KINETICS OF PHOTOCHEMICAL REARRANGEMENTS AND SPECTRAL BEHAVIOUR OF PYRAZOLONE DERIVATIVES IN SOLUTION

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Summary

The kinetics of photochemical rearrangements and the spectral behaviour of pyrazolone derivatives in dilute solution were studied at room temperature. The absorption spectra, effective rate constants and absolute quantum yields of photodecomposition are reported. It was found that the observed difference in the photostability (absolute quantum yields, 0.001 - 0.07) of the compounds studied depend upon the identity of the 4-substituents and the solvents.

1. Introduction

Derivatives of pyrazolone such as 2,3-dimethyl-1-phenyl-5-pyrazolone (I), 2,3-dimethyl-1-phenyl-4-dimethylamino-5-pyrazolone (II), 2,3-dimethyl-1-phenyl-4-methylamino-sodium-methane-sulphonate-5-pyrazolone (III) and 1,2-diphenyl-4-*n*-butyl-3,5-pyrazolidinedione (IV) are widely used in medicine as highly efficient drugs for their antipyretic, analgesic and spasmolitic properties. I is normally referred to as phenazone, antipyrine or sedatine; II is normally referred to as dimethylaminophenazone, pyrazone or amidopyrine; III is normally referred to as sulpyrine, novalgine or methamizole; IV is normally referred to as phenylbutazone or butadione.
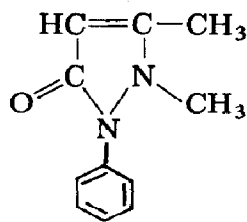
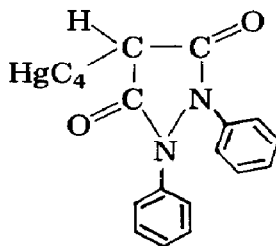I
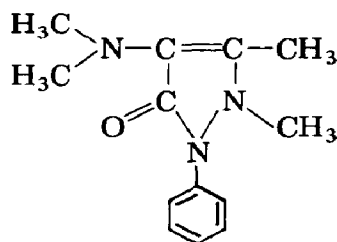
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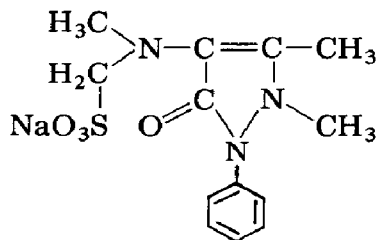
III   IV

It is known that these compounds acquire a yellow colour if kept in the light in the presence of atmospheric oxygen. The coloured drugs were found [1, 2] to have lower activity and higher toxicity. Therefore, it is of the utmost importance that the photostability of these compounds in the presence of oxygen is understood.

The decomposition products of II in aqueous [3 - 5], benzene and methanol [5, 7] solutions, and in the crystalline state [8 - 10] and III in aqueous solutions [11 - 12] were separated by means of thin-layer chromatography and analysed using the techniques of UV, IR, nuclear magnetic resonance and mass spectroscopy. Nevertheless, no data concerning the photochemical aspects of the decomposition of these compounds could be found in the literature.

In the present work quantitative parameters are sought for the photochemical degradation of these compounds in various solvents.

2. Experimental details

The solvents and the chemicals I - IV used in the experiments were of chemical pure grade; their purity was determined spectrophotometrically by comparing the spectra obtained and the extinction coefficients (Fig. 1 and Table 1) with reported data [13].

The quantum yields of photochemical degradation were determined spectrophotometrically from the changes in optical density during irradiation (Fig. 2).

