[Chem. Pharm. Bull. 28(3) 900—909 (1980)]

Photochemical Synthesis of Azepinoindoles and Azocinoindoles from N-Chloroacetylindolylethylamines, and a Mechanistic Study based on the Correlation between Quantum Yields and Calculated Frontier Electron Densities of Indole Radicals[1]

SHUNJI NARUTO[2a] and OSAMU YONEMITSU[2b]

Central Research Laboratories, Sankyo Co.[2a] *and Faculty of Pharmaceutical Sciences, Hokkaido University*[2b]

(Received September 28, 1979)

On irradiation in 50% aqueous ethanol, the N-chloroacetyl derivatives of seven isomeric indolylethylamines gave the corresponding azepinoindole and azocinoindole derivatives through photocyclization at the *ortho* and *peri* positions. Quantum yields for product formation with 2537 Å light showed the relative reactivity at each position of the indole ring to be in the order 3>6,4>7,2>5>1. In order to identify the reactive intermediary species and to establish the mechanism of the photocyclizations, frontier electron densities of several species of indole were calculated by CNDO/2 and INDO. The quantum yields for product formation from 1-substituted indole derivatives correlated fairly well (correlation coefficient $r=0.82$) with the singly occupied molecular orbitals (SOMO) electron densities (ED) of the 1-methylindole radical cation, but there was a better correlation ($r=0.90$) between the quantum yields for product formation from 1-unsubstituted compounds and the SOMO-ED of the indole-1-radical. These results show that the mechanism of the photocyclization of N-chloroacetylindolylethylamines involves both indole radical cations and indole-1-radicals as reactive intermediary species.

Keywords——photocyclization; azepinoindole; azocinoindole; quantum yield; MO calculation; indole radical cation; indole-1-radical

Since the photocyclization of N-chloroacetyltryptophan to the azocinoindole derivative was first found,[3] it has been extended to N-chloroacetyl derivatives of aromatic amino acids and pharmacodynamic amines having electron-donating substituents on aromatic rings to give many heterocyclic compounds.[4] Many mechanistic studies based on fluorescence quenchings,[5] solvent effects,[6] flash photolyses,[7] and kinetics[8] have shown that the mechanism involves intramolecular electron transfer or exciplex formation between the excited singlet state of the electron-donating aromatic chromophore and the electron-deficient chloroacetyl moiety.

The intermolecular photoreaction of indole and methyl chloroacetate gave the seven isomeric methyl indoleacetates,[9] though in very poor yields. The calculated electron spin densities appeared to reflect the reactivity of each position on the indole ring, but the yields were too poor to permit definite conclusions. In the present work, the photoreactions of seven isomeric N-chloroacetylindolylethylamines were examined in order to synthesize novel azepinoin-

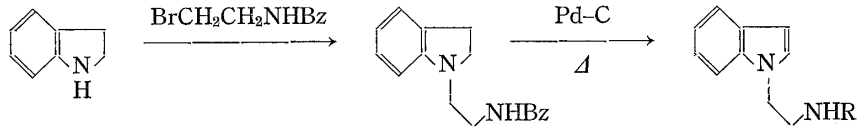
1) A preliminary communication of this work was reported in S. Naruto and O. Yonemitsu, *Tetrahedron Lett.*, **1975**, 3399.
2) Location: *a*) *Hiromachi, Shinagawa-ku, Tokyo 140, Japan*; *b*) *Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan.*
3) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 3941 (1966).
4) T. Hamada, Y. Okuno, M. Ohmori, T. Nishi, and O. Yonemitsu, *Heterocycles*, **8**, 251 (1977), and references cited therein.
5) M.T. McCall, G.S. Hammond, O. Yonemiteu, and B. Witkop, *J. Am. Chem. Soc.*, **92**, 6991 (1970).
6) O. Yonemitsu, H. Nakai, Y. Okuno, S. Naruto, K. Hemmi, and B. Witkop, *Photochem. Photobiol.*, **15**, 509 (1972); Y. Okuno and O. Yonemitsu, *Chem. Pharm. Bull.*, **23**, 1039 (1975).
7) S. Naruto, O. Yonemitsu, N. Kanamaru, and K. Kimura, *J. Am. Chem. Soc.*, **93**, 4053 (1971); S. Naruto and O. Yonemitsu, *Chem. Pharm. Bull.*, **21**, 629 (1973).
8) N. Numao, T. Hamada, and O. Yonemitsu, *Tetrahedron*, **43**, 1889 (1978).
9) S. Naruto and O. Yonemitsu, *Tetrahedron Lett.*, **1971**, 2297; *idem*, *Chem. Pharm. Bull.*, **20**, 2163 (1972).

doles and azocinoindoles as well as to clarify the reactivity of each position of indole and to establish the meachnism.

