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PHOTOCYCLIZATION OF N-CHLOROACETYL-3-METHOXYPHENETHYLAMINE.
VISCOSITY DEPENDENCE OF THE FORMATION OF THE TEN-MEMBERED LACTAM

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For the photolysis of N-chloroacetylphenethylamines, which afforded many novel heterocycles[1] we have proposed a dualistic mechanism, on the basis of fluorescence quenching,[2] flash photolysis[3] and solvent effect studies,[4] *viz.*, intramolecular electron or energy transfer from the aromatic systems to the chloroacetylamine *via* an exciplex.[3,4]

As reported,[4] photolysis of N-chloroacetyl-3-methoxyphenethylamine (1) *in aqueous solution* gave two benzazepinones (2a and 2b), while *in organic solvents* the formation of 2 decreased markedly and the N-acetyl compound 3 and the ten-membered lactam 4 became the main products. We now wish to report a detailed study of solvent effects as a function of polarity and viscosity, suggestive of a novel cage reaction operative in the formation of the lactam 4.

Table I. Quantum Yields in the Photolysis of N-Chloroacetyl-3-methoxyphenethylamine (1) under Various Conditions.

Solvent	Temperature	N_2 or O_2	ε	η	Φ1	Φ2	Φ3	Φ4
H_2O	25°C	N_2	78.5	0.89	0.649	0.547	0.017	0.003
MeOH	"	"	32.6	0.54	0.469	0.187	0.138	0.054
EtOH	"	"	24.3	1.08	0.439	0.135	0.171	0.071
"	5	"	27.9	1.6	0.439	0.123	0.169	0.082
"	15	"	26.2	1.33	0.445	0.126	0.171	0.080
"	37	"	22.9	0.88	0.429	0.137	0.173	0.065
"	5	O_2			0.306	0.080	0.025	0.058
"	15	"			0.293	0.085	0.015	0.055
"	25	"			0.272	0.080	0.014	0.050
"	37	"			0.293	0.099	0.011	0.047
n-PrOH	25	N_2	20.1	2.00	0.443	0.102	0.208	0.091
THF	"	"	7.58	0.46	0.318	0.029	0.197	0.054

A 10 mM solution of 1 labelled in the carbonyl group by ^{14}C was irradiated in several protic solvents or in tetrahydrofuran under nitrogen[5] with a 2537 A light (60 W low pressure mercury lamp) on a "merry-go-round" apparatus.[6] The quantum yields for the disappearance of 1 ($\Phi 1$) and the formation of products, 2a and 2b ($\Phi 2$), 3 ($\Phi 3$) and 4 ($\Phi 4$), in relation to the dielectric constants and viscosities of the solvents[7] are summarized in Table I.

The formation of 2 is clearly dependent on the polarity of the solvent, and an approximately linear relationship exists between $\Phi 2/\Phi 1$ and the dielectric constant. This indicates that the formation of 2 may involve an ionic process. On the other hand, the formation of 3 and 4 has a reverse tendency. If 2 arises by an ionic process, 3 and 4 may be formed by a radical process, almost independent of solvent polarity (Fig. 1).

In preliminary experiments,[3] the formation of the N-acetyl compound 3 by hydrogen abstraction was strongly suppressed by oxygen, a good radical scavenger, while the presence of oxygen did not alter the yield of the ten-membered lactam 4. Compound 4, therefore, arises by a different mechanism such as a cage intermediate. Quantum yields in some protic solvents at 25° and different temperature in ethanol, in the presence and absence of oxygen, are all summarized in Table I. $\Phi 4/\Phi 1$ ratios are plotted against solvent viscosity in Fig. 2. The clear viscosity

