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Mechanism of Photocyclization of N-Chloroacetyl-*m*-tyramine A Flash Photolysis Study[1)]

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The flash photolysis of N-chloroacetyl-*m*-tyramine (V) in non-degassed aqueous solution afforded a transient absorption spectrum which consists of two groups with different intensities and life-times. The weak bands at 380, 386, and 412 nm ($\tau=200$—$400\,\mu$sec), which were also observed in the photolysis of N-acetyl-*m*-tyramine (VIII), correspond with the spectrum of the phenoxy radical.

The strong bands at 322 and 330 nm decay according to a first-order kinetics ($\tau=530\,\mu$sec in neutral solution, $\tau=48\,\mu$sec in alkaline solution) and are attributed to the cyclohexa-2,4-dienone (1,2,4,5,9,9a-hexahydro-3H-3-benzazepin-2,9-dione (X)), which is an intermediate of the photocyclization of V to 9-hydroxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one (VI). In conclusion, the photocyclization of V may be initiated by an electron transfer from the aromatic system to the chlorinated amide group, followed by *ortho*-cyclization of X, which aromatizes to yield VI.

Photocyclization reactions of N-chloroacetyl derivatives of pharmacodynamic amines and aromatic amino acids afforded a number of novel heterocyclic compounds.[3)] A common process in these reactions appears to be homolytic or heterolytic cleavage of the C-Cl bond. On the basis of studies on fluorescence quenching of electron rich aromatics such as indole and anisole with chloroacetamide[4)] and on solvent effects in the photocyclization of N-chloroacetylmescaline (I), a dualistic mechanism has been proposed.[5)] In water the photocyclization reactions (i) may be initiated by an intramolecular electron transfer from the excited singlet state of the aromatic nucleus to the chlorinated amide *via* a loosely bound exciplex to cleave the C-Cl bond as follows:

$$\mathrm{ClCH_2CONHR} \xrightarrow{e^-} \mathrm{Cl^-} + \mathrm{CH_2CONHR}$$[6)]

On the other hand, in most organic solvents an intramolecular energy transfer from the excited aromatic chromophore may cause homolytic cleavage of the C-Cl bond leading to typical radical reactions (ii).

In order to learn more about the nature of intermediates, the photocyclization of N-chloroacetyl-*m*-tyramine (V) has now been studied by flash photolysis.

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1) The preliminary communication of this paper appeared in S. Naruto, O. Yonemitsu, N. Kanamaru, and K. Kimura, *J. Amer. Chem. Soc.*, **93**, 4053 (1971).

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3) *a*) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 5686 (1970); *b*) O. Yonemitsu, H. Nakai, Y. Kanaoka, I.L. Karle, and B. Witkop, *ibid.*, **92**, 5691 (1970); *c*) Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Commun.*, **1971**, 745; *d*) T. Iwakuma, O. Yonemitsu, D.S. Jones, I.L. Karle and B. Witkop, *J. Amer. Chem. Soc.*, **94**, 5136 (1972); *e*) Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **20**, 1164 (1972).

4) T. McCall, G.S. Hammond, O. Yonemitsu, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 6991 (1970).

5) O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi, and B. Witkop, *Photochem. Photobiol.*, **15**, 509 (1972).

6) *cf.* P.B. Ayscough, R.G. Collins, and F.S. Dainton, *Nature*, **205**, 965 (1965); A. Meybeck and J.J. Windle, *Photochem. Photobiol.*, **10**, 1 (1969).

