Photodecomposition of Sulfonamides and Tetracyclines at Oil–Water Interfaces

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Abstract □ Changes that occur in the interfacial tension of hydrocarbon oils floated on dilute aqueous solutions of some sulfonamides and tetracyclines and irradiated with UV light were measured. Photodecomposition products in the oil and aqueous lyers were identified, and reaction mechanisms are proposed.

Keyphrases □ Sulfonamides—photodecomposition at oil-water interface □ Tetracyclines—photodecomposition at oil-water interface □ Photodecomposition—of sulfonamides and tetracyclines at oil-water interface

Many patients undergoing treatment with sulfonamides (1–3) or tetracyclines (4–6) become photosensitive; when subsequently exposed to strong sunlight, they develop skin rashes, fluid in the tissues (edema), and other symptoms.

Storck (7) suggested that sulfonamides in the body are converted into activated species, which combine with protein to form allergens. Alternative mechanisms were proposed to explain the photosensitizing action of the tetracyclines (5, 8). Because of the difficulty in identifying and measuring the reaction products *in vivo*, the processes involved in photosensitization are not well understood.

In vitro techniques recently were developed for studying the reactions of these drugs at air–water and oil–water interfaces under UV light (9–11). One convenient method involves floating a layer of a suitable oil on an aqueous drug solution, irradiating the system with UV light for various times, and analyzing the changes in the interfacial tension of the oil and in the chemical composition of the oil and aqueous layers.

This method was used to study the photochemical decomposition of three sulfonamides and four tetracyclines.

EXPERIMENTAL

Materials—Isopropylbenzene[1] (Puriss) and commercial dodecylbenzene[2] were purified further by passing them three times under slight pressure through a tightly packed bed of fuller's earth (2.5 cm thick), which was renewed after each passage. Sulfanilamide[3] (mp 165°), sulfathiazole[3] (mp 201°), and sulfapyridine[4] (mp 191°) were recrystallized three times from boiling water.

The best available grades of tetracycline[5], chlortetracycline[5], demeclocycline[5], oxytetracycline[6], and deoxytetracycline[7] were used without further purification. Reference standards of epitetracycline (quatrimycin), epichlortetracycline, epidemeclocycline, anhydrotetracycline, anhydrochlortetracycline, and anhydrodemeclocycline were obtained[8].

Triple-distilled water (surface tension 72.1 mN/m at 21°; specific conductivity $1.2 \times 10^{-6}\ \Omega^{-1}\ cm^{-1}$ at 21°; pH 5.7) was used.

Apparatus and Technique—The irradiation chamber is shown in Fig. 1. The UV-light source was a 125-w MB/U medium-pressure arc[9] equipped with a silica filter transmitting from 290 to 325 nm (9–11).

Twelve milliliters of isopropylbenzene or dodecylbenzene was floated on 20 ml of a dilute aqueous drug solution in a 6-cm diameter glass pot forming a 0.6-cm deep layer. Each system was placed in turn in the chamber and was irradiated for a predetermined time with its temperature maintained at 25 ± 2°.

After irradiation, the interfacial tension, γ, of the sample was measured *in situ* with a tensiometer[10] using a platinum ring. This technique required the floating hydrocarbon layer to be at least 0.5 cm deep. Wetting of the ring was achieved either by pulling it upward or pushing it downward through the interface, whichever gave the higher reading. The ring had a circumference of 3.86 cm and was made from 0.015-cm radius wire. The tensiometer readings, P, were converted to interfacial tension values, γ, by (12):

$$\gamma = P\left[0.725 + \left(\frac{0.0145P}{C^2(D-d)}\right)^{1/2}\right] \qquad \text{(Eq. 1)}$$

where D and d are the densities of water and the hydrocarbon oil at 20°, respectively. This equation incorporates correction terms for buoyancy and the weight of the liquid raised by the ring (13). The accuracy of the