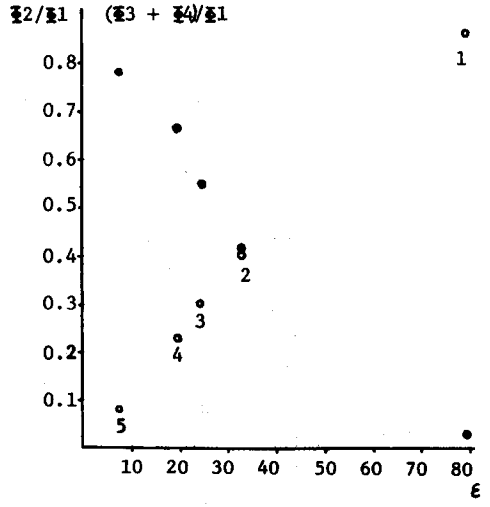


Figure 1. Quantum yields for the formation of 2 [$\Phi 2/\Phi 1$ --- ○] or 3 and 4 [$(\Phi 3 + \Phi 4)/\Phi 1$ --- ●] as a function of the dielectric constant (ε) of the solvents: 1, water; 2, methanol; 3, ethanol; 4, n-propanol; 5, tetrahydrofuran.

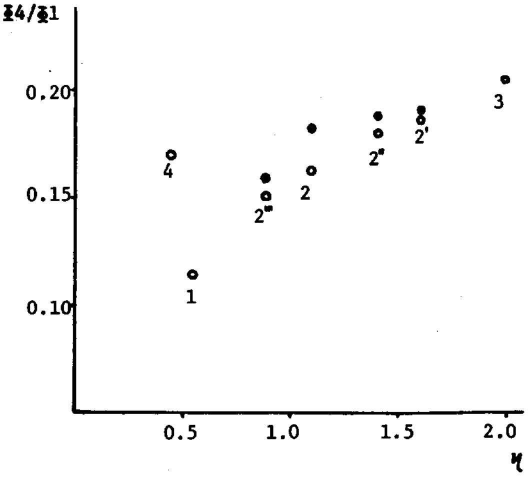
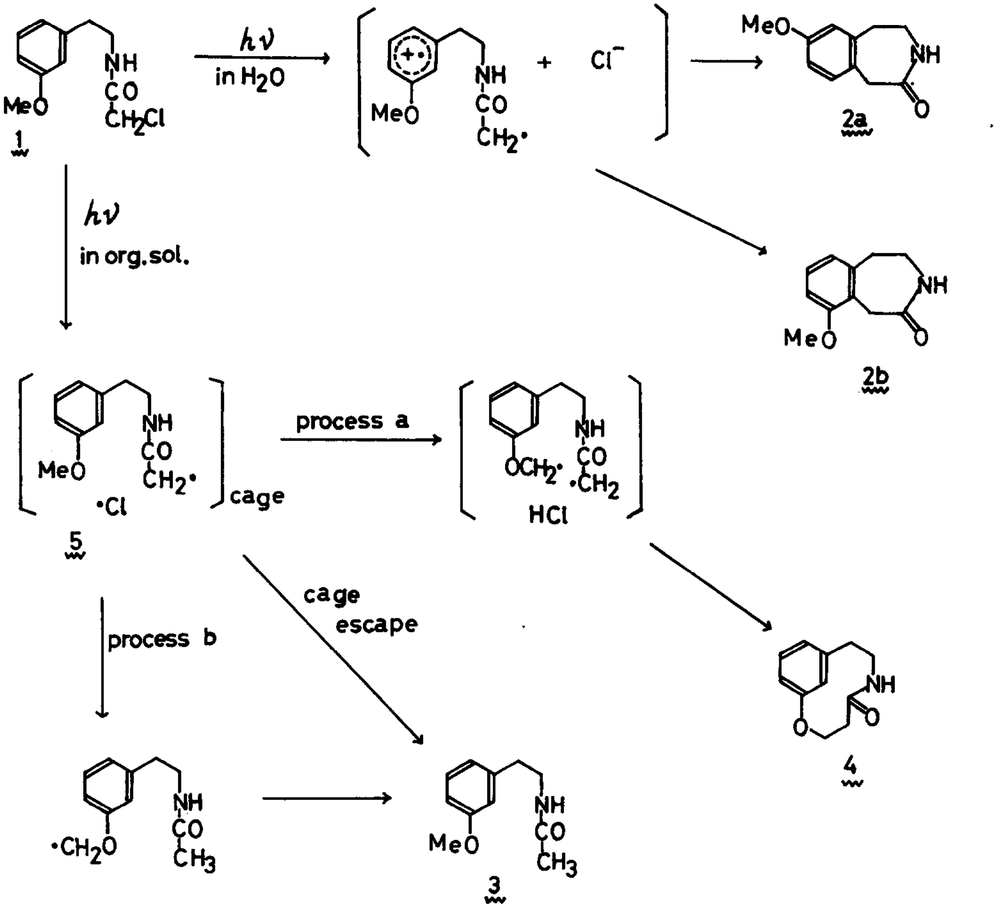


