

# Cage Effect for the Photochemical Formation of the Ten-Membered Lactam from N-Chloroacetyl-3-methoxyphenethylamine

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Photocyclization of N-chloroacetyl-3-methoxyphenethylamine (I) in water gave 7- and 9-methoxy-1,2,4,5-tetrahydro-3H-3-benzazepin-2-ones (V and VI), whereas in organic solvents the main products changed to N-acetyl-3-methoxyphenethylamine (XVII) and 2-oxa-6-azabicyclo[7,3,1]trideca-1(13),9,11-trien-5-one (XIII).

Quantum yield for the formation of V and VI is clearly dependent on the polarity of solvent indicating that the formation of V and VI involves an ionic process. In organic solvents, viscous media favor the formation of XIII. Viscosity dependence in some alcohols is probably an indication of a novel cage reaction operative in the formation of the lactam XIII.

Recent reports<sup>2)</sup> from our laboratory have shown that N-chloroacetylphenethylamines having a methoxy group at C-3 in their aromatic nuclei gave four types of photo-products, benzazepinones (V—X), azabicyclo compounds (XI, XII), ten-membered lactams (XIII—XVI) and N-acetylphenethylamines (XVII—XX), whose yields depend clearly on reaction conditions and solvent. Among the four products, the former two were isolated by the irradiation in aqueous solutions, whereas in anhydrous organic solvents main products were the latter two as shown in Chart I.

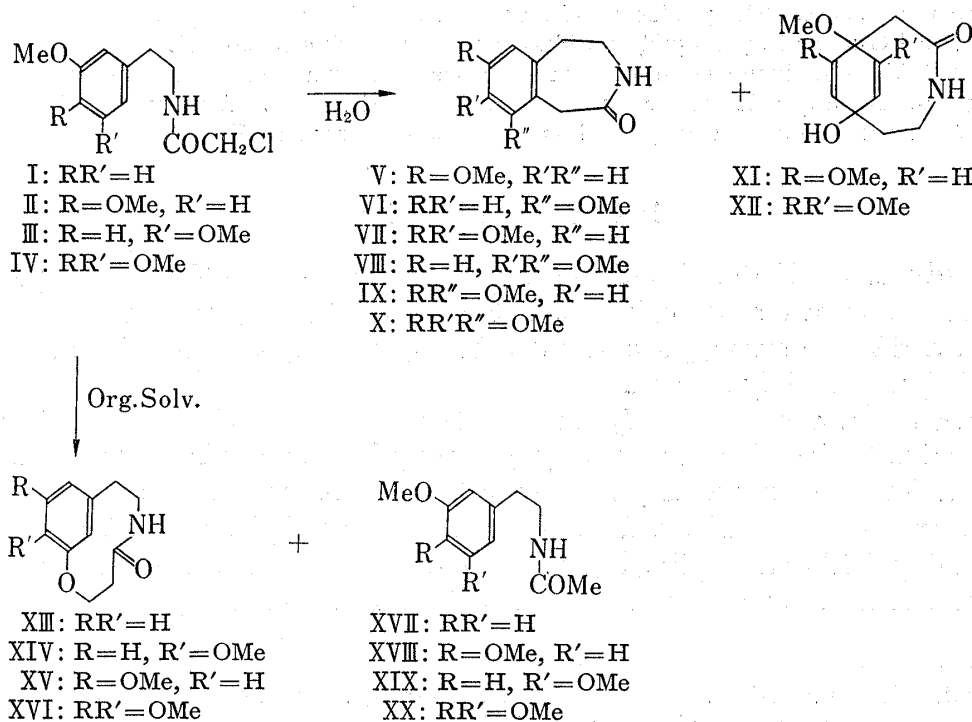


Chart 1

1) Location: Kita-12, Nishi-6, Kita-ku, Sapporo.

2) a) O. Yonemitsu, Y. Okuno, Y. Kanaoka, and B. Witkop, *J. Am. Chem. Soc.*, **92**, 5686 (1972); b) O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi, and B. Witkop, *Photochem. Photobiol.*, **15**, 509 (1972); c) Y. Okuno, K. Hemmi, and O. Yonemitsu, *Chem. Pharm. Bull. (Tokyo)*, **20**, 1164 (1972).