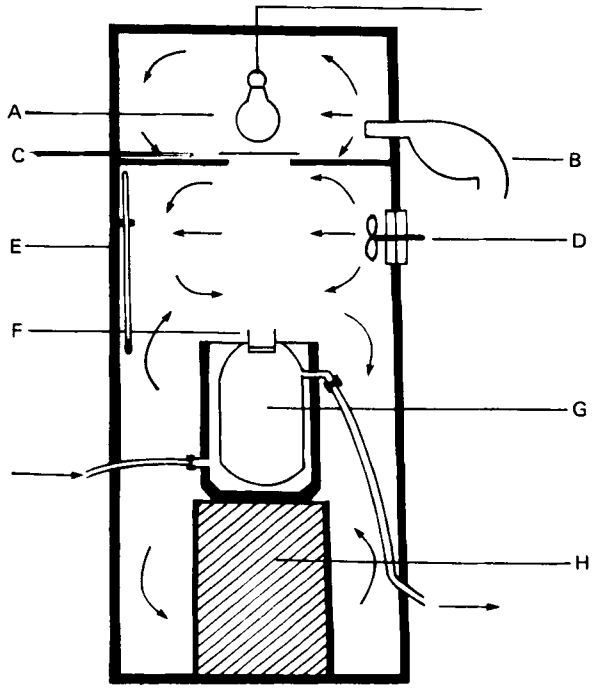

Figure 1—*UV irradiation chamber. Key: A, mercury lamp; B, cool air blower; C, silica filter; D, exhaust fan; E, thermometer; F, duNouy pot; G, glass thermostat (25 ± 2°); and H, support.*

[1] Aldrich Chemicals (surface tension 30.1 mN/m and interfacial tension 37.8 mN/m at 20°; n_D^{20} +1.4917; d_4^{20} +0.864; and UV transmission cutoff λ_{max} 287 nm).

[2] Dobane JN, Shell Chemicals (surface tension 32.2 mN/m and interfacial tension 45.9 mN/m at 20°; n_D^{20} +1.4865; d_4^{20} +0.878; and UV transmission cutoff λ_{max} 398 nm).

[3] British Drug Houses.

[4] May and Baker.

[5] Lederle Laboratories.

[6] Imperial Chemical Industries.

[7] Pfizer.

[8] World Health Organization.

[9] Phillips.

[10] DuNouy, Cambridge Instrument Co.

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Table I—Photosensitive Indexes

Additive	Isopropylbenzene	Dodecylbenzene
Sulfanilamide	0.36	0.37
Sulfathiazole	0.50	0.53
Sulfapyridine	0.58	0.62
Demeclocycline	1.4	1.1
Tetracycline	1.4	1.4
Chlortetracycline	2.0	2.0
Oxytetracycline	2.4	2.4

measurements was estimated at ±1%. Although higher accuracies can be achieved by drop weight or drop volume methods, these methods are unsuited to continuous *in situ* monitoring of samples. Since comparative rather than absolute values were required for this study, the accuracy was considered sufficient. It was confirmed by calibrating the instrument against pure benzene and isopropylbenzene[1] samples. If necessary, results were corrected to 20° by the factor of −0.04 mN/m/deg.

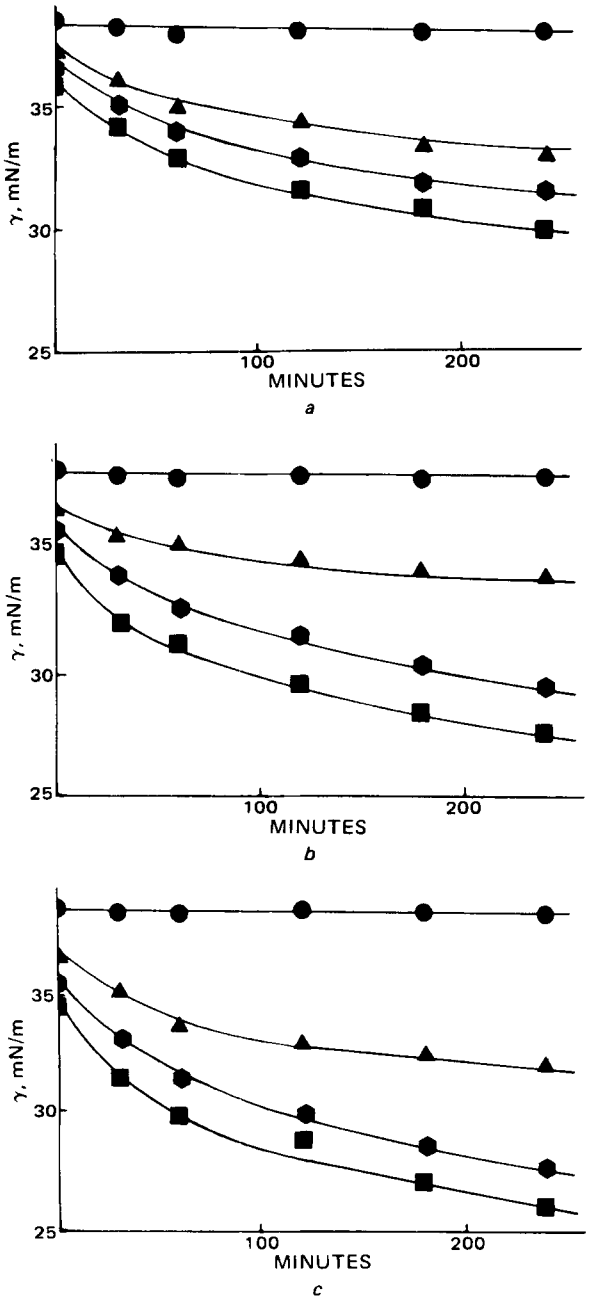
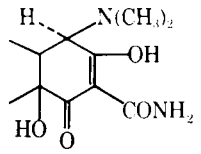
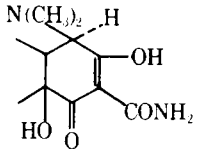


