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Researches on the Reactivity of Mannich Bases Part VIII

Synthesis of *N*-methyl(vinylaryl)quinolinium Salts and Their Photosensitivity (1)

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Described in this communication is a new synthesis of *N*-methyl-4-(vinylaryl)quinolinium salts by cyclization of the aminoketones, $\text{Ar}-\text{CH}=\text{CH}-\text{CO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{C}_6\text{H}_4-\text{X}$. The aminoketones were obtained by replacement of the alkylamino group of the ketoarylidene Mannich bases with various *N*-methylarylamines. The U.V. spectra of the compounds were obtained. The photosensitivity characteristics in solution are reported. These data show the possibility of dimerization and probable *trans* \rightarrow *cis* isomerization on exposure to visible and ultraviolet light.

The exchange reaction between the Mannich bases of type I and primary arylamines, followed by cyclization of the 1-aryl-5-arylamino-pentenones gave 4-styrylquinolines (2). In this research the exchange reaction was successfully carried out on a number of *N*-alkylaniline derivatives with piper-

idinoethyl arylvinyl ketones followed by cyclization of the 1-aryl-5-(*N*-methylarylamino)pentenones (II), thus *N*-alkyl-4-vinylarylquinolinium salts (III) were obtained in good yields. These *N*-alkylquinolinium salts are of interest since they may be considered as analogs of the cyanine series. Recently some interest in the pharmacological properties of styrylquinoline derivatives has developed (3).

An interesting fact that emerged in the course of these investigations was the sensitivity that solutions of these compounds exhibited to the action of visible and ultraviolet light in bringing about a probable *trans* (III) \rightarrow *cis* (IIIa) isomerization. This isomerization was found to be reversible by heat. Furthermore III was photochemically dimerized to compounds of type (IV).

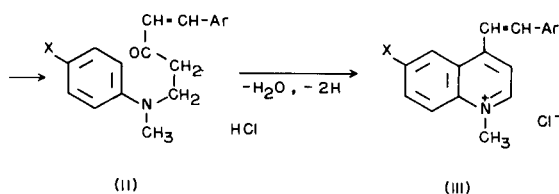
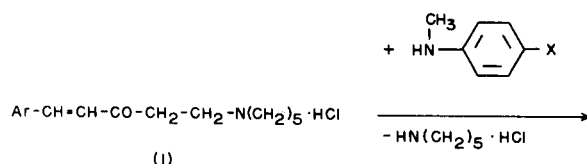
The ultraviolet spectral characteristics of III and IV were examined with a view to demonstrating the influence of substituents on the chromophoric systems. These data contributed to the determination of the structure of III and IV.

EXPERIMENTAL

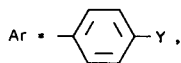
1-Aryl-5-(*N*-methylarylamino)pent-1-en-3-ones (II).

Ten g. of 1-aryl-5-piperidinopentenone hydrochloride (I) and an equimolecular quantity of *N*-methylarylamine, dissolved in 80 ml. of ethanol/water (1:1), were heated under reflux for one hour. The product separated from the cooled reaction mixture, often as an oil. By allowing the product to stand in contact with a small quantity of ethanol, the 1-aryl-5-(*N*-methylarylamino)pentenones (II) were obtained as crystalline solids with yields of 60-75%. The products were all purified by crystallization from ethanol. Only the 1-furyl-5-(*N*-methyl-anilino)pentenone after being separated from the reaction mixture was recovered with ether and dried. After the removal of the solvent, the product was purified by distillation at reduced pressure, the yields being 35-40%.