In order to interpret these photo-reactions, we have proposed a dualistic mechanism, electron transfer from the excited singlet state of an aromatic chromophore in aqueous medium and energy transfer in organic solvents to the chloroacetyl moiety, on the basis of fluorescence quenching,<sup>3)</sup> solvent effect<sup>2b)</sup> and flash photolysis.<sup>4)</sup>

We have now studied in detail the effect of oxygen and solvents as a function of polarity and viscosity on the photocyclization of N-chloroacetyl-3-methoxyphenethylamine (I) as a representative compound.<sup>5)</sup>

### Experimental

**N-Chloroacetyl-carbonyl-<sup>14</sup>C-3-methoxyphenethylamine (I)**—To a stirred solution of 75.6 mg (0.8 mmole, 20  $\mu$ Ci) of monochloroacetic acid-1-<sup>14</sup>C in 4 ml of benzene was added at 6–7° 181.6 mg (0.88 mmole) of dicyclohexylcarbodiimide (DCC) in 4 ml of benzene and after 5 min, 133 mg (0.88 mmole) of 3-methoxyphenethylamine. Stirring was continued for 1 hr at the same temperature and for 40 min at room temperature. Four drops of acetic acid was added to decompose excess of DCC, and the mixture was stirred for 2.5 hr. After removal of the precipitated dicyclohexylurea by filtration, the filtrate was washed with dilute hydrochloric acid, water, saturated sodium bicarbonate solution and again water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was dissolved in a small amount of benzene and a trace of the undissolved urea was removed again by filtration. The filtrate was evaporated to leave 189 mg of I as colorless needles, which was further purified by preparative thin-layer chromatography (TLC).

**Photolysis of I**—Aliquots (1 ml) of a 10 mM solution of I in a variety of solvents were transferred from a standard flask to 15  $\times$  1.0 cm quartz tubes. The solution and the free space above the solution were pre-saturated with purified nitrogen<sup>6)</sup> or oxygen. After the tubes were sealed tightly with a rubber stopper, they were placed on a "merry-go-round" apparatus (Rayonet MGR-500) in a thermostat and irradiated with 2537 Å light from a 60 W low pressure mercury lamp (PIL-60, Eikosha, Osaka) for ca. 10 min.

**Quantitative Analysis of Photo-products**—Aliquots (0.04 ml) of an irradiated solution and a small amount of a cold mixture of the starting material (I) and products (V, XIII, XVII), which facilitated to collect the separated zones, were applied as a narrow band using a micropipette on a 20  $\times$  5 cm alumina preparative thin-layer chromatoplate. Twice development with ethanol-ethyl acetate-benzene (1:50:50) gave well separated zones. The products and starting material were obtained by scraping off the zones and analyzed for <sup>14</sup>C content by a liquid scintillation counter (Beckman LS-230).

**Quantum Yields**—Aliquots (1 ml) of 12 mM aqueous potassium ferrioxalate solutions were photolyzed in the merry-go-round apparatus at the same time as the solutions of I. A value of 1.25 was used for the quantum yield of ferrous ion from the potassium ferrioxalate actinometer.<sup>7)</sup>

### Results and Discussion

As already reported,<sup>1b,c)</sup> on irradiation in 10% aqueous ethanol N-chloroacetyl-3-methoxyphenethylamine (I) gave benzazepinones, V (30%) and VI (27%), whereas in ethanol the formation of V and VI was strongly suppressed and N-acetyl compound (XVII) and ten-membered lactam (XIII) were mainly isolated.

In order to learn more precisely solvent effects in the photolysis of I, a 10mM solution of a radioactive I labelled in the carbonyl group by <sup>14</sup>C was irradiated with a 2537 Å light from a 60 W low pressure mercury lamp on a "merry-go-round" apparatus in a thermostat. The radioactive I was synthesized from 3-methoxyphenethylamine and monochloroacetic acid-1-<sup>14</sup>C using DCC as a coupling agent. At the same time, a 12 mM solution of potassium ferrioxalate solution as an actinometer was irradiated in the same apparatus.

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

4) S. Naruto, O. Yonemitsu, N. Kanamaru, and K. Kimura, *J. Am. Chem. Soc.*, **93**, 4053 (1971); S. Naruto and O. Yonemitsu, *Chem. Pharm. Bull. (Tokyo)*, **21**, 629 (1973).

