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Coloration and Photolytic Degradation of Some Sulfonamide Tablets under Exaggerated and Ordinary Ultraviolet Irradiation[1]

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Five sulfonamide tablets, those of sulfaphenazole, sulfadimethoxine, sulfisomidine, sulfisoxazole, and sulfamethizole, were exposed to exaggerated and ordinary ultraviolet (UV) rays for stability studies in the solid state, and the relationship between coloration stability and chemical degradation was investigated. The color change of tablet surface was measured by colorimetric method. Sulfisoxazole and sulfamethizole were photostable in coloration, and sulfadimethoxine was eventually not colored contrary to what was stated in the Pharmacopeia of Japan. Photosensitive similarity between exaggerated and ordinary exposure was not established in coloration.

Photolytic degradation was examined spectrophotometrically and crystallographically. Interesting absorption changes were observed in UV spectra, whereas no apparent changes in either infrared spectra or X-ray diffraction patterns. These evidences were discussed in relation to the results obtained by the complementary tristimulus colorimetry using the UV absorption data. For all the sulfonamides, evident correlation did not exist between coloration and photolytic degradation.

Keywords——sulfonamide tablets; sulfisomidine; sulfisoxazole; sulfadimethoxine; sulfamethizole; sulfaphenazole; photostability; solid-state stability; photolytic degradation; coloration

Coloration of solid pharmaceutical medicaments during storage may give to patients the sense of uneasiness and doubt about the drugs, even though they are actually unchanged. If the exact relationship between coloration and chemical change can be obtained, it may be possible to estimate the appearance of the degradation of pharmaceuticals by observing the change in appearance. This method will contribute to the selection of a desirable pharmaceutical formulation and the method of storage. However, the solid-state reactions of molecular crystals governed by various environmental factors are complex due to their heterogeneity; the reactivity of organic compounds to light is especially so because it shows dependence on the wavelength. Reports of this type of research dealing with the effect of light on physical and chemical properties of solid dosage forms have apparently not been published in spite of the presence of many photosensitive medicaments. A knowledge of solid-state chemistry must, therefore, be useful for developing methods for stabilizing solid dosage forms.

According to the Pharmacopeia of Japan (JP IX), sulfonamides are gradually colored by light. They have been adopted as examples of photosensitive medicaments, and coloration in the form of injection has been investigated.[3] In a solid state, coloration and photolytic degradation of sulfisomidine,[4] and its protection by a film coating containing ultraviolet (UV) absorver[1] have been studied; it was suggested that the evident correlation did not always exist between coloration and photolytic degradation.

The purpose of the present paper was to examine the possibility of the simulation of ordinary storage condition by exaggerated exposure test for some commercially available

1) This paper forms Part IV of "Stability of Solid Dosage Forms." Part III: Y. Matsuda, H. Inouye, and R. Nakanishi, *J. Pharm. Sci.*, **67**, 196 (1978).
2) Location: *Motoyama-Kitamachi, Higashinada, Kobe 658, Japan.*
3) S. Naito and S. Mizoguchi, *Yakuzaigaku*, **18**, 48 (1958).
4) Y. Matsuda and Y. Minamida, *Chem. Pharm. Bull.* (Tokyo), **24**, 2229 (1976).

sulfonamides, and to investigate whether the evidence between coloration and photolytic degradation observed for sulfisomidine can be extended to other sulfonamides or not.

Experimental

Materials——Sulfaphenazole (JP VIII), sulfadimethoxine (JP VIII), sulfisomidine (JP IX), sulfisoxazole (JP IX), and sulfamethizole (JP IX) were used as samples. Sulfamine was also used as a reference sample. Each 1 g of these powdered samples was compressed into tablet by the same method as described previously.[4]