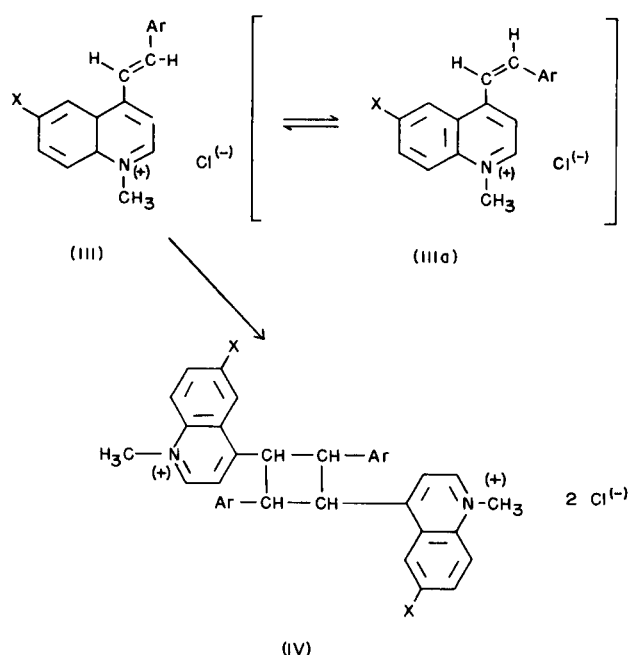
The data on these compounds are recorded in Table I.



X = H, Cl, OCH₃;



(Y = H, Cl, OCH₃; Z = O, S)



N-Methyl-4-(vinylaryl)quinolinium Chlorides (III).

The arylaminopentenone (II) (0.01 mole) dissolved in 20 ml. of absolute ethanol was refluxed for 2-3 hours in the presence of 0.01 mole of stannic chloride pentahydrate, 0.002 mole of anhydrous zinc chloride and 0.01 mole of the hydrochloride of the amine used in the previous exchange reaction. At the end of the reaction, the solid

which separated from the reaction was filtered hot and washed with acetone. The quinolinium-stannic chloride complex thus obtained was decomposed by boiling in a 1% aqueous solution (shielded from light) for 3-4 hours (4). The white gelatinous precipitate was removed by filtration after the addition of charcoal. The water was evaporated at reduced pressure and the residual crystalline mass was treated with acetone-ether and filtered.

The *N*-methyl-4-(vinylaryl)quinolinium chlorides thus obtained in yields of 35-45% formed coloured crystalline solids (yellow, orange and orange-red).

These salts were crystallized from ethanol, some of the solvent being retained which could be removed only after prolonged drying at 80-100° at reduced pressure over phosphorus pentoxide. Furthermore the salts were hygroscopic and generally retain small quantities of zinc compounds which it was difficult to eliminate even with several recrystallizations (5). Therefore the analysis of these compounds was carried out on the corresponding picrates which, unlike the chlorides, were more easily purified. For this purpose a saturated aqueous solution of picric acid was added to an almost saturated aqueous solution of the vinylarylquinolinium chloride. The expected picrate was immediately formed (the filtration was facilitated by gently heating the mixture) and was crystallized from aqueous dioxan, sometimes in the presence of dimethylformamide.

The characteristics of the compounds described are recorded in Table II.

The U.V. spectroscopic data, determined in ethanol solution, are given in Table IV. For greater clarity the curves of some compounds are drawn in Fig. 1.

Photo-dimerization of *N*-Methyl-4-(vinylaryl)quinolinium Chlorides (III).

The saturated alcoholic or aqueous-alcoholic solution containing 4-6% of vinylarylquinolinium chloride (III) was exposed to the action of sunlight.

During the period of exposure, which varied from 15-30 days for most of the chlorides (III) and up to two months for the *p*-methoxy-styryl derivative, the dimer (IV) was formed in appreciable yields that increased with time.