5) The preliminary communication of this paper appeared in Y. Okuno and O. Yonemitsu, *Tetrahedron Letters*, **1974**, 1169.

6) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, 1967, p. 393.

7) C.G. Hatchard and C.A. Parker, *Proc. Roy. Soc. Ser. A*, **235**, 518 (1956).

The quantitative analysis of I and products by gas-liquid chromatography (GLC) was not reliable in terms of accuracy, because they are less volatile. Therefore, the analysis of  $^{14}\text{C}$  contents in radioactive compounds by a liquid scintillation counter was employed to give more reliable results. Quantum yields in the disappearance of the starting material ( $\Phi_1$ ) and the formation of the sum of V and VI ( $\Phi_2$ ), XVII ( $\Phi_3$ ) and XIII ( $\Phi_4$ ) were measured relative to a ferrioxalate actinometer<sup>7)</sup> with a precision of less than  $\pm 5\%$ .

Results on the photolysis of the radioactive I in several protic solvents and tetrahydrofuran in the presence and absence of oxygen, in relation to the dielectric constants and viscosities of the solvents,<sup>8)</sup> are summarized in Table I.

TABLE I. Quantum Yields in the Photolysis of N-Chloroacetyl-3-methoxyphenethylamine (I) under Various Conditions

Solvent	Temperature (°C)	N <sub>2</sub> or O <sub>2</sub>	$\epsilon$	$\eta$ (cp)	Conversion (%)	$\Phi_1$	$\Phi_2$	$\Phi_3$	$\Phi_4$
H <sub>2</sub> O	25	N <sub>2</sub>	78.5	0.89	30.6	0.649	0.547	0.017	0.003
MeOH	25	N <sub>2</sub>	32.6	0.54	22.1	0.469	0.187	0.138	0.054
EtOH	25	N <sub>2</sub>	24.3	1.08	20.7	0.439	0.135	0.171	0.071
EtOH	5	N <sub>2</sub>	27.9	1.6	21.2	0.439	0.123	0.169	0.082
EtOH	15	N <sub>2</sub>	26.2	1.33	21.1	0.445	0.126	0.171	0.080
EtOH	37	N <sub>2</sub>	22.9	0.88	22.6	0.429	0.137	0.173	0.065
EtOH	5	O <sub>2</sub>			14.8	0.306	0.080	0.025	0.058
EtOH	15	O <sub>2</sub>			13.9	0.293	0.085	0.015	0.055
EtOH	25	O <sub>2</sub>			14.8	0.272	0.080	0.014	0.050
EtOH	37	O <sub>2</sub>			15.4	0.293	0.099	0.011	0.047
<i>n</i> -PrOH	25	N <sub>2</sub>	20.1	2.00	20.9	0.443	0.102	0.208	0.091
THF	25	N <sub>2</sub>	7.58	0.46	18.6	0.318	0.029	0.197	0.054

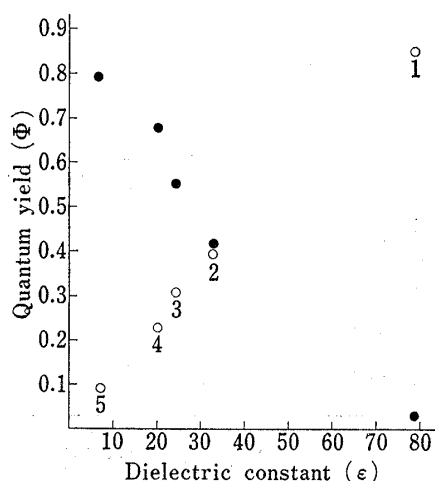


Fig. 1. Quantum Yields for the Formation of V and VI [ $\Phi_1/\Phi_2$ — $\circ$ ] and XVII and XIII [ $(\Phi_3+\Phi_4)/\Phi_1$ — $\bullet$ ] as a Function of the Dielectric Constant ( $\epsilon$ ) of the Solvent: 1, Water; 2, Methanol; 3, Ethanol; 4, *n*-Propanol; 5, Tetrahydrofuran.