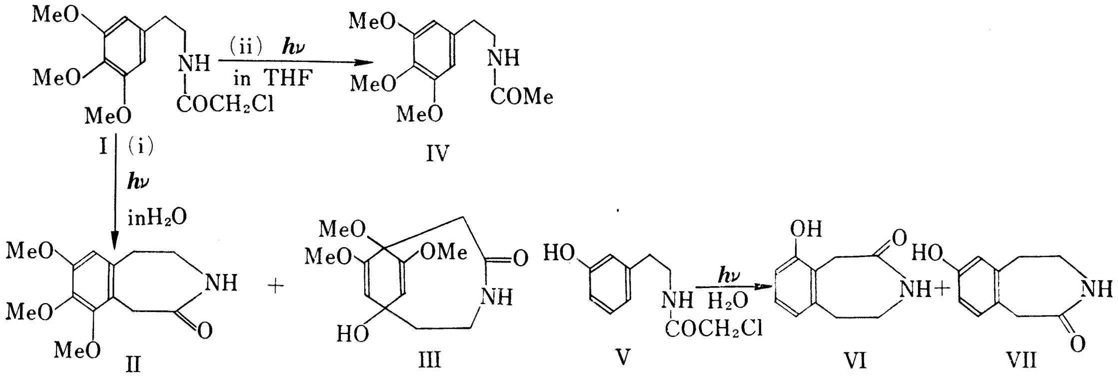

Chart 1

Experimental

Materials——N-Chloroacetyl-*m*-tyramine (V)[7] and phenoxyacetamide (XII)[8] were synthesized and purified according to the published procedures. N-Acetyl-*m*-tyramine (VIII) was synthesized from *m*-tyramine in 2N sodium hydroxide solution with acetyl chloride in the usual manner. Recrystallization from ethyl acetate–*n*-hexane afforded colorless prisms, mp 109—110°. *Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.87; H, 7.41; N, 7.71. IR ν^{Nujol} cm^{-1}: 3390, 1645.

Flash Photolysis——The flash photolysis results were obtained by irradiation of the samples in a cylindrical cell (20-mm i.d., 200-mm spectro light path or length; 10-mm, 260-mm; or 10-mm, 150-mm) with a light flash from two argon-filled lamps placed parallel to the long axis of the cell and operated at 300—600 *J* input. The transient spectra were taken with Shimazu GE-100 grating spectrophotograph on Fuji Neopan SS film (ASA 100) using a spectro flash from a small argon lamp energized at 20—30 *J* input. The half-width of the photolysis flash light and the spectro flash light was *ca.* 5 and 3.5 μsec respectively. The time interval between the two flashes was arbitrarily controlled in the range from 1 μsec to 0.1 sec through a delay circuit. The electric power supply and the trigger pulse generator of this instrument were provided by the Nakano Electric Co. The spectroscopic film were scanned on a Rikagaku-denki MP-3 microphotometer and the photographic density differences were converted to optical density differences.

The decay curves at the peaks of the transient absorptions were measured by recording the cathod currents of a photomultiplier coupled to a Iwasaki Tsushinki SS-5103B memory scope. As a monitoring lamp a 50 W halogen lamp for visible region or a 150 W xenon lamp for ultraviolet region was used.

Result and Discussion

After some unsuccessful trials to get transient absorption spectra of radical-cations by flash photolyses of N-chloroacetylmescaline (I), other methoxy benzene derivatives and indole derivatives, the flash photolysis of an aqueous solution (not degassed) of N-chloroacetyl-*m*-tyramine (V)[9] at room temperature resulted in the appearance of a new absorption spectrum of transient species as shown by a solid curve in Fig. 1. The spectrum consists of two groups with different intensities and life-times. In the alkaline solution at pH 12.4, the phenolate anion of V(Va) also gave almost the same spectrum (a dashed-dotted curve in Fig. 1). However, in the transient absorption spectrum of N-acetyl-*m*-tyramine (VIII) (a dotted curve in Fig. 1), the strong bands at 320—330 nm disappeared, whereas the weak bands at around 400 nm were also observed.

The common weak bands (i=380, 386 and 412 nm; ii=385, 391 and 412 nm; iii=380, 386 and 412 nm) quite close to the absorption bands of the phenoxy radical reported by

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7) O. Yonemitsu, T. Tokuyama, M. Chaykovsky, and B. Witkop, *J. Amer. Chem. Soc.*, **90**, 776 (1968).

8) C.A. Bischoff, *Chem. Ber.*, **34**, 1836 (1901).

9) In the previous paper,[7] it was reported that a 50% aqueous methanol solution of V was irradiated with a 200 W high pressure mercury lamp to yield mainly VII. However, the main product from the flash photolysis in water as determined by gas chromatography was VI (VI: VIII=10: 1).