The product, which partly precipitated spontaneously, was separated by the addition of a mixture of ether and acetone to the solution, after

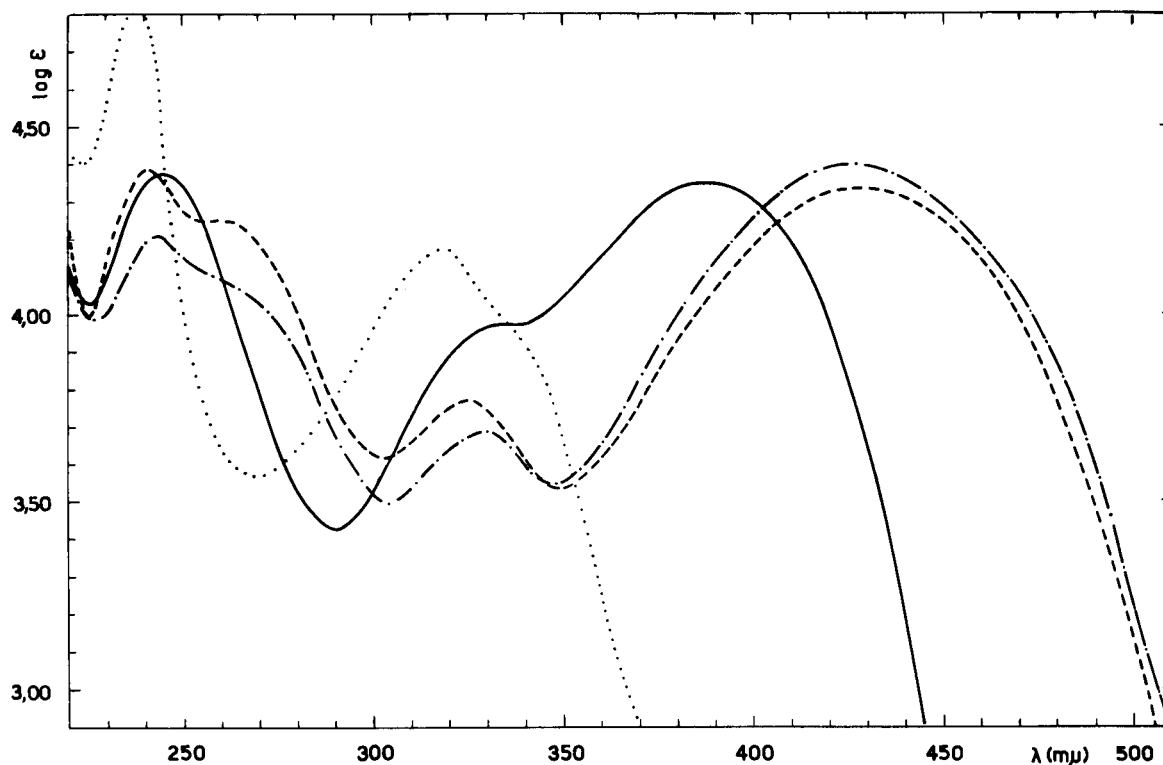


Fig. 1. Ultraviolet spectroscopic characteristics of some *N*-methyl-4-(vinylaryl)quinolinium chlorides (III) and the corresponding dimers (IV).

it had been concentrated in the cold. The product was filtered, and crystallized from a little water or from ethanol-water. These compounds possessed the same disadvantages as the vinylarylquinolinium chlorides (III) therefore they were analyzed after conversion into the corresponding picrates.

The characteristics of this series of compounds (with the exception of the furyl derivative, which gave only tarry products on irradiation) are reported in Table III. The ultraviolet spectral data (determined in water because of the reduced solubility of these dimers in other solvents) are given in Table IV (see also Fig. 1).

The Action of Visible and Ultraviolet Light on Solutions of *N*-Methyl-4-styrylquinolinium Chloride (III, Ar = C₆H₅).

Fifty ml. of the styrylquinolinium chloride solution in absolute methanol or in water was placed in a quartz flask and irradiated by means of an ultraviolet-ray lamp (HANAU type, 1.4 A., 220 volts) or by means of an ordinary white-light lamp (60 watt, 140 volt) placed at a distance of 15 cm.

The ultraviolet spectra were determined on samples withdrawn at various times and diluted to concentrations of 1.2/100,000. The characteristics of these spectra are reported in Table V and a typical curve is shown in Fig. 2.