Figure 2. Quantum yields for the formation of 4 ($\Phi 4/\Phi 1$) as a function of the solvent viscosity (η) in the presence (●) or absence (○) of oxygen: 1, in methanol at 25°; 2, in ethanol at 25°; 2', at 5°; 2'', at 15°; 2''', at 37°; 3, in n-propanol at 25°; 4, in tetrahydrofuran at 25°.

dependence, at least in protic solvent,[8] is suggestive of the following pathway leading to **4**: Intramolecular energy transfer from the excited aromatic chromophore to the chloroacetyl group, homolytic cleavage of the carbon-chlorine bond, formation of the radical intermediate **5** together with the chlorine radical in a solvent cage. The chlorine radical may then abstract a hydrogen atom from the *m*-methoxy residue, probably because of its proximity to the carbon-chlorine bond in the exciplex **1***. Intramolecular recombination of the resultant diradical then



leads to the ten-membered lactam **4**. This type of hydrogen abstraction by a chlorine radical within the solvent cage seems to be without precedent. The initial step of the Barton reaction,[9] and probably the Hofmann-Löffler[10] and the hypochlorite reactions[11] provide related examples of hydrogen abstraction within the solvent cage. They may proceed *via* a favorable quasi-six-membered transition state. Different from these reactions, intramolecular hydrogen abstraction of the intermediate **5** (process b) may be ruled out because it must occur through an eleven-membered transition state. Energy calculations from bond-energy data[12] show that process b is more unfavorable than process a, which produces an energy gain of at least 15 Kcal/mol.

In conclusion, for the photolysis of N-chloroacetyl-3-methoxyphenethylamine (**1**) we favor the pathways and mechanisms shown in the scheme.

REFERENCES

1) T. Iwakuma, H. Nakai, O. Yonemitsu, D. S. Jones, I. L. Karle and B. Witkop, *J. Amer. Chem. Soc.*, **94**, 5136 (1972), and references cited therein.
2) T. McCall, G. S. Hammond, O. Yonemitsu and B. Witkop, *ibid.*, **92**, 6991 (1970).
3) S. Naruto, O. Yonemitsu, N. Kanamaru and K. Kimura, *ibid.*, **93**, 4053 (1971).
4) O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi and B. Witkop, *Photochem. Photobiol.*, **15**, 509 (1972).
5) A solution presaturated with purified nitrogen gave practically the same result with a degassed solution.
6) Since the quantitative analysis of **1** and products by vpc was not reliable in terms of accuracy, the ^{14}C content was determined by a liquid scintillation counter. The labelled **1** was synthesized from monochloroacetic acid-1-^{14}C and 3-methoxyphenethylamine with DCC. After irradiation of the labelled **1** (less than 20% conversion), the reaction mixture was separated by alumina preparative tlc and analyzed for ^{14}C content by a liquid scintillation counter. Quantum yields, with a precision of less than ± 5%, were measured relative to a ferrioxalate actinometer.
7) "Techniques of Chemistry" ed. by A. Weissberger, Vol. II, "Organic Solvents" by J. A. Riddick and W. B. Bunger, p 61 (1970), Wiley-Interscience, New York; "International Critical Tables", Vol. 6, p 85, McGraw-Hill (1929).
8) The apparent deviation in tetrahydrofuran may be caused by the low dielectric constant of the solvent.
9) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pecket, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961); M. Akhtar and M. M. Pecket, *ibid.*, **86**, 265 (1964).
10) R. S. Neale, M. R. Walsh and N. L. Marcus, *J. Org. Chem.*, **30**, 3683 (1965).
11) C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1597 (1963).
12) J. A. Kerr, *Chem. Ber.*, **66**, 465 (1966).