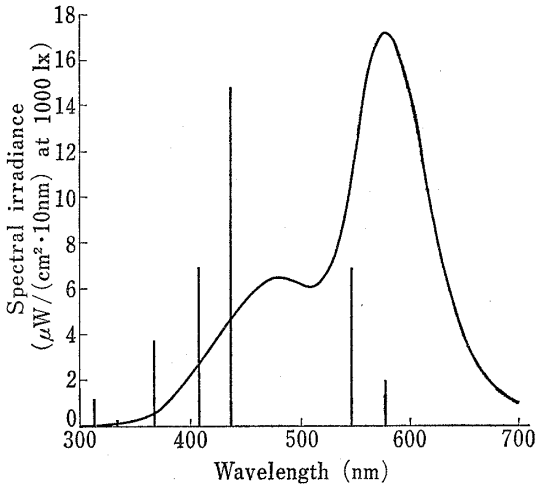

Fig. 1. Spectral Irradiance of Fluorescent Lamp

Exposure Test——The exposure test under a severe condition was made with the same fading tester as described previously.[5] In addition to this test, the following storage condition was added as a test under a practical illumination: The sample tablets were exposed to light directly below a commonly used 20W fluorescent lamp (white light, Type FL-20SW, Mitsubishi Electric Co., Tokyo). The distance between samples and the lamp was 40 cm, and the illuminance on the tablet surface was 1030 lx, as measured with an illumination meter, Model UVR-365 (Tokyo Optical Instruments Co., Tokyo). The spectral irradiance of this lamp is given in Fig. 1.

Colorimetric Measurements——The surface color of tablets in the *Lab* system was measured at designated time intervals with the same color and color difference meter as described previously,[5] and Hunter's color difference (ΔE), the degree of coloration after exposure, was calculated.

Absorption Measurements——UV absorption spectra (more exactly, semi-integral attenuance spectra) of solid-state samples were measured by the method proposed previously.[4] Each sample was exposed in the fading tester under the same condition as the tablets, and spectra were recorded at every exposure time. For the measurement of infrared (IR) spectra in the solid state, KBr pellets incorporating these powdered samples were enclosed together with P_2O_5 as a drying agent in the quartz glass cylinder, and exposed to light in the fading tester. IR spectra were measured both before and after 3-hr exposure.

X-Ray Diffraction Analysis——X-Ray diffraction patterns of samples before and after 3-hr exposure were obtained using an X-ray powder diffractometer, Geigerflex, Model 2011 (Rigaku Denki, Co., Tokyo), employing iron filtered cobalt K_α radiation.

Complementary Tristimulus (CTS) Colorimetry——According to Flaschka's theory,[6] the complementary tristimulus colorimetry was applied to the analysis of photolytic reaction system. The outline of this method is as follows:[7] Three wavelength ranges (named u, v, and w range) were set up on each UV absorption spectrum, and the color point, an important factor in the CTS method, was defined. In this case, each range was set up so as to include either the characteristic absorption bands or the region which varied remarkably in absorption intensity. The color point Q_r was calculated from the following equations (Eq. 1a—c) using the areas, R_u, R_v, and R_w which were surrounded by the limiting wavelengths of each range and absorption curve. The point plotted on the rectangular

$$Q_u = \frac{R_u}{R_u+R_v+R_w} \quad \text{(Eq. 1a)}$$

$$Q_v = \frac{R_v}{R_u+R_v+R_w} \quad \text{(Eq. 1b)}$$

$$Q_w = \frac{R_w}{R_u+R_v+R_w} \quad \text{(Eq. 1c)}$$

coordinate (Q_u-Q_v, Q_v-Q_w, or Q_w-Q_u) in combination with any two among the three Q_r values (Q_u, Q_v, and Q_w) was defined as the Q_r plot. Since the Q_r values denotes the relative intensity of UV absorbance, it gives a definite value for the specified chemical species, independent of its concentration and consequently, the Q_r plot gives a certain point for the same composition.

5) Y. Matsuda and Y. Minamida, *Yakugaku Zasshi*, **96**, 425 (1976).
6) C.N. Reilley, H. Flaschka, S. Laurent, and B. Laurent, *Anal. Chem.*, **32**, 1218 (1960); H. Flaschka, *Talanta*, **7**, 90 (1960).
7) S. Yoshida, Dr. Thesis (Kyoto University, 1976).

Results and Discussion

Coloration of Tablet Surface

Since a series of sulfonamides have the same basic skeleton but different structure in the heteroaromatic ring, there must be some difference in their behavior to light. Fig. 2 shows the color difference of samples before and after exaggerated exposure. It is evident from this graph that sulfisomidine and sulfaphenazole are more markedly colored than the other three. Among these three, sulfisoxazole and sulfamethizole were similar in the process of coloration, and gave nearly 2 NBS units in color difference after a 1-hr exposure. On the contrary, sulfadimethoxine remained less than 1 NBS unit. It was stated that acceptable samples were required to have color difference of less than 3 NBS units when calculated to the standard.[8] It was also confirmed that two adjacent colors with less than 1 NBS unit in difference could not be distinguished visually.[9] On the basis of these facts, sulfisoxazole and sulfamethizole are photostable in coloration, and sulfadimethoxine is eventually not colored contrary to what is stated in the Pharmacopeia of Japan.