The ultraviolet spectra were determined using a Beckmann DU spectrophotometer.

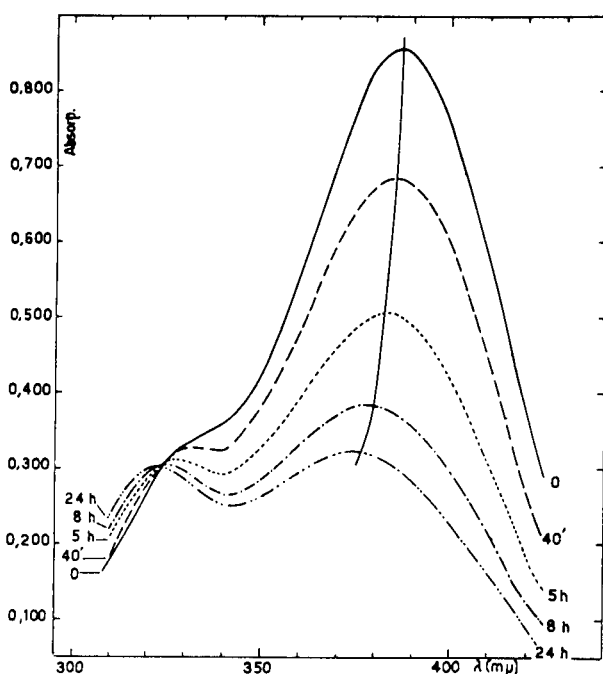


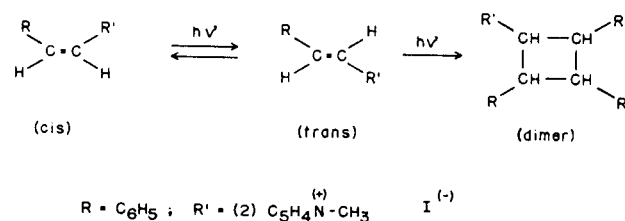
Fig. 2. The action of white light on the methanol solution 0.002 *M* of *N*-methyl-4-styrylquinolinium chloride (form. III; X = H, Ar = C₆H₅). Variations in ultraviolet absorption in the range of higher wavelengths of the irradiated solution in relation to the period of irradiation.

DISCUSSION OF THE RESULTS

The synthesis of the *N*-methyl-4-(vinylaryl)quinolinium salts (III), studied in this paper, is a cyclizing-dehydrogenative condensation of *N*-methylarylaminopentenones (II) as a result of the action of zinc chloride and stannic chloride, similar to that

of the 4-styrylquinolines described in a previous paper (2). Therefore the synthesis represents a new general method of preparation of these salts, usually prepared (sometimes with difficulty) by the condensation between *N*-alkylquinolinium-4-methyl substituted salts and aromatic aldehydes (6,7,8). In this synthesis, which represents part of the studies that have been pursued for sometime on the reactivity of the Mannich bases (9), one can make additional observations on the reactivity of the β -ketobase derivatives with respect to the electrophilic behaviour of the carbonyl group towards the *ortho* position of the aniline moiety.

The formation of compounds (IV) by the photodimerization of vinylarylquinolinium chlorides (III) can be compared with the analogous behaviour of stilbene (10) or, more closely, with that of *N*-methyl-2-styrylpyridinium salts (11). In fact Williams *et al.*, observed that the methiodide of 2-styrylpyridine undergoes isomerization by the action of light to a *cis* derivative and at the same time dimerization according to the following scheme:



Before proceeding with the discussion of the photosensitivity shown by solutions of vinylarylquinolinium salts it is necessary to consider the ultraviolet spectral characteristics of these compounds. From the data reported in Table IV and Figure 1, it can be observed that the spectrum in ethanol of *N*-methyl-4-styrylquinolinium chloride shows a band at 246 $m\mu$ and a region of absorption at higher wavelengths, characterized by a point of inflexion at 333 $m\mu$ and a peak at 388 $m\mu$ (12).