Figure 2—*Plots of interfacial tension* versus *irradiation time for isopropylbenzene systems with sulfapyridine* (a), *sulfathiazole* (b), *and sulfanilamide* (c). *Key (moles/dm³ of additive):* ●, *zero;* ▲, *1.5 × 10⁻⁵;* ●, *2.8 × 10⁻⁵; and* □, *1.0 × 10⁻⁴.*



partial tetracycline structure



partial epimer structure

The reaction products that formed in the oil and aqueous layers after irradiation for 4 hr were analyzed by GLC and TLC combined with UV spectroscopy. Peroxides were determined in the oil phase by iodometric titration (14); the quantum efficiency of each additive was calculated from the amount of product and the light intensity, which was determined by an actinometric method using potassium ferrioxolate reagent (15).

RESULTS

The sulfonamides and tetracyclines were more soluble in water than in hydrocarbon oils and thus partitioned mainly in the aqueous phase. They also were adsorbed at the oil–water interface, causing the interfacial tension decreases with concentration that can be observed from the positions at which the various curves intersect the ordinates in Figs. 2 and 3 before irradiation was started.

Irradiation effects on the interfacial tensions of representative samples are shown in Figs. 2 and 3; all samples exhibited interfacial tension decreases with increasing irradiation time. The decrease, expressed as $-\delta\gamma/\delta t$ after 120 min of irradiation, depended on the nature and concentration of the additive but was nearly independent of the oil phase. For example, for a 1.6×10^{-4} mole/dm³ aqueous solution of sulfapyridine in contact with isopropylbenzene, $\delta\gamma/\delta t$ was −0.022; for the same solution in contact with dodecylbenzene, $\delta\gamma/\delta t$ was −0.023.

When the values of the moduli $|\delta\gamma/\delta t|$ were plotted against the square root of the additive concentration, $\sqrt{c}$ in $(\text{moles/dm}^3)^{1/2}$, straight lines were obtained (Figs. 4 and 5) (16). The slopes of these lines are given in Table I and are designated as the photosensitive indexes, X (*cf.*, Ref. 17).

Chemical analysis of the oil layers from systems containing tetracycline, chlortetracycline, and demeclocycline showed that irradiation caused peroxides–hydroperoxides to form fairly rapidly after induction for ~60 min. The peroxide buildup is shown in Figs. 6*a* and 6*b*, and it coincided with a gradual migration of the yellow color from the aqueous phase into the oil phase. Less peroxide was produced by oxytetracycline and by the sulfonamide additives (the latter produced a blue color), and the graphs for these systems approximately coincided with those for the isopropylbenzene and the dodecylbenzene alone, *i.e.*, with the bottom curves in Figs. 6*a* and 6*b*, respectively.

The other reaction products detected in the oil phases of the three tetracyclines (Fig. 6) were anhydrotetracycline, anhydrochlortetracycline, and anhydrodemeclocycline. They were identified by TLC combined with UV spectroscopy. Their R_f values were 0.88, 0.82, and 0.87, respectively. No other reaction products in the oil phases of the systems containing oxytetracycline or the three sulfonamides could be identified, except for the small peroxide amounts already mentioned.