The solutions were irradiated by the filtered emission from a medium pressure PRK-2 mercury lamp with a "2537 A" liquid filter [14]. The irradiation at λ_{ex} = 254 nm was considered photoactive since the amount of 265 nm radiation present in our experiments did not exceed 10%; emission at 313 nm was not absorbed by the solutions studied. The exciting emission was focused on the entrance wall of a 1 cm × 1 cm × 4 cm quartz cell which contained the solution. The intensity of the incident exciting beam (λ_{ex} = 254 nm) was measured with a ferrioxalate actinometer [15] and was about 1.40×10^{14} photons cm^{-2} s^{-1} and was kept constant to ±15% during the
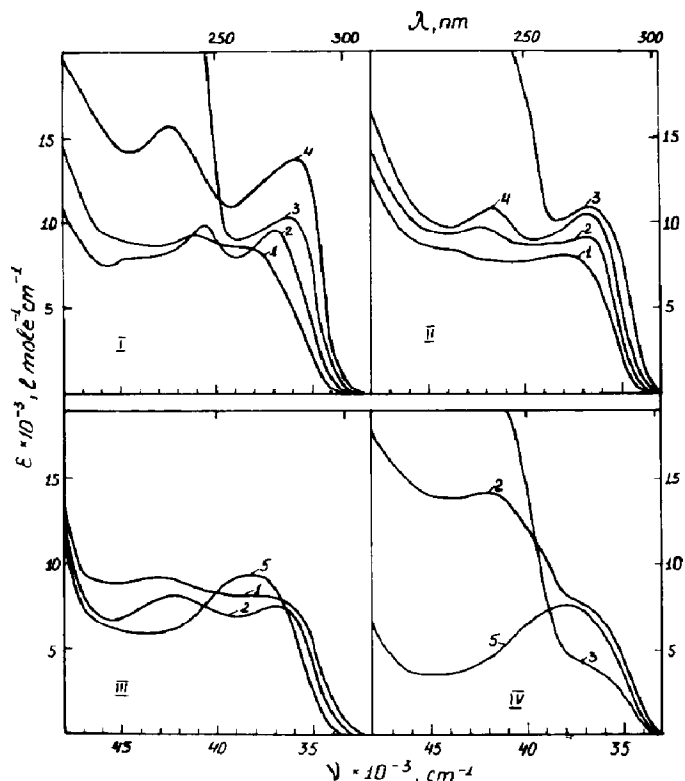
Fig. 1. Absorption spectra of solutions of pyrazolone derivatives at room temperature: curve 1, water; curve 2, ethanol; curve 3, chloroform; curve 4, hexane; curve 5, 0.1 N NaOH.

experiments. The photochemical reactions in the irradiated solutions were monitored by using a Specord UV—visible spectrophotometer. The experiments were carried out with solutions containing dissolved atmospheric oxygen at temperatures of about 20 °C.

3. Results and discussion

3.1. Absorption spectra

All of the compounds under investigation contain the five-membered ring pyrazole and hence these compounds are structurally similar and consequently possess similar properties. They all have a phenyl substituent in the 1-position. I - III have a C=O group in the 5-position, while IV has two of these in the 3- and 5-positions. Substituents at the carbon atom in the 4-position are responsible for the particular pharmacological, chemical, photochemical and spectral behaviour of the molecules. The following spectral properties have been found for the compounds studied. The spectrum of pyrazole (the parent molecule for the compounds under investigation) has two absorption bands: $\lambda_{max} = 210$ nm and $\log_{10} \epsilon = 3.5$; $\lambda_{max} = 250$ nm and

TABLE 1

Spectral and photochemical parameters of pyrazolone derivatives at about 20 °C in the presence of atmospheric air

Solvent	ν_{max} [a] (cm^{-1})	ϵ [b] (l mol^{-1} cm^{-1})	K ($\times 10^{-6}$ s^{-1})	ϕ [c]
I				
Water	41500 (241)	9480	2	0.001
	39400 (254)[d]	8540		
Ethanol	40800 (245)	9840	2	0.001
	37300 (268)[d]	9580		
Chloroform	36000 (278)[d]	10380	100	0.03
Hexane	42500 (235)	15550	25	0.01
	36000 (278)[d]	13650		
II				
Water	43500 (230)	8770	20	0.01
	38700 (258)[d]	8320		
Ethanol	42500 (235)	9840	100	0.05
	36800 (272)[d]	9060		
Chloroform	36600 (273)[d]	10960	150	0.07
Hexane	41700 (240)	10920	15	0.008
	36600 (273)[d]	10830		
III				
Water	43500 (230)	9125	75	0.04
	37400 (267)[d]	8370		
Ethanol	42500 (235)	8240	35	0.02
	37300 (268)[d]	7540		
0.1 M NaOH	38500 (260)	9410		
IV				
Ethanol	41700 (240)	14300	2	0.001
	37000 (270)[d]	7620		
Chloroform	36000 (278)[d]	3460	1	0.003
Hexane	41700 (240)	20270	3	0.005
	36000 (278)[d]	4000		
0.1 M NaOH	37700 (265)[d]	7600	3	0.005

[a]Numerals in parentheses, λ_{max} in nanometres.
[b]Experimental accuracy, ±10%.
[c]Experimental accuracy, ±30%.
[d]The indicated value is λ_{obs}.