The spectra of the other derivatives studied all show these characteristics, more or less modified by the various substituents. It is interesting to observe that the spectrum of each of these compounds is almost identical to that of the hydrochlorides of the corresponding styrylquinoline (2). This indicates the presence in the two series of compounds of very similar chromophores as might be expected.

The band at the higher wavelengths may be attributed to the chromophore constituted by the vinylarylquinolinium cation as a whole. This is supported by the considerable bathochromic effect introduced by a strong electron donor such as a methoxyl group whenever it is located in positions in conjugation with the cationic nitrogen. Analogous effects occur when in the group -CH=CH-Ar, the phenyl is re-

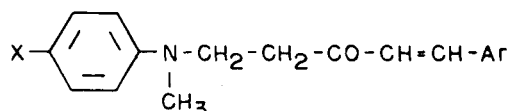
placed by furyl or thienyl groups, which being less aromatic, make possible a greater displacement of the electrons towards the quinolinium cation. Absorption around 330 $m\mu$ (point of inflexion for the styryl and the *p*-chlorostyryl derivative) should, on the contrary, be associated with the electronic

system of the quinolinium nucleus, especially if one considers that only the methoxyl group in position 6 of the nucleus causes an appreciable bathochromic effect on the band.

From the data given in Table IV and Figure 1 one can observe that the spectrum of the dimer (IV);

TABLE I

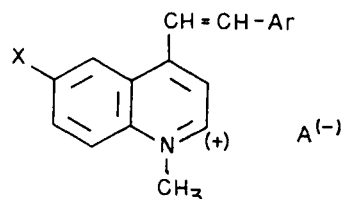
Characteristics of the 1-aryl-5-(*N*-methylarylamino)pent-1-en-3-ones (II)



X	Ar	M. P. B. P. (°C)	C%		Analyses H%		N%	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C ₆ H ₅	55-56	81.48	81.86	7.22	7.26	5.28	5.04
H	<i>p</i> -ClC ₆ H ₄	52-53	72.11	72.02	6.05	5.94	4.67	4.52
Cl	C ₆ H ₅	78-79	72.11	72.40	6.05	6.24	4.67	4.79
H	<i>p</i> -CH ₃ OC ₆ H ₄	83-84	77.25	77.15	7.17	7.24	4.74	4.68
OCH ₃	C ₆ H ₅	73-74	77.25	77.13	7.17	7.20	4.74	4.58
H		158-160 (0.9 mm Hg)	75.27	75.10	6.71	6.48	5.49	5.71
H		62-63	70.81	71.10	6.32	6.56	5.16	5.19

TABLE II

Characteristics of the *N*-methyl-4-(vinylaryl)quinolinium Salts (III).



X	Ar	chlorides (A ⁻ =Cl ⁻) M. P. (°C) (with dec.)	M. P. (°C) (with dec.)	C%		Picrates [A ⁻ = (O ₂ N) ₃ C ₆ H ₂ -O ⁻] Analyses H%		N%	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C ₆ H ₅	247-248	275-276	60.76	60.90	3.82	3.68	11.81	12.08
H	<i>p</i> -ClC ₆ H ₄	245-246	268-270	56.64	56.40	3.37	3.33	11.01	11.16
Cl	C ₆ H ₅	241-242	286-287	56.64	56.38	3.37	3.31	11.01	11.30
H	<i>p</i> -CH ₃ OC ₆ H ₄	243-244	243-245	59.52	59.82	3.99	4.07	11.11	11.35
OCH ₃	C ₆ H ₅	201-202	240-242	59.52	59.43	3.99	3.98	11.11	11.30
H		218-219	233-234	56.90	56.71	3.47	3.46	12.07	12.06
H		242-243	244-245	55.00	54.75	3.36	3.35	11.67	11.77

Ar = C₆H₅) is characterized by two peaks, at 238 m μ and 318 m μ . This spectrum is in every way comparable to that of all the other dimeric compounds not substituted in the quinolinium nucleus (IV; X = H) and to that of the *N*-methyllepidinium salt (6), but the spectra of the compounds with methoxyl groups and a halogen in the quinolinium nucleus (IV, X = Cl, OCH₃) show considerable modifications. This fact indicates that, as a consequence of dimerization, the quinolinium nucleus is isolated from the aryl by the disappearance of the vinyl system; this is in accord with the structure of the compounds of type IV.