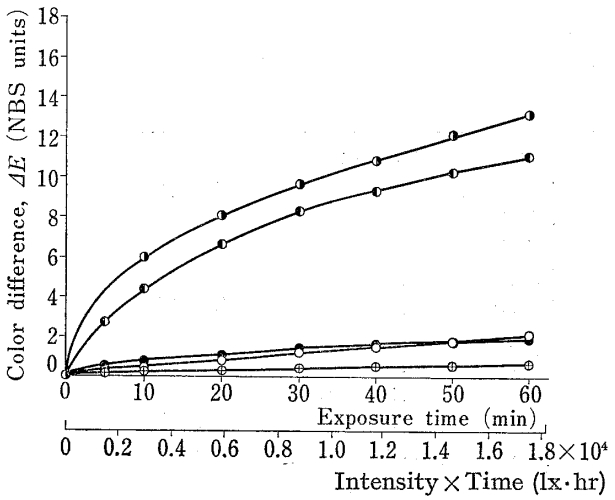

Fig. 2. Degree of Coloration under the Irradiation of Mercury Vapor Lamp for Color Fading

—◑—: sulfisomidine, —◐—: sulfaphenazole,
—●—: sulfamethizole, —○—: sulfisoxazole,
—⊕—: sulfadimethoxine.

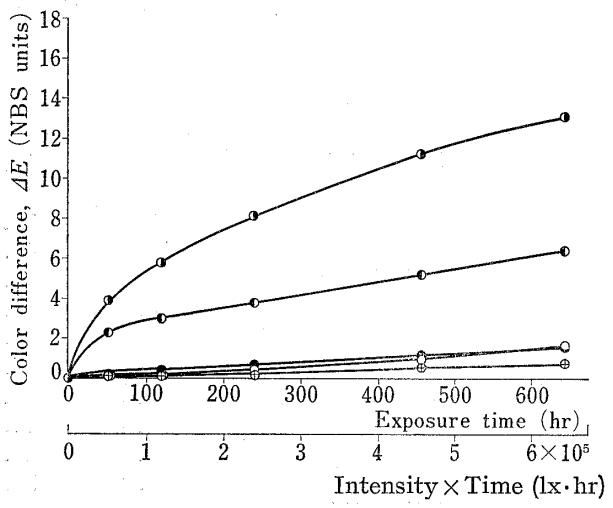

Fig. 3. Degree of Coloration under the Irradiation of Fluorescent Lamp

—◑—: sulfisomidine, —◐—: sulfaphenazole,
—●—: sulfamethizole, —○—: sulfisoxazole,
—⊕—: sulfadimethoxine.

The spectral irradiation energy of mercury vapor lamp for color fading presented in the earlier study[5] and that of the fluorescent lamp in Fig. 1 are much different in the spectral pattern and intensity of irradiation in the UV region. It is, therefore, interesting to compare the coloration characteristics by these lamps, and this may lead to successful prediction of the physical stability under ordinary storage conditions.

Fig. 3 shows color changes obtained under the fluorescent lamp. It has been shown that coloration of sulfisomidine is strongly affected by UV rays absorption.[4] The UV irradiation energies of mercury vapor lamp and fluorescent lamp calculated from the data on the spectral irradiance below 400 nm were 3.8×10^3 and 10.0 $\mu W/cm^2$, respectively. Therefore, the intensity ratio of these lamps can be considered to be roughly several hundreds. Consequently, if these samples did not show selectivity of a wavelength upon coloration, results similar to the

8) F.M. Bogdansky, *J. Pharm. Sci.*, **64**, 323 (1975).
9) G. Kawakami, *Acta Chromat.*, **3**, 54 (1977).

data from 1-hr exposure in Fig. 2 should be obtained after several hundred hours of exposure to the fluorescent lamp. A good correspondence between Fig. 2 and 3, except for sulfaphenazole, was obtained after about 650-hr (6.5×10^5 lx·hr) exposure, which is equivalent to the practical storage period of 6 months in a hospital pharmacy.[10] Therefore, a 1-hr exposure under the mercury vapor lamp is enough long period for coloration stability test. The presence of such an exception suggests that the coloration is also affected by the wavelength.