Examination of the aqueous phases from all samples after irradiation for 240 min showed that the pH decreased from 5.4, 5.8, and 5.8 to 3.8, 4.1, and 4.4 in the systems containing sulfanilamide, sulfathiazole, and sulfapyridine, respectively. In the same period, between ~40 and 20% of each additive was converted into the corresponding 2,4-hydroxylaminebenzenesulfonamido derivative. These products were identified by comparing their UV spectra with those of authentic standards (7). Furthermore, the systems containing oxytetracycline produced β-deoxytetracycline, R_f 0.13, and the systems containing tetracycline, chlortetracycline, and demeclocycline produced the corresponding epimers (18) with R_f 0.21, 0.22, and 0.19, respectively.

The quantum efficiencies (moles of product per Einstein) of the additives were: sulfanilamide, 3.70; sulfathiazole, 2.90; sulfapyridine, 1.20; demeclocycline, 2.80; tetracycline, 2.00; and chlortetracycline, 1.60. The fact that the values were greater than unity indicates that the photochemical reactions proceeded by chain mechanisms (19).

DISCUSSION

The main decomposition products from the sulfonamides, *i.e.*, the 2,4-hydroxylaminobenzenesulfonamido derivatives, were soluble in water

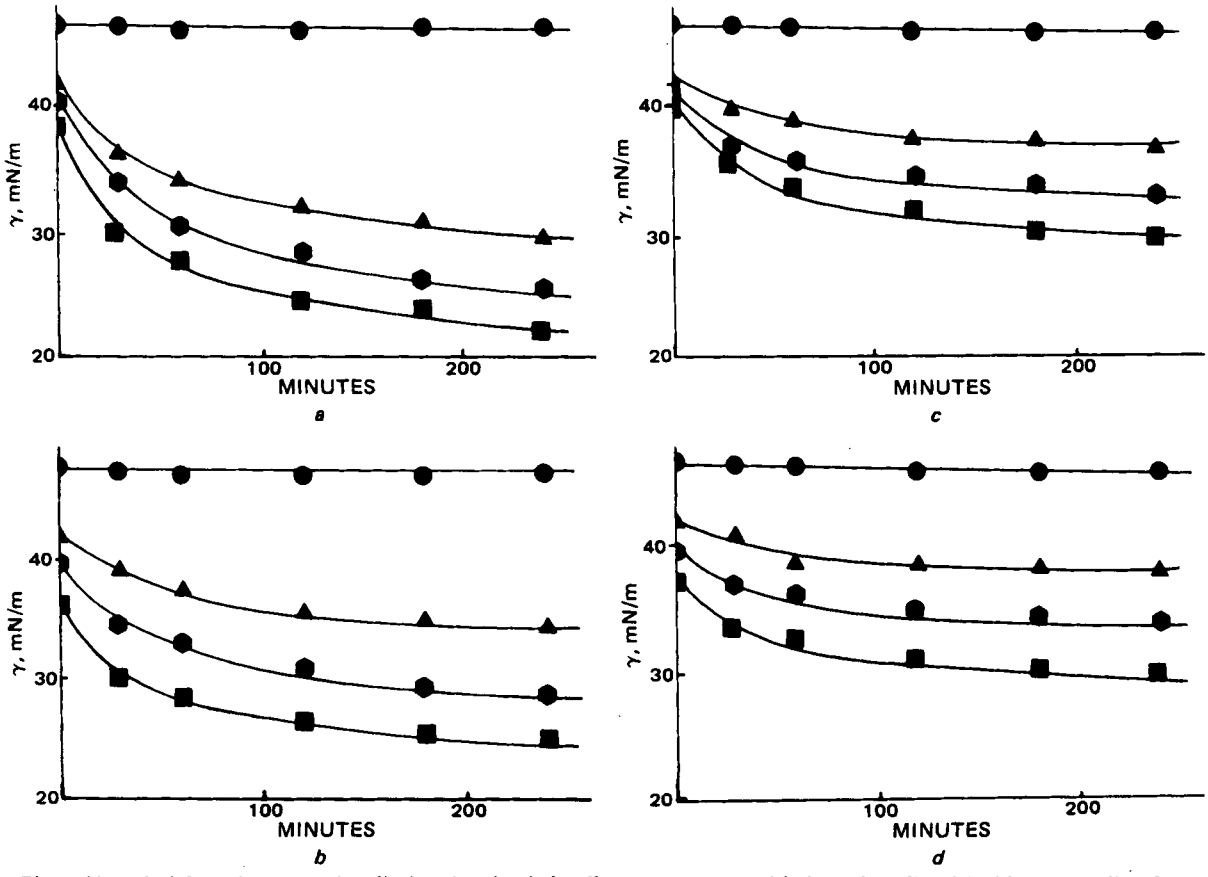