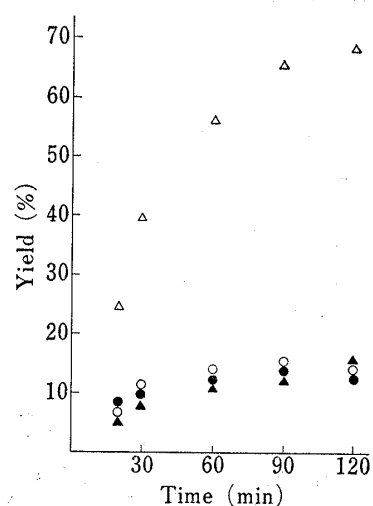


Fig. 2. Yields of XIII and XVII under Nitrogen and Oxygen in the Photolysis of I in Ethanol: XIII under N<sub>2</sub> ( $\circ$ ); XIII under O<sub>2</sub> ( $\bullet$ ); XVII under N<sub>2</sub> ( $\triangle$ ); XVII under O<sub>2</sub> ( $\blacktriangle$ ).

8) J.A. Riddick and W.B. Bunger, "Organic Solvents," Wiley-Interscience, New York, 1970, p. 61; E.W. Washburn, "International Critical Tables," Vol. 6, McGraw-Hill, New York, 1929, p. 85.

### Effect of Solvent Polarity

In Fig. 1 quantum yields for the formation of benzazepinones V and VI ( $\Phi_2$ ) divided by those for the disappearance of I ( $\Phi_1$ ) in the photolysis at 25° are plotted against the dielectric constant ( $\epsilon$ ) of the solvents, which may be one of most reliable indications of the solvent polarity. An approximately linear relationship in Fig. 1 indicates clearly that the process for the formation of V and VI involves an ionic species in the rate-determining step, therefore the electron transfer mechanism proposed already<sup>1b)</sup> may be correct.

The sum of quantum yields for the formation of N-acetyl compound XVII and ten-membered lactam XIII ( $\Phi_3 + \Phi_4$ ) are also plotted in Fig. 1. The plots form approximately a reverse straight line. Since the sum of quantum yields of all products,  $(\Phi_2 + \Phi_3 + \Phi_4)/\Phi_1$ , in the photolysis under nitrogen, is always close to unity, if V and VI arise by an ionic process, XVII and XIII may be formed by a radical process, almost independent of solvent polarity.

### Effect of Solvent Viscosity

In preliminary experiments, the photolysis of I under oxygen-free nitrogen gave N-acetyl compound XVII as a main product in nearly 70% yield, while its formation was strongly suppressed under oxygen, a good radical scavenger,<sup>9)</sup> as shown in Fig. 2. On the other hand, the presence and absence of oxygen did not change the yield of ten-membered lactam XIII. The same result is shown in Table I and Fig. 1 as changes in their quantum yields, and suggestive of that XIII is formed by a mechanism such as cage reaction different from the typical radical process, which acts in the formation of XVII. If the above assumption is correct, the extent of hydrogen abstraction by a free radical, the formation of XVII, should depend on the ease of escape from a solvent cage, while the formation of XIII should be explained as a function of solvent viscosity. Viscous media favor the formation of XIII at the expense of cage escape. In order to avoid unwanted and unknown solvent effects, some protic solvents at 25° and ethanol at different temperatures were chosen as a solvent system in which the viscosity can be varied. In Fig. 3 and 4, quantum yields for the formation of XVII and XIII in the presence and absence of oxygen are plotted against the solvent viscosity ( $\eta$ ).

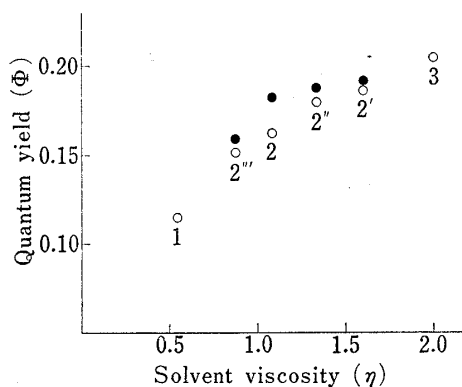


Fig. 3. Quantum Yields for the Formation of XIII ( $\Phi_4/\Phi_1$ ) as a Function of the Solvent Viscosity ( $\eta$ ) in the Presence (●) and Absence (○) of Oxygen: 1, in Methanol at 25°; 2, in Ethanol at 25°; 2', in Ethanol at 5°; 2'', in Ethanol at 15°; 2''', in Ethanol at 37°; 3, in *n*-Propanol at 25°