In further experiments on the photosensitivity of the *N*-alkyl(vinylaryl)quinolinium salts (III) in solution, the 4-styryl derivative (III; X = H, Ar = C₆H₅) was subjected to irradiation for various lengths of time. The solvent, the concentration and the light source was varied. The results recorded in Table V and Fig. 2 show that light radiations, whether visible or ultraviolet, always cause a diminution of intensity in the higher wavelength bands, accompanied by a shift in the peak towards 377 m μ and the occurrence of a peak about 320 m μ . Dilution increases the rate of the process, while the effect of heat on the irradiated solutions reverses the process.

After very long periods of exposure to light even the peak at 377 m μ tends to diminish and in aqueous

solutions eventually disappears, thus practically arriving at the spectral characteristics of the dimer (IV; X = H, Ar = C₆H₅), whose solutions are no more affected on being heated.

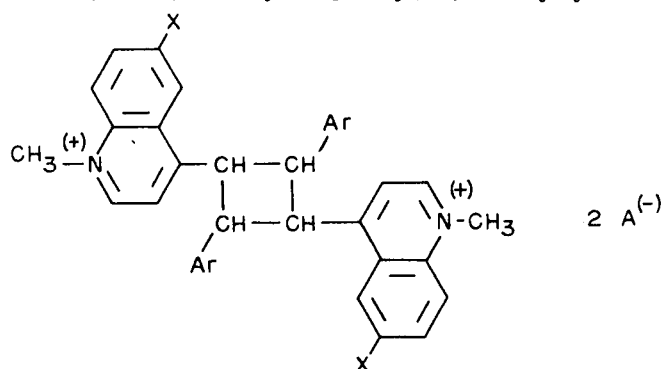
In the light of these experiments and of the studies carried out on analogous systems, stilbene (10) and styrylpyridine (11), it seems reasonable to draw the following conclusions.

The action of light seems to produce dimerization of the compounds (III) as is shown by the occurrence of bands around 320 m μ in the spectrum of the irradiated solutions and in the method itself of obtaining the dimers (IV).

In summary, irradiation brings about the isomerization of *N*-methyl-*trans*-styrylquinolinium chloride (III) into the corresponding *cis* derivative (IIIa), such a reaction being favored by dilution, as well as producing the phenomenon of dimerization. Unfortunately the isolation of the *cis* form was not possible in spite of numerous attempts. Careful removal of the solvents in the cold from the irradiated solutions always gave a mixture of dimer (IV) and of *trans* form (III). However, the presence of the *cis* isomer in solution is highly probable both from a consideration of the hypsochromic effect of the band at 388 m μ (the spectra of mixtures of *trans* form (III) and dimer (IV) in various ratios always gave the peak at 388 m μ) and also the reversibility observed on heating the irradiated solutions.

TABLE III

Characteristics of 1,3-Di-(*N*-methyl-4-quinolyl)-2,4-diarylcyclobutanes (IV).