Figure 3—*Plots of interfacial tension* versus *irradiation time for dodecylbenzene systems with demeclocycline (a), chlortetracycline (b), tetracycline (c), and oxytetracycline (d). Key (moles/dm³ of additive): ●, zero; ▲, 1.5 × 10⁻⁴; ●, 5.2 × 10⁻⁴; and □, 1.0 × 10⁻³.*

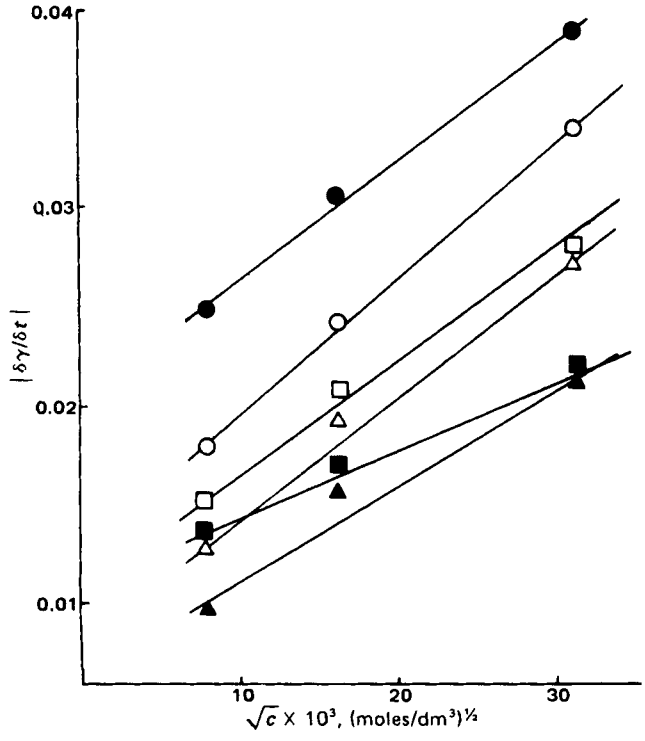


Figure 4—*Plots of* $|\delta\gamma/\delta t|$ versus $\sqrt{c}$. *Key: ●, sulfanilamide-dodecylbenzene; ▲, sulfathiazole-dodecylbenzene; ■, sulfapyridine-dodecylbenzene; ○, sulfanilamide-isopropylbenzene; △, sulfathiazole-isopropylbenzene; and □, sulfapyridine-isopropylbenzene.*

and probably were formed as shown in Scheme I in which the asterisk indicates an excited state (20).

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

$$RNHSO_2C_6H_4NH^- \xrightarrow{O_2,\ h\nu} RNHSO_2C_6H_4NHOH + H_2O_2$$

Scheme I

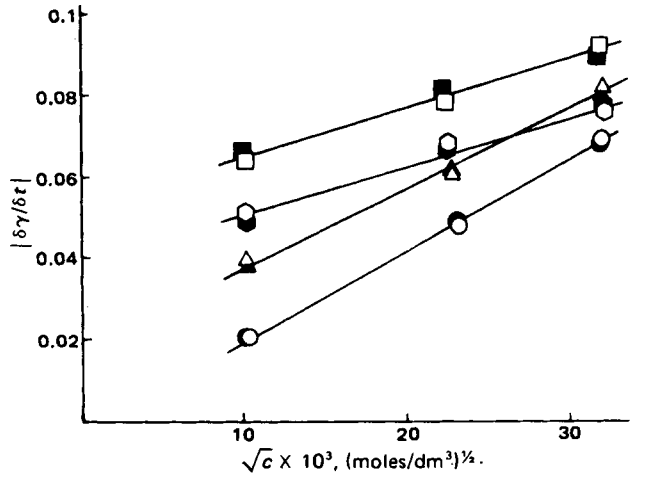


Figure 5—*Plots of* $|\delta\gamma/\delta t|$ versus $\sqrt{c}$. *Key: ●, oxytetracycline-dodecylbenzene; ▲, chlortetracycline-dodecylbenzene; ●, tetracycline-dodecylbenzene; ■, demeclocycline-dodecylbenzene; ○, oxytetracycline-isopropylbenzene; △, chlortetracycline-isopropylbenzene; ○, tetracycline-isopropylbenzene; and □, demeclocycline-isopropylbenzene.*