More exact examination can be made as follows: Assuming the photosensitive similarity between the evidences on coloration by these lamps is established, equation (2) should hold.

$$k = \frac{T_1}{t_1} = \frac{T_2}{t_2} = \cdots = \frac{T_i}{t_i} = \cdots = \text{const.} \qquad \text{(Eq. 2)}$$

where k is the time scale ratio, and t_i and T_i are the exposure periods corresponding to the specified color difference for the mercury vapor lamp and fluorescent lamp, respectively. If the selectivity in wavelength was not observed in coloration, the ratio should be the same for all the samples. The ratios calculated from the smoothed curves in Fig. 2 and 3 are summarized in Table I. Results shown in Table I indicate that the ratios are different among

Table I. Time Scale Ratios between Exaggerated and Ordinary Exposure

Samples	ΔE [NBS units]	t [min][a]	T [hr][b]	k [—]	k_{av} [—]
Sulfisomidine	6	10.0	125.0	0.75×10^3	
	8	19.4	229.5	0.71	0.68×10^3
	10	32.6	351.3	0.65	
	12	49.4	512.5	0.62	
Sulfaphenazole	4	8.9	270.0	1.8×10^3	
	4.5	10.6	345.0	1.9	1.9×10^3
	5	12.6	420.0	2.0	
	6	17.1	572.5	2.0	
Sulfisoxazole	0.8	20.0	390.0	1.2×10^3	
	1.0	26.8	450.0	1.0	1.0×10^3
	1.1	29.0	475.0	1.0	
	1.2	32.5	502.5	0.9	
Sulfamethizole	1.2	22.8	455.0	1.2×10^3	
	1.4	31.3	540.0	1.0	1.0×10^3
	1.6	40.3	625.0	0.93	
Sulfadimethoxine	0.3	27.0	280.0	0.62×10^3	
	0.4	38.0	365.0	0.58	0.56×10^3
	0.5	45.3	400.0	0.53	
	0.6	57.5	500.0	0.52	

a) Exposure time under the mercury vapor lamp.
b) Exposure time under the fluoresecent lamp.

samples but that they can be considered to be almost constant for the same sample, and that photosensitive similarity is established individually. However, the fact that the ratio for sulfaphenazole differed very much from those of other samples clearly supports the selectvity. Thus, it is difficult in the present study to predict exactly the color change under an ordinary storage condition by the exaggerated exposure test.

Photolytic Degradation

Typical UV absorption spectra are shown in Fig. 4(a)—(e). It was not possible under the fluorescent lamp to obtain the precise absorption change, because the electric stability

10) T. Saito, *Yakuzaigaku, Separate Ed.*, **36**, 3 (1976).