X	Ar	Chlorides (A ⁻ =Cl ⁻)		Picrates A ⁻ = (O ₂ N) ₃ C ₆ H ₂ -O ⁻ Analyses					
		M. P. (°C) (with dec.)	M. P. (°C) (with dec.)	C%		H%		N%	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C ₆ H ₅	193-195	220-221	60.76	60.56	3.82	3.60	11.81	11.97
H	<i>p</i> -ClC ₆ H ₄	204-205	226-227	56.64	56.44	3.37	3.45	11.01	10.75
Cl	C ₆ H ₅	271-273	274-275	56.64	56.69	3.37	3.42	11.01	11.22
H	<i>p</i> -CH ₃ OC ₆ H ₄	191-193	195-197	59.52	59.33	3.99	4.07	11.11	11.38
OCH ₃	C ₆ H ₅	247-249	206-208	59.52	59.63	3.99	3.96	11.11	11.16
H		225-226	199-200	55.00	54.83	3.36	3.46	11.67	11.43

TABLE IV

 Ultraviolet Spectroscopic Characteristics of the *N*-Methyl-4-(vinylaryl)quinolinium Chlorides (III) and of the Corresponding Dimers (IV)



X	Ar	<i>N</i> -methyl-4-(vinylaryl)quinolinium Chlorides (III) (In Ethanol)		Dimeric Chlorides (IV) (In Water)	
		λ max (m μ)	log ϵ	λ max (m μ)	log ϵ
H	C ₆ H ₅	246	4.37	238	4.81
		333 (f)	3.97	318	4.18
		388	4.35		
H	<i>p</i> -ClC ₆ H ₄	247	4.38	240	4.84
		335 (f)	4.01	319	4.22
		391	4.43	380 (f)	3.49
Cl	C ₆ H ₅	248	4.37	244	4.75
		337	3.92	324	4.11
		397	4.36	370 (f)	3.39
H	<i>p</i> -CH ₃ OC ₆ H ₄	242	4.38	236	4.85
		260	4.25	318	4.18
		326	3.77		
		428	4.33		
CH ₃ O	C ₆ H ₅	260	4.38	250	4.73
		355	4.15	320	4.05
		400	4.31	355	4.08
H		242	4.21		
		330	3.69		
		427	4.39		
H		240	4.45	236	4.82
		267 (f)	4.08	319	4.11
		323	3.84		
		420	4.12		

TABLE V

 Spectroscopic Effects Caused by the Irradiation of Solutions of *N*-methyl-4-styrylquinolinium Chlorides (a).

Time of Irradiation	Conc. 0.02 <i>M</i> in methanol		Ultraviolet Light Conc. 0.002 <i>M</i> in methanol		Conc. 0.002 <i>M</i> in water		Visible Light Conc. 0.002 <i>M</i> in methanol	
	λ max (m μ)	Absorp.	λ max (m μ)	Absorp.	λ max (m μ)	Absorp.	λ max (m μ)	Absorp.
0'	387	0.853	387	0.853	381	0.752	387	0.853
10'	386	0.800	385	0.572	380	0.517	386	0.830
40'	384	0.642	377	0.372	375	0.334	386	0.680
1h, 30'	382	0.481	377	0.363	370	0.293	385	0.630
16h	377	0.351	377	0.346	365	0.185	378	0.350
24h	377	0.337			362 (f)	0.156	377	0.320

(a) The data are limited to the variations that occurred at the higher wavelength bands, which are the most significant.

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- (3) C. T. Bahner, H. Kinder and T. Rigdon, *J. Med. Chem.*, **8**, 137 (1965).
- (4) This and the other operations such as crystallization, preparation of solutions for spectra, etc., in which the *N*-methyl(vinylaryl)quinolinium chlorides were in solution, were conducted in the dark in order to prevent the photodimerization of the compounds.
- (5) Cyclization in the absence of zinc chloride would obviate this disadvantage, but gave generally lower yields. In some cases the aqueous solutions of styrylquinolinium salts were treated with quin-aldinic acid with a view to precipitating all the zinc.
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- (11) J. L. R. Williams, S. K. Webster and J. A. Van Allan, *J. Org. Chem.*, **26**, 4893 (1961).
- (12) The differences shown by the spectrum of the corresponding iodide of Sutherland *et al.*, (6), such as the occurrence of a peak at 317 m μ and the relatively low intensity of the band at higher wavelengths, are due in all probability to the presence in the solution of a certain quantity of dimer.

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