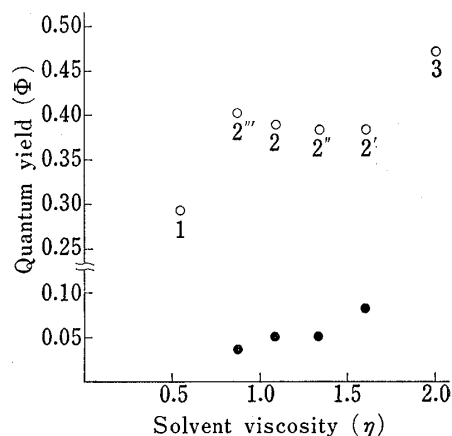


Fig. 4. Quantum Yields for the Formation of XVII ( $\Phi_3/\Phi_1$ ) as a Function of the Solvent Viscosity ( $\eta$ ) in the Presence (●) and Absence (○) of Oxygen: 1, in Methanol at 25°; 2, in Ethanol at 25°; 2', in Ethanol at 5°; 2'', in Ethanol at 15°; 2''', in Ethanol at 37°; 3, in *n*-Propanol at 25°

9) J.G. Calvert and J.N. Pitts, Jr., "Photochemistry," Wiley, New York, 1967, p. 393; D.P. Dingley and J.G. Calvert, *J. Am. Chem. Soc.*, **85**, 856 (1963).

In the formation of XIII, the variation both of solvent and of temperature in ethanol forms nearly a single straight line (Fig. 3), and Fig. 4 shows that XVII forms through an ordinary radical reaction. This clear viscosity dependence is suggestive of the following pathway, including a novel cage mechanism leading to XIII.

When I is irradiated by a 2537 Å light, almost all of the incident light is absorbed by the methoxybenzene nucleus to cause the formation of its singlet excited state, from which an energy transfers to the chloroacetyl group *via* an intramolecular exciplex (I\*) at least in organic solvents.<sup>9)</sup>

Homolytic cleavage of the carbon-chlorine bond in the excited chloroacetyl group forms the radical intermediate (XXI) together with the chlorine radical in a solvent cage. The radical (XXI) escapes from the solvent cage and abstracts a hydrogen from a hydrogen donating solvent such as ethanol and tetrahydrofuran to form N-acetyl compound (XVII). At this hydrogen abstraction process the added oxygen acts as a radical scavenger. With increasing the viscosity of solvents the rate of the cage escape decreases to result in an increase of the formation of XIII.

In the solvent cage, the chlorine radical may abstract a hydrogen atom from the *m*-methoxy residue, probably because of its proximity to the carbon-chlorine bond in the exciplex I\*, to form a diradical (XXII) and hydrogen chloride. The diradical (XXII) then recombines intramolecularly to result in the formation of ten-membered lactam (XIII).

To the best of our knowledge this type of hydrogen abstraction by a chlorine radical within the solvent cage seems to be without precedent. Related, but not the same, examples of hydrogen abstraction within the solvent cage are provided in the initial step of the Barton reaction,<sup>10)</sup> and probably of the Hofmann-Löffler reaction<sup>11)</sup> and the hypochlorite reaction.<sup>12)</sup> They may proceed *via* a favorable quasi-six-membered transition state,<sup>13)</sup> however, larger and smaller ring transition states are always unfavorable for these reactions. If the same type of reaction takes place in the photolysis of I, intramolecular hydrogen abstraction of XXI to form XXIII (process b in Chart 2) must occur through an eleven-membered transition state. Therefore this may be ruled out.