Grossweiner, *et al.*,[10] *e. g.*, the absorption maxima of the phenoxy radical from *m*-cresol are at 373, 387 and 412 nm. Their estimated life-times (200—400 μsec), though the intensities of the weak bands were too low to determine their accurate life-times, also resemble the value of *m*-cresol ($\tau > 100$ μsec). Therefore these transient weak bands can be assigned to the corresponding phenoxy radical (IX).

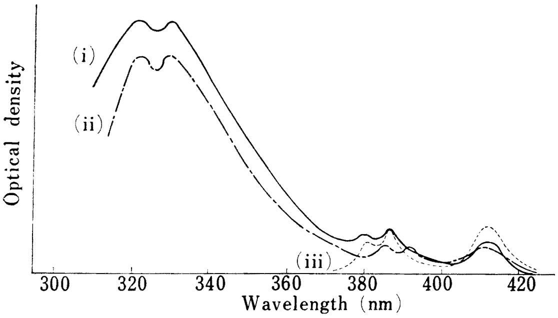

Fig. 1. A Transient Absorption Spectrum obtained with a Delay Time of 5 μsec by the flash Photolysis of N-Chloroacetyl-*m*-tyramine (V) in Water is shown by a Solid Curve (i), in Aqueous Solution at pH 12.4 by a Dashed-dotted Curve (ii) and That of N-Acetyl-*m*-tyramine (VIII) in Water by a Dotted Curve (iii).

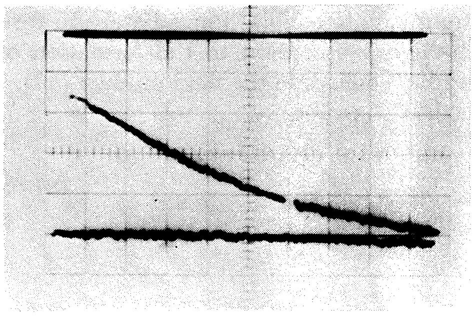

Fig. 2. A Decay Curve of the Cyclohexa-2,4-dienone (X) at $\lambda=320$ nm formed by Flash Photolysis of Aqueous Solution of N-Chloroacetyl-*m*-tyramine (V) (7.6×10^{-5}M) at Room Temperature. The Upper and Lower Lines Indicate 0 % and 100 % Transmittance, Respectively. The Time Scale is 0.2 msec per Main Division.

The slower decay of the strong absorption bands at 322 and 330 nm ($\varepsilon=ca.$ 6500)[11] is attributed to another transient species, which decays according to first-order kinetics ($k=1.9\times10^3$ sec^{-1}, $\tau=530$ μsec) as shown in Fig. 2. In the alkaline solution at pH 12.4, the strong bands also appear at the same positions (322 and 330 nm, $\varepsilon=ca.$ 5500)[11], which decay fairly faster ($k=2.1\times10^4$ sec^{-1}, $\tau=48$ μsec)[12] than in the neutral solution.

This transient species, which was not observed in the photolysis of N-acetyl-*m*-tyramine (VIII), must be a fairly long-lived intermediate in the photocyclization of V, which is considered to be the ground state form of the cyclohexa-2,4-dienone (X) for the following reason. (1) There is no oxygen effect, excluding the posibility of triplet-triplet absorption, because excited triplet states are usually quenched strongly by oxygen.[13] (2) Since the absorption and emmision spectra of *m*-cresol as a model compound of V in water (excitation max=231 and 279 nm; emmision max=298 nm, measured with Hitachi Fluorometer MPF-2A) were unchanged by the addition of excess of chloroacetamide, a charge transfer process can be ruled out. (3) Since the phenoxide anion (Va) gave the same spectrum, a radical cationic form of V cannot be the transient intermediate. (4) The more rapid decay of the transient species under alkaline conditions would be expected, because the rate of the decay probably represents that of deprotonation (enolization) from the dienone (X), which can be accelarated with alkali. (5) The absorption maximun (326 nm, the middle of two maxima) is almost the same as that predicted by Woodward rule for 5,5-dialkyl homoannular conjugated cyclohexadienone

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[10] H.I. Joschek and L.I. Grossweiner, *J. Amer. Chem. Soc.*, **88**, 3261 (1966).