$\log_{10} \epsilon = 1.7$. The more intense short wavelength absorption band is assigned [16] to a π,π^* transition in the entire conjugated system of the molecule, while the longer wavelength band is thought to be due to an n,π^* transition within the carbonyl fragment. The absorption spectra of compounds I - IV also have two absorption bands which are red-shifted with respect to those of the unsubstituted pyrazole; the position and the intensity of these bands are determined by the identity and the position of substituents as well as by the solvent used (Fig. 1 and Table 1). The absorption spectra of I - III are
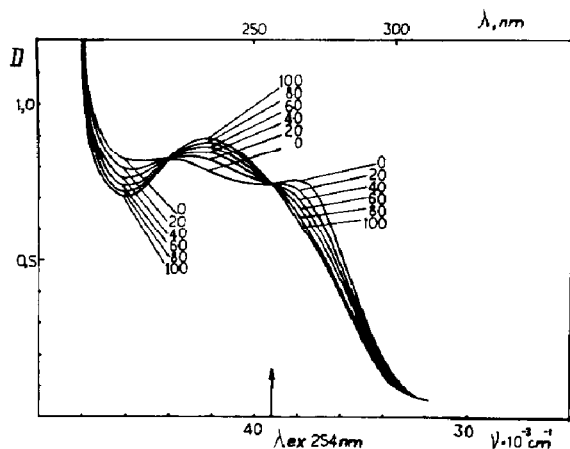
Fig. 2. Photodecomposition of II in aqueous solution at room temperature; λ_{ex} = 254 nm and λ_{obs} = 265 nm. The numerals denote the irradiation times in minutes.

similar in appearance and intensity. The absorption spectrum of III is more shallow and possesses two smoothed-out absorption bands.

Owing to the larger number of C=O groups and the greater degree of conjugation caused by the presence of the phenyl substituent in the 2-position, the absorption spectrum of IV is changed in appearance. The presence of the long wavelength band may be established from the inflexion due to the overlap between the n,π^* and the π,π^* absorption bands. The absorption spectrum of IV is more strongly influenced by the nature of the solvent. In hexane and ethanol, compound IV reveals strong short wavelength absorption, while in a 0.1 M aqueous solution of NaOH an absorption appears within the region 255 - 300 nm (λ_{max} = 265 nm). This may be due to the occurrence of keto–enol tautomerism. IV has acidic properties which result from the presence of a mobile hydrogen at the carbon atom in the 4-position which is capable of forming the enol modification with neighbouring carbonyl groups. The absorption in the region 255 - 300 nm may evidently be assigned to the enol form of IV, while that in the region 230 - 250 nm may be assigned to the ketone.

In chloroform, I, II and IV (III is insoluble) have only long wavelength bands which are almost identical for each of these compounds (Fig. 1 and Table 1).

3.2. Kinetics of the photochemical rearrangements

Qualitative data concerning the stability of II - IV under the action of both light and atmospheric oxygen may be found in the literature [3 - 12, 17]. However, quantitative data such as quantum yields of photodegradation for these compounds have not yet been reported.

In the present paper we report the kinetics and quantum yields of photodegradation for compounds I - IV in liquid solution. Solutions (10^{-5} - 10^{-4} M) were irradiated in the 1 cm X 1 cm X 4 cm quartz cells by mono-

chromatic radiation with $\lambda_{ex} = 254$ nm; the absorption spectra of the solutions were recorded at different exposure times (Fig. 2). The data thus obtained were treated in the following way.