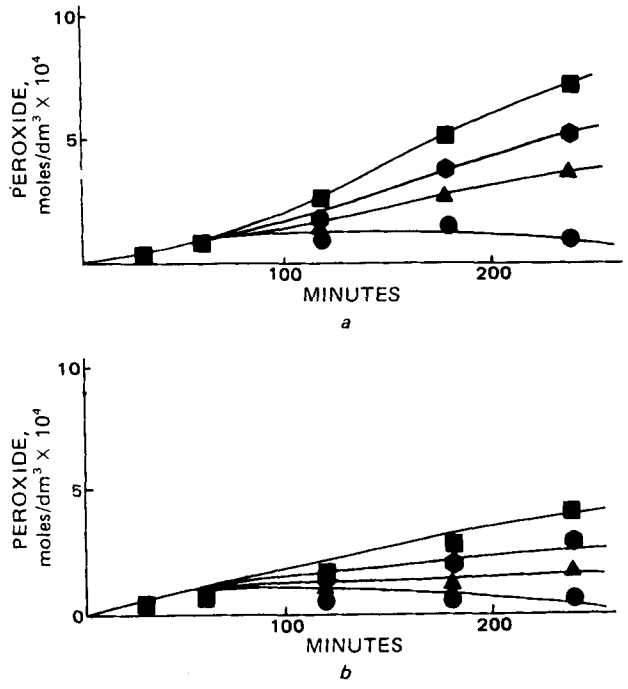


Figure 6—*Peroxide concentration* versus *UV irradiation time for isopropylbenzene systems (5 × 10^{-4} mole/dm³) (a) with isopropylbenzene alone (●), chlortetracycline (▲), tetracycline (●), and demeclocycline (■), and for dodecylbenzene systems (5 × 10^{-4} mole/dm³) (b) with dodecylbenzene alone (●), chlortetracycline (▲), tetracycline (●), and demeclocycline (■).*

This reaction scheme would account satisfactorily for the observed pH decreases in these systems.

The sulfonamides did not produce appreciable amounts of oil-soluble products. If they had, these products might have been expected to catalyze or sensitize the photodecomposition of the supernatant isopropylbenzene or dodecylbenzene (9, 10). In fact, the two oils yielded about the same amount of peroxide whether irradiated on their own or in the presence of the sulfonamides.

In contrast, when the same oils were irradiated in the presence of at least three of the tetracyclines, much larger amounts of peroxide were formed (Fig. 6). This increase presumably was due to the formation of the oil-soluble anhydrotetracycline (AT) derivatives (detected by analysis) as shown in Schemes II and III (8, 21):

$$AT \xrightarrow{h\nu} AT^*$$

Scheme II

$$AT^* + {}^3O_2 \rightarrow AT + {}^1O_2^*$$

Scheme III

The excited singlet molecular oxygen then could react with the hydrocarbon oil, *e.g.*, isopropylbenzene (Scheme IV):

$$C_6H_5CH(CH_3)_2 + {}^1O_2^* \xrightarrow{h\nu} \underset{\text{peroxide}}{C_6H_5C(CH_3)_2OO\cdot}$$

Scheme IV

thus producing the hydroperoxides. (A similar reaction would be expected to occur with dodecylbenzene, and this hypothesis is confirmed by the similarly shaped curves in Figs. 6*a* and 6*b*.)

The present work shows that the breakdown products from both drug classes considerably reduce the tension at an oil–water interface, and a measure of the effect is provided by the drug's photosensitive index, X (Table I) (*cf.*, Ref. 17). As defined, a small X implies a large reduction in interfacial tension during irradiation; on this basis, the sulfonamides (and sulfanilamide in particular) produce substantially larger effects than the tetracyclines.

Some connection eventually may be found between the photochemical decomposition of sulfonamides and tetracyclines at the oil–water interface *in vitro* and at the lipid–water interface of the cell wall (22). Such a connection might assist in elucidating the photosensitization mechanisms that occur *in vivo* and explain, for example, the observation that the ranking order of photosensitivity in Table I for the sulfonamides and oxytetracycline is the same as was obtained from *in vivo* experiments on patients (1, 3).

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