Results and Discussion

Photocyclization of N-Chloroacetylindolylethylamines to Azepinoindoles and Azocinoindoles

The starting materials, indolylethylamines, were synthesized as follows: indoline (**1**) was treated with N-benzoyl-2-bromoethylamine (**2**) to give **3**,[10] which was heated with Pd–C to give aromatized **4**, followed by hydrolysis to 1-indolylethylamine (**5**). The other amines (except for the 3-substituted compound, which is commercially available) were prepared from the corresponding indolylaldehydes in the manner described by Troxler.[11] 1-Methyl derivatives of 5- (**7**) and 6-indolylethylamines (**8**) were prepared from the acetates[12] by treatment with methyl iodide in the presence of sodium hydride, followed by hydrolysis.



1 **3** **4**: R=Bz **5**: R=H

Chart 1

The amines were treated with chloroacetic acid in the presence of dicyclohexylcarbodiimide in tetrahydrofuran to give readily the corresponding N-chloroacetylindolylethylamines (**9**—**15**); physical data for these compounds are given in the experimental section.

When a 50% aqueous ethanol solution of N-chloroacetyl-1-indolylethylamine (**9**, 12.7 mM) and potassium carbonate (9.6 mM) was irradiated with a 400 W high pressure mercury lamp for 1.5 hr, *ortho* and *peri* photocyclizations occurred. After separation by silica gel column chromatography, the azepinoindole (**16**), the azocinoindole (**17**), and the N-acetate (**18**) were isolated (though only in 9.9, 16.3, and 2.6% yields, respectively) with 6.8% recovery of the starting material (**9**). The structures of **16** and **17** were determined on the basis of their spectral data, especially the nuclear magnetic resonance (NMR) spectra. The C(6)-H signal (δ 6.30 ppm, singlet) of **16** is clearly different from the C(7)-H signal (6.43 ppm, doublet, J=3 Hz) of **17**.

On similar irradiation, **10** gave **19** (31.3%) as the only isolable cyclization product and **20** (3.7%) with recovery of **10** (17.3%). In the NMR spectrum of **19**, the original C(3)-H signal of **10** was absent. No cyclization at the indolic N position was detected.

Although the irradiation of N-chloroacetyl derivatives of tryptophan and 5-methoxytryptamine gave only the corresponding azocinoindole derivatives,[3,13] on irradiation of the tryptamine derivative (**11**),[14] two cyclization products, **21** (3.8%) and **22** (22%), the N-acetate (**23**, 0.9%), and the starting **11** (2.5%) have now been isolated.[15] The NMR spectrum of **22** has a singlet signal (7.07 ppm) of C(2)-H, whereas no corresponding signal was observed in the spectrum of **21**.

10) *Cf.* J. Blake, J.R. Tretter, G.J. Juhasz, W. Bonthrone, and H. Rapoport, *J. Am. Chem. Soc.*, **88**, 4061 (1966).
11) F. Troxler, A. Harnisch, G. Bormann, F. Seemann, and L. Szabo, *Helv. Chim. Acta*, **51**, 1616 (1968).
12) S. Naruto and A. Terada, *Chem. Pharm. Bull.*, **23**, 3184 (1975).
13) T. Kobayashi, T.F. Spande, H. Aoyagi, and B. Witkop, *J. Med. Chem.*, **12**, 636 (1969).
14) J.V. Braun, A. Bahn, and W. Münch, *Chem. Ber.*, **62**, 2766 (1929).
15) The results of quantitative analyses by high-speed liquid chromatography (HSLC) are as follows: **21** (6.8%), **22** (45%), **23** (1%), and **11** (7.4%).