If it is assumed that the photodegradation of the compounds studied obeys first-order kinetics (at least in the initial stages of the photolysis), then the reaction rate may be written as [18]

$$\frac{dC}{dt} = \phi I_0 (1 - e^{-\chi Cl}) \qquad (1)$$

where C (mol l^{-1}) is the concentration, χ (mol^{-1} cm^{-1}) is the extinction coefficient (base e), l (cm) is the path length, I_0 (mol l^{-1} s^{-1}) is the intensity of the incident exciting radiation and ϕ is the quantum yield of photodegradation. On integration and transforming to base 10, we obtain the expression

$$D + \log_{10}(1 - 10^{-D}) = -\phi I_0 \epsilon l t + \text{const} \qquad (2)$$

where ϵ (l mol^{-1} cm^{-1}) is the decadic extinction coefficient and $D = \epsilon Cl$ is the optical density of the solution. When the optical density of the solution studied was small, the approximation

$$\log_{10} \frac{D}{D_0} \approx -\phi I_0 \epsilon l t \qquad (3)$$

was used in treating the experimental data.

The plots of $\{D + \log(1 - 10^{-D})\}$ *versus* t (or $\log_{10}(D/D_0)$ *versus* t) are given in Fig. 3. It should be noted that in the initial stages of photolysis the degradation kinetics obeys a first-order law. The deviation from first-order kinetics may be due to the absorption of the exciting radiation by the degradation products.

An effective rate constant $K = \phi I_0 \epsilon l$ and the corresponding absolute quantum yields $\phi = K/I_0 \epsilon l$ have been calculated from the slopes of the linear portions of the plots. The data thus obtained are collected in Table 1.

As is seen, the quantum yields of photodegradation for II and III are greater than those for compounds I and IV by as much as an order of mag-
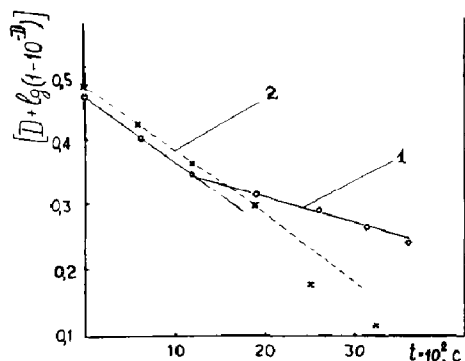

Fig. 3. Linear approximation of kinetic curves for III (curve 1) and II (curve 2) in aqueous solutions at room temperature.

nitude. The quantum yields may also depend on the nature of the solvent (Table 1): the photodegradation of I in chloroform is faster by an order of magnitude than that of I in the other solvents studied. As is seen, II is most stable in water, while III is most stable in ethanol. It may be assumed that the stabilization of II in water is due to the formation of a hydrogen bond between nitrogen and/or oxygen from the C=O group. III is a salt and therefore it will be somewhat dissociated in water; this results in the lower stability and photostability of compound III.

Thus, Table 1 shows that I and IV are much more stable than II and III, and this may be explained by the structural features of these compounds and primarily by the different substituents in the 4-position.

An analysis of the photodegradation products of solutions [3 - 7, 11, 12] and crystals [8 - 10] of II and III showed the presence of about 18 products, including 4-aminoantipyrine, 4-formylaminoantipyrine, 4-formylmethylaminoantipyrine and 4,4'-methylenebis(methylimino)diantipyrine [3, 9 - 11]. All of these result from the varied oxidation and substitution of the dimethylamino group in the 4-position and the subsequent secondary reaction leading to the formation of dimerization products. These products are formed with considerable efficiency and this is shown by the photodegradation quantum yields for II and III (Table 1). It may therefore be concluded that the dimethylamino group in the 4-position plays the specific role of "active site" in the process of photodecomposition of II and III.

I and IV are much more stable than II and III, and they decompose by a different method [17]. Because of the absence of an active site in these compounds, the excitation energy becomes delocalized over the entire molecule, and photodecomposition occurs by the rupture of the bonds between the nitrogen atom of the pyrazolone ring accompanied by the substitution of hydrogen in the 4-position by OH or MeO groups, thus giving different dianilides [17]. It is clear that the rupture of the cyclic structure in IV requires a larger energy than the photodecomposition of II and III where the cyclic structure remains unaffected. This apparently leads to the observed difference in the efficiency of photodecomposition of the compounds studied.

4. Conclusions

Absorption spectra and extinction coefficients for pyrazolone derivatives in various solvents have been measured and discussed. It was found that the spectral parameters of these compounds depend on the substituents and the solvent used.

Effective rate constants and absolute quantum yields of photodecomposition have been measured by using a spectrophotometric technique; these values were found to depend upon the identities of the 4-substituents and solvents. The photostability of I and IV was found to be greater than that of III by an order of magnitude.

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