[11] The estimated extinction coefficients were calculated from the optical densities obtained be extrapolating the decay curves to zero time.

[12] In the preliminary communication,[1] we reported on a erroneous result with $k=7\times10^3$ sec^{-1}.

[13] J.G. Calvert and J.N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N.Y., 1966, p. 599.

with an exocyclic double bond (325 nm),[14] and the extinction coefficients are also resonable because those of usual 2,4-cyclohexadienones are in the range between 3000 and 6000.[15]

On the basis of the above evidence combined the results of the quenching[4] and the solvent effect studies,[5] the mechanism of the photocyclization of V is best described as shown in the Chart 2. The phenol moiety of V absorbs almost all of the insident light to form the singlet excited state, from which an ejected electron transfers intramolecularly to the chlorinated amide moiety *via* a loosely bound exciplex to cleave the C-Cl bond. The resultant biradical intermediate couples immediately to form the cyclohexa-2,4-dienone (X). The process from the light absorption to the formation of X seems to proceed very fast. The dienone (X) readily enolizes to the final product (VI). This final process was observed in the flash photolysis in this paper.

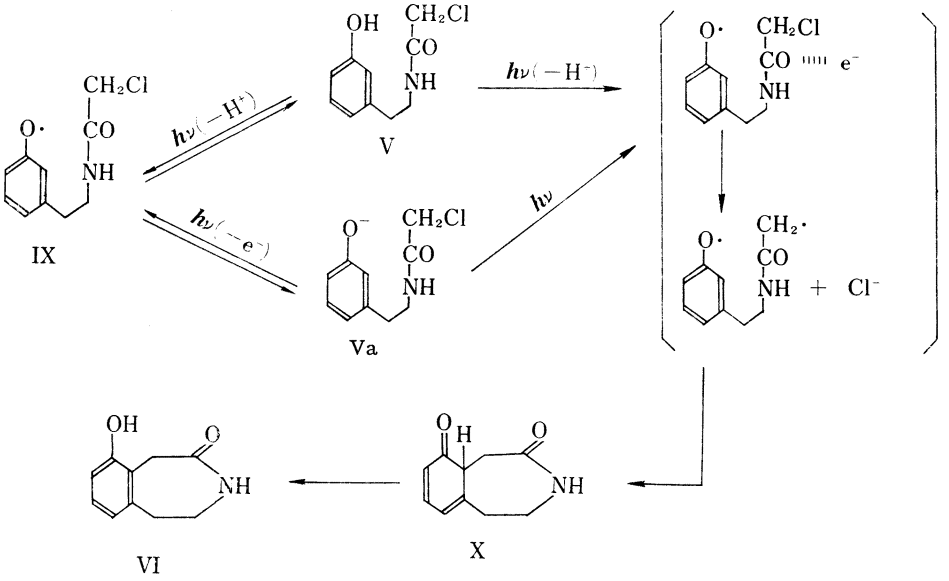

Chart 2

However there is a little doubt on the mechanism, which cannot exclude completely the presence of a ether (XI) in Chart 3 as an intermediate. In fact, on irradiation of phenol with chloroacetamide gave phenoxyacetamide (XII) accompanied mainly with XIII, and XII converted easily to XIII by further irradiation.[16] Moreover, when an aqueous solution of phenoxyacetamide (XII) was flash phtolyzed, as shown in Fig. 3, a similar transient absorption spectrum attributed to a cyclohexa-2,4-dienone (XIV) was observed (λ_{max}=309 and 318 nm), whose decay curve followed first-order kinetics with $k=7.0\times10^3$ sec^{-1}, $\tau=140$ μsec (Fig. 4).

