changes produced by irradiation in the pH values and in the chemical compositions of the oil and aqueous phases of the various systems can be explained as follows.

Methyl-, isopropyl- and dodecyl-benzene are slowly oxidized by UV light when floating on water forming hydroperoxides, free radicals, aldehydes, alcohols, ketones (which were detected by analysis) by schemes such as (Chien, 1965; Emanuel, 1965)

$$2\,PhCH_3 \xrightarrow[2\,O_2]{h\nu} PhCH_2OOH + Ph\dot{C}H_2 + H\dot{O}_2$$
(hydroperoxide)
$$\downarrow$$
$$PhCH_2\dot{O}H + \dot{O} \rightarrow PhCHO + H_2O$$
(Benzyl alcohol) (Benzaldehyde) (4)

and

$$2\,PhCH(CH_3)_2 \xrightarrow[2\,O_2]{h\nu} PhC(CH_3)_2OOH + Ph\dot{C}(CH_3)_2 + H\dot{O}_2$$
(hydroperoxide)
$$\downarrow$$
$$PhC\dot{O}CH_3 + C\dot{H}_3 + H\dot{O}$$
(acetophenone) (5)

where Ph = phenyl and similarly for dodecyl-benzene.

Phenothiazines, sulphonamides and tetracyclines introduced at the oil/water interface undergo decomposition and act as photosensitizers by causing the oils to produce more free radicals which accelerate their oxidation. Thus the phenothiazines, cpz, tpz and tpp, are converted to the corresponding sulphoxides (Felmeister and Discher, 1964) and hydroxy-derivatives (Grant, 1974). The liberated H^+ and HCl (or HF) contribute to the observed decreases in pH of the systems, which were also noted by Felmeister and Discher (1964). In addition $Cl^{\cdot}$ and possibly $F^{\cdot}$ free radicals are also probably formed from cpz and tpp and from tpz respectively (Grant, 1974) and these would then be expected to photosensitize the hydrocarbons by abstracting hydrogen and converting them into the free radicals shown in schemes 4 and 5 (Gollnick and Schenck, 1964).

The fact that cpz and tpp reduced the amount of peroxide/hydroperoxide produced in the irradiated isopropyl-benzene systems, but not in the methyl-benzene systems could be due to the well-known ability of phenolic compounds (of which the hydroxyphenothiazines are examples) to act as free radical scavengers (Maizus et al., 1960), the different results produced by the different phenothiazines in the different hydrocarbon oils being due to differences in the scavenging abilities of these hydroxy-products and differences also in the stabilities of the respective hydroperoxides to further decomposition.

The main decomposition products from the sulphonamides were the 2,4-hydroxylaminobenzene sulphonamido-derivatives which were probably formed as shown in scheme 6 (Turro et al., 1968)

$$RNHSO_2C_6H_4NH_2 \xrightarrow{h\nu} RNHSO_2C_6H_4NH_2^* \xrightarrow{H_2O} RNHSO_2C_6H_4NH^- + H_3O^+$$

$$\downarrow h\nu \mid O_2$$

$$RNHSO_2C_6H_4NHOH + H_2O_2 \qquad (6)$$

(* denotes an excited state).

These products were soluble in the aqueous phase and the reaction would again account satisfactorily for the decreases observed in the pH values during irradiation. The sulphonamides did not form oil-soluble products which might have been expected to accelerate peroxide formation in the supernatant oils.

In contrast, at least 3 of the tetracyclines investigated produced quite large amounts of peroxide in the oil phases. This was presumably due to the oil-soluble anhydrotetracyclines which were detected by analysis. It is postulated (Wiebe and Moore, 1977) that under UV the anhydro-compounds are first excited and then react with triplet molecular oxygen to form excited singlet molecular oxygen, which reacts with methyl-, isopropyl- or dodecyl-benzene to form free radicals and hydroperoxides as shown in schemes 4 and 5.

Of the various reaction products detected in the present investigation, the hydroperoxides, aldehydes, alcohols and hydroxy-derivatives are all surface active and their formation is responsible for the decreases observed in the interfacial tensions of the systems during irradiation. An overall measure of the effect is provided by the photosensitive indices in Table 3.

It was found than when the logarithms of the absolute values of the slopes (taken over the first 60 min of irradiation) of the graphs illustrated in Fig. 3A–C were plotted against the logarithms of the molar concentrations of the various drugs, straight lines were obtained in every case. Typical plots are shown in Fig. 5 and they obey the equation

$$\log \left| \frac{d\gamma}{dt} \right| = \log K + n \log c$$

or alternatively

$$\frac{d\gamma}{dt} = Kc^n \qquad (7)$$

where K is a constant and n is the slope.