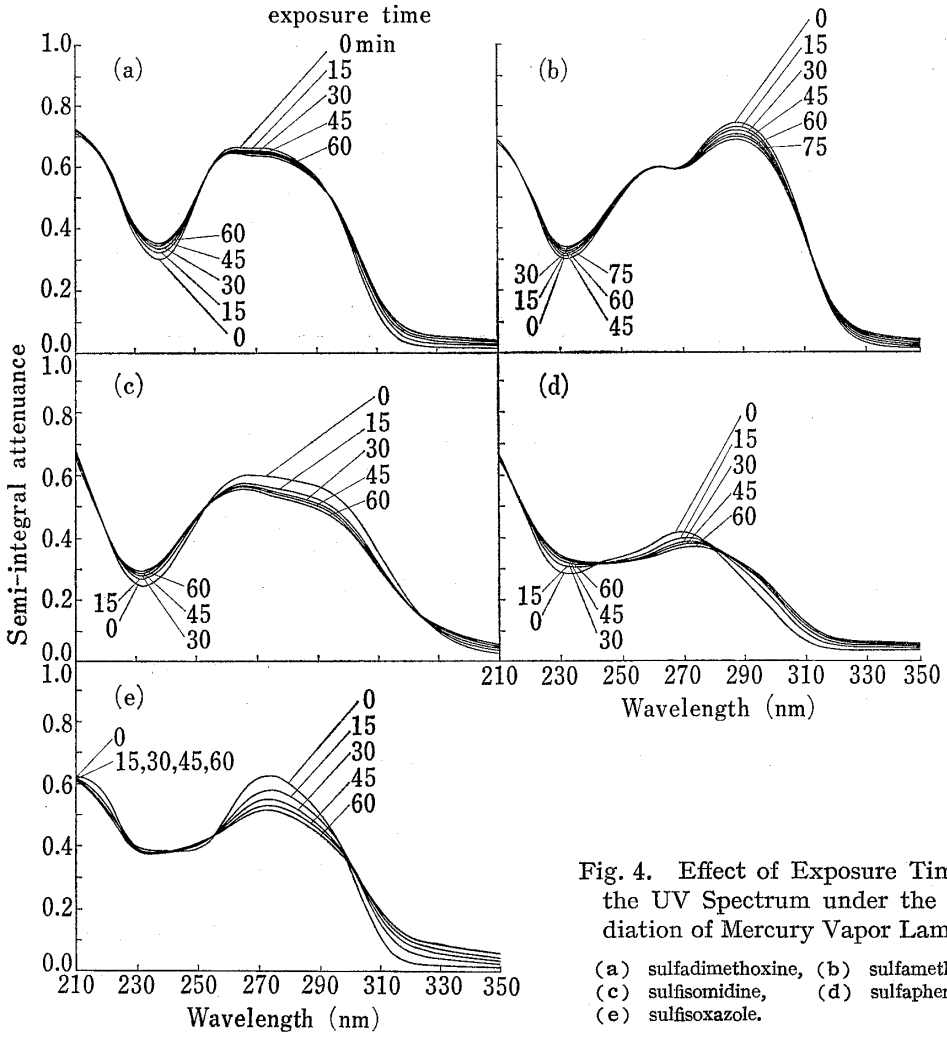

Fig. 4. Effect of Exposure Time on the UV Spectrum under the Irradiation of Mercury Vapor Lamp

(a) sulfadimethoxine, (b) sulfamethizole, (c) sulfisomidine, (d) sulfaphenazole, (e) sulfisoxazole.

of spectrophotometer could not be kept over a long period of exposure. All the samples showed a maximum absorption in the region between 260 and 270 nm, which was likely to be the characteristic absorption band of sulfanilamide group. As the exposure period proceeds, these absorption curves showed a flattening tendency of increasing at the minimum and decreasing at the maximum, indicating simple spectrophometric change. The characteristic evidence for the presence of isosbestic points also in the solid-state reaction was confirmed for other samples, except for sulfaphenazole; they were at 254 and 295 nm for sulfadimethoxine, 263 and 313 nm for sulfamethizole, 219, 253, and 317 nm for sulfisomidine, and 302 nm for sulfisoxazole. For sulfadimethoxine, sulfisomidine, and sulfamethizole, neither maximum nor minimum absorptions were affected by exposure, whereas for sulfisoxazole, minimum absorption was shifted slightly to a shorter wavelength and became sharper, with the maximum absorption unchanged. Sulfaphenazole showed a

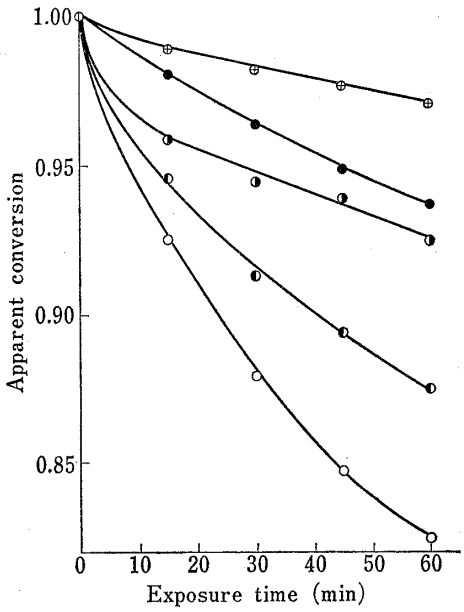

Fig. 5. Apparent Conversion as a Function of Exposure Time

—◑—: sulfisomidine, —◐—: sulfaphenazole, —●—: sulfamethizole, —○—: sulfisoxazole, —⊕—: sulfadimethoxine.

peculier behavior; maximum absorption shifted to a longer wavelength and minimum absorption disappeared gradually without any isosbestic point.