If XI were an intermediate, the photocyclization of V must need at least two photons. However this is not the case. In Fig. 5, the optical density of the cyclohexa-2,4-dienone (X) obtained by extrapolating the decay curve to zero time, is plotted against the exciting light intensity shown in the input energy *J*.[11,17] The fact that the optical density is proportional

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[14] H.H. Jaffe and M. Orchin, "Theory and Application of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York N.Y., 1962, p. 215.

[15] H. Hart and R.M. Lange, *J. Org. Chem.*, **31**, 3776 (1966); E.C. Friedrich, *ibid.*, **33**, 413 (1968); B. Miller, *ibid.*, 35, 4262 (1970); B. Miller, *J. Amer. Chem. Soc.*, **92**, 6252 (1970).

[16] O. Yonemitsu and S. Naruto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1158 (1971).

[17] *cf.* Y. Nakato, N. Yamamoto, and H. Tsubomura, *Bull. Chem. Soc. Japan*, **40**, 2480 (1967).

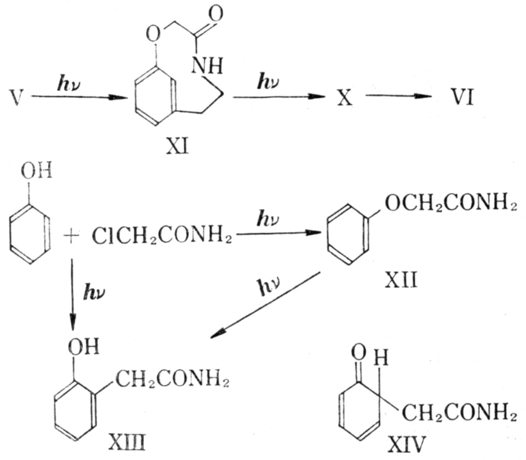

Chart 3

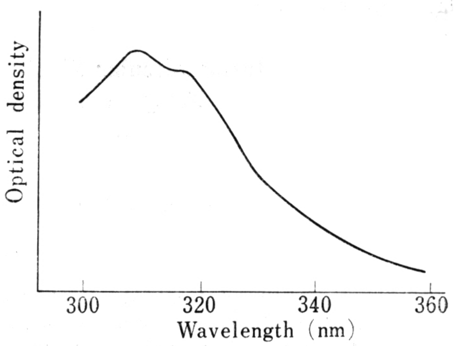

Fig. 3. A Transient Absorption Spectrum obtained by the Flash Photolysis of Phenoxyacetamide (XII) in Water is Shown by a Solid Curve.

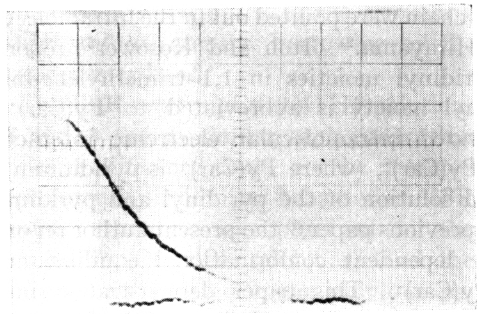

Fig. 4. A Decay Curve of the Cyclohexa-2,4-dienone (XIV) at $\lambda = 309$ nm formed by Flash Photolysis of aqueous Solution of Phenoxyacetamide (XII) (2.14×10^{-4}M) at Room Temperature. The Time Scale is 0.1 msec per Main Division.

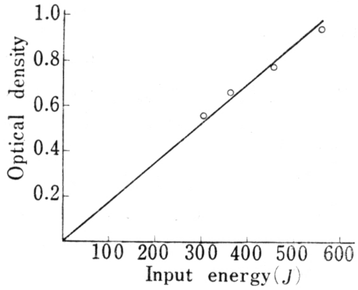

Fig. 5. Relation between the Optical Density of the Transient Absorption at $\lambda = 320$ nm in Aqueous Solution (7.6×10^{-5}M) of N-Chloroacetyl-*m*-tyramine (V) and the Light Intensity (Showed by the Input Energy *J*).

to the light intensity, not to its square, clearly explained that the photocyclization of V proceeds in the single photon mechanism, excluding completely the presence of XI as an intermediate.

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