At the low drug concentrations employed

$d\gamma = 2.303\Gamma RT \, d\log c$ (Gibbs' equation)

and therefore

$$\frac{d \log c}{dt} = \frac{Kc^n}{2.303\Gamma RT} \qquad (8)$$

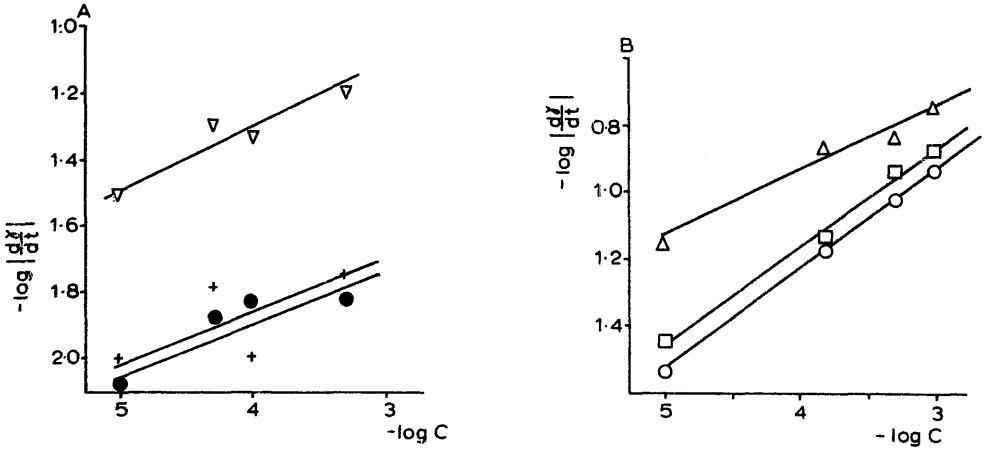

Fig. 5. Plot of $-\log|d\gamma/dt|$ vs log drug concentration. A: •, cpz; △, tpp; +, tpz; (long wave) in methyl-benzene. B: ○, tc; □, ctc; △, dmctc; (long wave) in dodecyl-benzene.

Values of n for the different systems at the two different wavelengths are given in Table 6.

It is seen that n is less at short wavelengths than at long ones, (though again it should be noted that the light intensities were different) and that n tends to increase as the oil phase is changed from methyl- to dodecyl- to isopropyl-benzene.

Eqn. 12 is formally similar to the general kinetic equation for chemical reactions and the term, n, can therefore be interpreted as the overall kinetic order with respect to c of the photochemical reactions producing surface active products at the oil/water interface. The kinetic orders are seen to vary slightly from one hydrocarbon oil and from one class of drug to another but are in all cases fractional between zero and one. Thus the photochemical reactions are probably occurring mainly at the two dimensional interface between water and oil rather than in the 3 dimensional bulk phases.

TABLE 6

VALUES OF n

Oil	Methyl-benzene		Isopropyl-benzene		Dodecyl-benzene
UV wavelength Drug	Short	Long	Short	Long	Long
cpz	0.00	0.15	0.00	0.21	–
tpp	0.11	0.21	0.15	0.18	–
tpz	0.00	0.15	0.10	0.35	–
sa	–	–	–	0.33	0.12
st	–	–	–	0.53	0.48
sp	–	–	–	0.23	0.23
tc	–	–	–	0.59	0.27
ctc	–	–	–	0.30	0.28
dmctc	–	–	–	0.30	0.16
otc	–	–	–	0.65	0.37

Relevance to photosensitization in vivo

The results of the present work are consistent with observations that have been made both in vivo and in vitro by several other workers (Epstein et al., 1957; Forrest et al., 1958; Beckett et al., 1963; Blois, 1965; Satanove, 1965; Allison et al., 1966; Grant, 1974; Ljunggren, 1977; Wiebe et al., 1977). The formation of H^+ and HCl by phenothiazines and of H_3O^+ and H_2O_2 by sulphonamides which are responsible for the decreases in the pH of these systems during irradiation, could account for the sensitivity inflammation and dermatitis of the skin associated with large doses of these drugs. Ljunggren (1977) showed that irradiated solutions of phenothiazines injected into the skin caused the same photosensitive reactions reported in patients taking these drugs and subsequently exposed to sunlight.

The 2 hydroxy-derivatives formed by cpz and tpp could have potential toxicity in vivo since they are only formed by the action of UV and do not otherwise appear in the body. However, the sulphoxides are natural metabolites of phenothiazines in the body and are therefore unlikely to be responsible for adverse side-effects associated with sunlight.

All the drugs now investigated produced species which were surface active at the oil/water interface and this activity can be related to potentially adverse side-effects by means of photosensitive indices (Felmeister and Schaubman, 1969). If the oil/water interface is assumed to be a model for the lipid/water interface of the cell wall in vivo (Rosano et al., 1961; Moore and Schlowsky, 1969) then it is to be expected that the present photo-products would also be active at the cell wall. In fact Allison et al. (1966) have shown that several of the present drugs produce changes in the permeability of cell walls towards liquids and ions and there may possibly be some connection between these changes and the accumulation of fluid (oedema) that occurs in certain cases.

The peroxides, hydroperoxides and free radical intermediates that might be formed from lipids in the cell wall by analogous mechanisms to those given in schemes 4–6 might be expected to react with proteins, microsomes, melanin, nucleic acids and other cell constituents to produce both allergic and phototoxic responses in patients (Jarvick, 1970).