Apparent conversion with time is shown in Fig. 5 in the form of a non-dimensionarized absorbance at maximum absorption of each sample. No correspondence existed between the order of coloration (Fig. 2 and 3) and that of conversion. It should be pointed out that, although sulfisoxazole was hardly colored, its degradation proceeded to the extent of more than 15% conversion, indicating it to be the most photolabile among the samples. This fact denies the statement[11] that the color change which is not indicative of significant degradation may be visually unacceptable, and also suggests that the relation between coloration and photolytic degradation obtained for sulfisomidine can be extended to other sulfonamides.

Fig. 4 and 5 indicate that irradiation of such crystals evidently yields photo-products. However, they must be restricted to on or just below the crystal surface, since all the conversions are low even after exaggerated irradiation and are likely to be saturated in a few hours of exposure.

It is possible to estimate qualitatively the state of reaction from these absorption data. Fig. 6 (a)—(e) shows Q_r plots calculated by the CTS method. In these graphs, the change

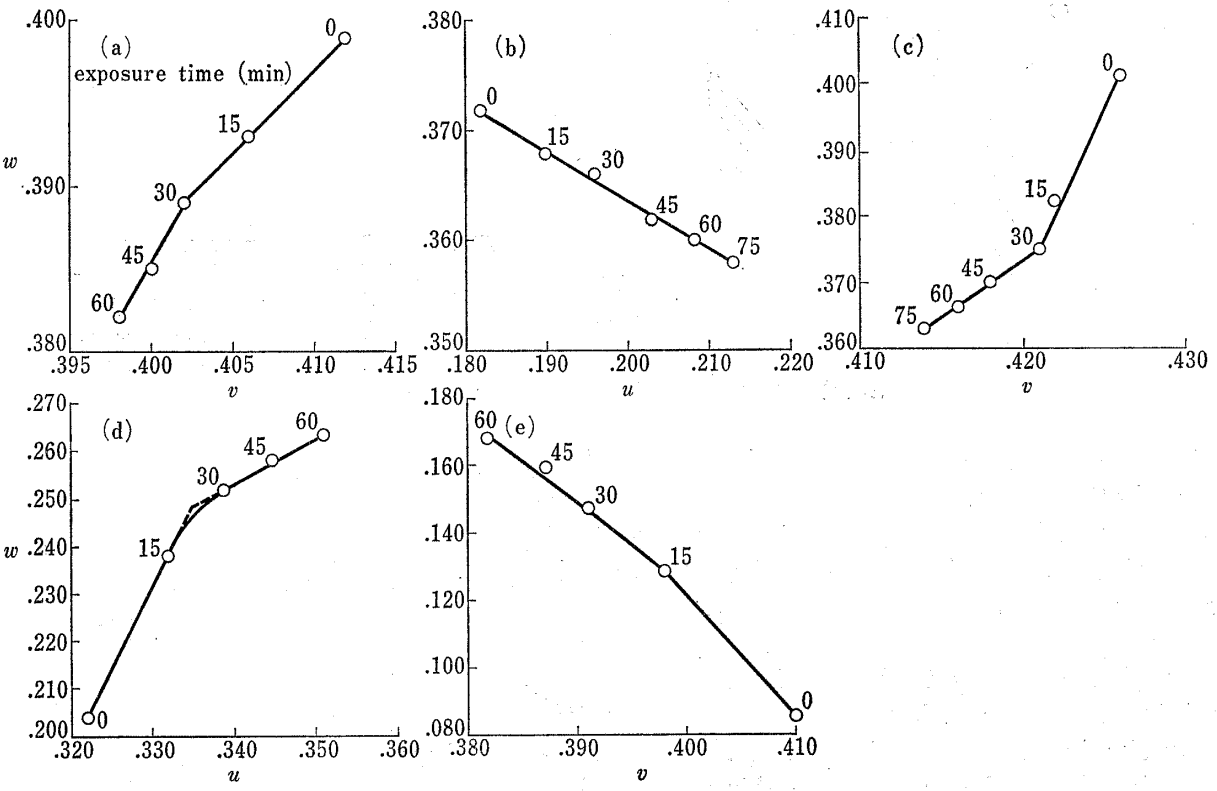

Fig. 6. Q_r Plots as a Function of Exposure Time

(a) sulfadimethoxine, (b) sulfamethizole, (c) sulfisomidine, (d) sulfaphenazole, (e) sulfisoxazole.