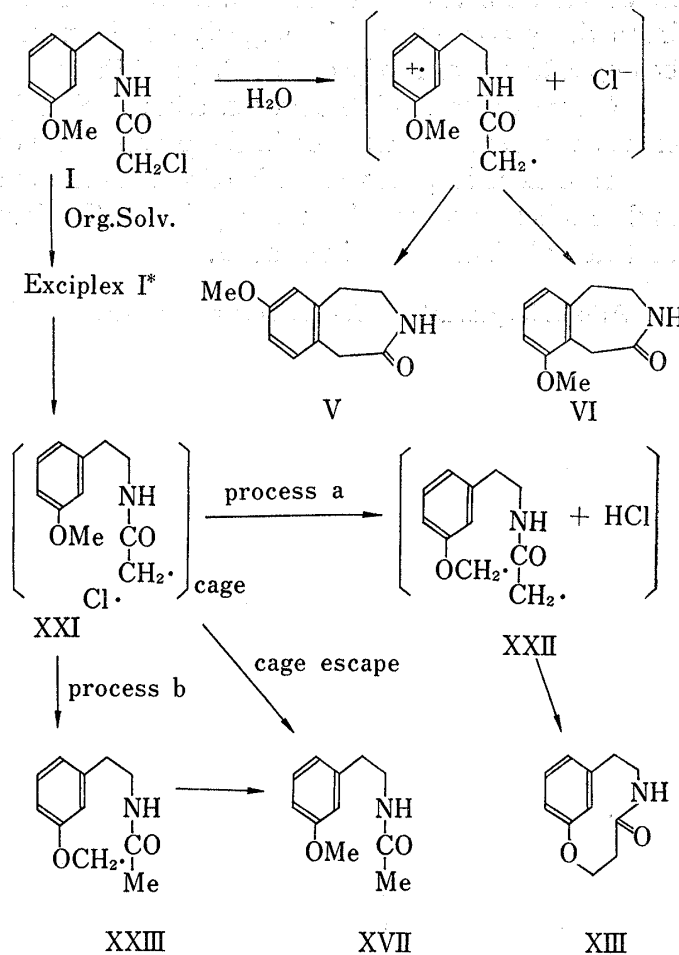


Chart 2

- 10) D.H.R. Barton, J.M. Beaton, L.E. Geller, and M.M. Pecket, *J. Am. Chem. Soc.*, **82**, 2640 (1960); *idem*, *ibid.*, **83**, 4076 (1961); M. Akhtar and M.M. Pecket, *ibid.*, **86**, 265 (1964).
- 11) R.S. Neale, M.R. Walsh, and N.L. Marcus, *J. Org. Chem.*, **30**, 3683 (1965).
- 12) C. Walling and A. Padwa, *J. Am. Chem. Soc.*, **85**, 1597 (1963).
- 13) E.J. Corey and W.R. Hertler, *J. Am. Chem. Soc.*, **82**, 1657 (1970).

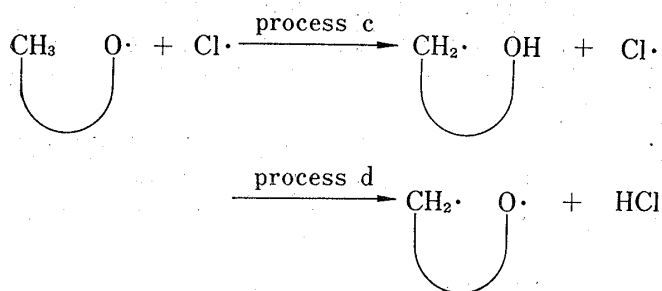


Chart 3

The most important reason of the formation of XIII, which is quite unusual in ordinary thermal and photochemical reactions, may lie in the formation of the intramolecular exciplex I\*, in which the methoxy group and the chlorine lie close together.

Another reason may be provided by a consideration of the reaction heat estimated from bond dissociation ene-

rgies. Although the reactions being discussed here are difficult to say to be true free radical reactions, the use of dissociation energies of simple molecules may be allowed as an approximation.<sup>14)</sup>

In the hypochlorite reaction, which is the most similar to the photolysis of I, there is no difference between process c and process d in Chart 3 judging by the energy calculation. Both the processes may be slightly exothermic. The predominance of the process c may be dependent exclusively on the shape of its transition state.

On the other hand, the process a in the photolysis of I may proceed as a *ca.* 13 kcal/mole exothermic reaction, whereas in the process b no energy gain is expected.

In conclusion, on the basis of the results and discussion presented here the pathways and mechanisms for the photolysis of N-chloroacetyl-3-methoxyphenethylamine (I) are best described as shown in Chart 2.

**Acknowledgement** The authors are grateful to the Takeda Science Foundation for financial support.

14) J.A. Kerr, *Chem. Rev.*, **66**, 465 (1966).