REFERENCES

Allison, A.C., Magnus, I.A. and Young, M.R., Role of lysosomes and of cell membranes in photosensitization. Nature (London) 209 (1966) 874–878.

Ayd, F.J., Drug induced extrapyramidal reactions. J. Am. Med. Assoc., 175 (1961) 1054–1060.

Beckett, A.H., Beaven, M.A. and Robinson, A.E., Metabolism of chlorpromazine in humans. Biochem. Pharmacol., 12 (1963) 779–794.

Blois, M.S., Chlorpromazine binding in vivo. J. Invest. Dermatol., 44 (1965) 475–481.

Calvert, J.G. and Pitts, J.N., Photochemistry, 1st Edn. John Wiley, N.Y., 1966, pp. 378–544.

Chien, J.C.W., On the possible initiation of photo-oxidation by charge-ttansfer excitation. J. Phys. Chem., 69 (1965) 4317–4325.

Emanuel, N.M.E., The oxidation of hydrocarbons in the liquid phase, 1st edn. Pergamon, London, 1965.

Epstein, J.H., Brunsting, L.A., Petersen, M.C. and Schwarz, B.E., Photosensitivity occurring with chlorpromazine therapy. J. Invest. Dermatol., 28 (1957) 329–338.

Felmeister, A. and Schaubman, R., Photo induced interaction of phenothiazine drugs with a lecithin monomolecular film. J. Pharm. Sci., 58 (1969) 64–67.

Felmeister, A. and Discher, C.A., Photodegradation of chlorpromazine hydrochloride. J. Pharm. Sci., 53 (1964) 756–762.

Forrest, I.S., Forrest, F.M. and Berger, M., Free radical and metabolites of drugs derived from phenothiazine. Biochim. Biophys. Acta, 29 (1958) 441–442.

Freegarde, M., Hatchard, C.G. and Parker, C.A., Oil spilt at sea. Lab. Practice, 20 (1971) 35–40.

Gollnick, K. and Schenck, G.O., Mechanism and stereoselectivity of photosensitised oxygen transfer reactions. Pure Appl. Chem., 9 (1964) 507–525.

Grant, F.W., Phototoxicity and chlorpromazine photochemistry. Adv. Biochem. Biopharmacol., 9 (1974) 539–546.

Hatchard, C.G. and Parker, C.A., A new sensitive chemical actinometer. Proc. Roy. Soc. A, 235 (1956) 518–536.

Jarvick, M.E., In The Pharmacological Basis of Therapeutics. Goodman and Gilman (Eds.) 4th edn., Macmillan, London, 1970.

Klein, A.E. and Pilpel, N., The effects of artificial sunlight upon floating oils. Water Res., 8 (1974) 79–83.

Klein, A.E. and Pilpel, N., Photo-oxidation of alkyl benzenes initiated by 1-naphthol. J. Chem. Soc. Farad. Trans., 1 70 (1974) 1250–1256.

Lea, C.H., The determination of the peroxide values of edible fats and oils. J. Soc. Chem. Ind., 65 (1946) 286–290.

Ljunggren, B., Phenothiazine toxicity. J. Invest. Dermatol., 69 (1977) 383–386.

Maizus, Z.K., Emanuel, N.M. and Yakovleva, V.N., Mechanism of decomposition of intermediate hydroperoxides during liquid-phase oxidation of *n*-decane. Doklady Abad Nauk SSSR, 131 (1960) 351–353.

Mathalone, M.B.R., Oculocutaneous effects of chlorpromazine. Lancet, 2 (1965) 111–112.

Moore, T.J. and Schlowsky, B., Effect of erythrocyte lipid and glucose and galactose concentration on transport of the sugars across a water–butanol interface. J. Lipid Res., (1969) 216–219.

Pilpel, N., The sizes of molecules adsorbed at the benzene–water interface. J. Colloid Sci., 11 (1956) 51–59.

Rosano, H.L., Duby, P. and Schulman, J.H., Mechanism of selective flux of salts and water migration through non-aqueous liquid membranes. J. Phys. Chem., 65 (1961) 1704–1708.

Sams, W.M., Photosensitizing therapeutic agents. J. Am. Med. Ass., 174 (1960) 2043–2048.

Sanniez, W.H.K. and Pilpel, N., Photodecomposition of sulphonamides and tetracyclines at oil-water interfaces, J. Pharm. Sci., 69 (1980) 5–8.

Satanove, A., Pigmentation due to phenothiazines in high and prolonged dosage. J. Am. Med. Ass., 191 (1965) 263–268.

Turro, N.J., Hammond, G.S., Pitts, J.N. Jr. et al., Annual Survey of Photochemistry Vol. 2, Interscience, N.Y., 1968, p. 25.

Wiebe, J.A. and Moore, D.E., Oxidation photosensitized by tetracyclines. J. Pharm. Sci., 66 (1977) 186–189.

Zelickson, A.S. and Zeller, H.C., A new and unusual reaction to chlorpromazine. J. Am. Med. Ass. 188 (1964) 394–396.

Zuidema, H.H. and Waters, G.W., Ring method for the determination of interfacial tension. Ind. Engng. Chem. Anal. Edn., 13 (1941) 312–313.