of Q_r plot with time resulted in two straight lines which intersected after 15—30 min for the samples, except for sulfamethizole. It was expressed by a single line throughout the period of exposure for sulfamethizole. Flaschka's theory states that, when the Q_r plot moves on the segment of a line, the number of components contained in this reaction system is two, which are indicated as the two end points, and that the number increases by one for increase of each

11) S.S. Kornblum, *Drug and Cosm. Ind.*, **106**[4], 42 (1970).

line. In such a case, chemical species related to the reaction are different between the first and subsequent segment. On the basis of this theory, it can be concluded from the results in Fig. 6 that the photolytic degradation of sulfamethizole is a single reaction composed of only the original substance and a photo-product, whereas it will be consecutive reactions containing an intermediate within the period of the measurement for the others. The interesting fact that the isosbestic point was observed from the beginning of exposure only for sulfamethizole supports the above consideration.

To examine these chemical changes in detail, IR spectra were measured, and the charts for sulfisoxazole and sulfaphenazole, whose conversions were the highest among the samples used, are shown in Fig. 7. Fig. 7 indicates that IR spectra in the finger print region are identical before and after 3-hr exposure, and remained unexpectedly, not changed, though with a slight change in the transmittance in the region above 1600 cm^{-1}. These phenomena were also observed for other samples. X-ray diffraction patterns which indicated that all the samples were in good crystallinity (not presented in this paper) also did not show any change, suggesting no apparent change in the crystal structure. Sulfamine showed no change in either UV or IR spectra, or in X-ray diffraction patterns.

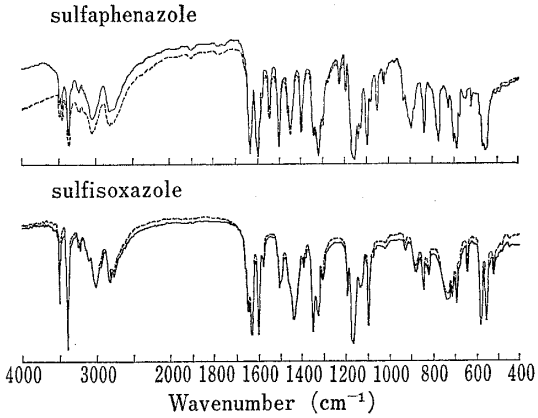

Fig. 7. Effect of Exposure Time on the IR Spectrum under the Irradiation of Mercury Vapor Lamp

——: before exposure, – – –: after 3-hr exposure.

The discussion on these spectrophometric and crystallographic data can be summarized as follows: From the information on sulfamine, it is estimated that the heteroaromatic ring in the structure might be subjected to photo-induced reaction. However, no report has dealt with such a reaction in the solid state, and its mechanism is unknown at present. The effect of topochemical factors is also not known. The reason why there were no apparent changes in IR spectra or X-ray diffraction patterns in spite of noticeable change in UV spectra, may be ascribed to the poorness in the conversion, in comparison with the sensitivity of these methods of measurement. Another possible estimation derived from the results in X-ray diffraction patterns is that the photo-products may be amorphous or poor in crystallinity. It is difficult in an X-ray diffraction pattern to detect an impurity which is poor in crystallinity, even though contained rather in excess.[12]

The failure to observe different spectra and crystallographic structures between the original and exposed samples is consistent with studies on the photochromism and thermochromism, in which IR spectrophotometric and crystallographic differences were not observed between the colored and colorless forms of the sample.[13] Apparently, the color change in these crystals was due to a small concentration of highly colored species of unknown structure.

In the present study, the photolytic degradation was found to be a surface phenomenon, as described above, and, therefore, it will not progress into the crystals so easily, when the photo-product on the surface is poor in the permeability of UV rays. It is also sufficiently possible to consider that the reaction may be saturated and stopped under the condition where

12) J.H. Burns, *J. Chem. Phys.*, **25**, 1218 (1956); K. Kubo ed., "Chemical Analysis by X-ray Diffraction Analysis," Nikkan Kogyo Shinbun Co., Tokyo, 1971, p. 22.

13) M.D. Cohen and G.M.J. Schmidt, *J. Phys. Chem.*, **66**, 2442 (1962); J. Bernstein and G.M.J. Schmidt, *J. Chem. Soc., Perkin II*, **1972**, 951.

the UV rays cannot permeate into the crystal lattice due to the photoxidation.[14] Further discussion is beyond the scope of the present study; work is in progress to clarify the mechanism of this reaction.

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14) H. Nakanishi and F. Nakanishi, Private communication.