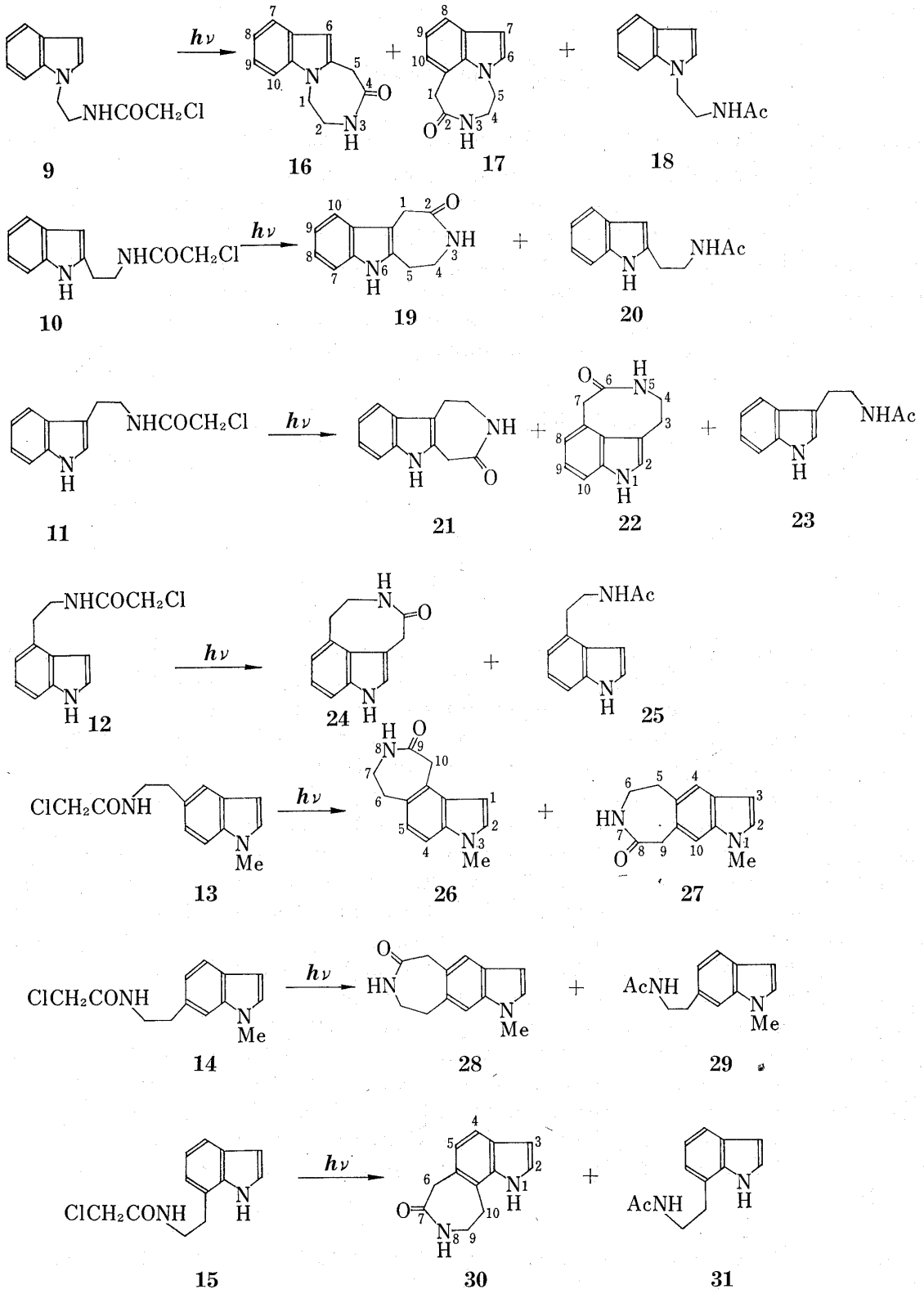


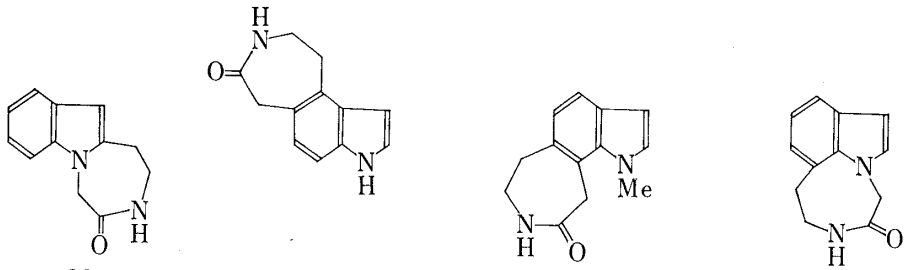
Chart 2

Compound **12** again gave the *peri* cyclization product (**24**, 33%).[16] Its NMR spectrum also has the C(2)-H singlet signal (7.33 ppm) but not the signal which was assigned to C(3)-H of the starting material (**12**).

Compound **13** gave two *ortho* cyclization products, **26** (15.6%) and **27** (30%),[17] which are easily differentiated in terms of the NMR spectra. Compound **26** has AB protons at 6.85 and 7.13 ppm (J=9 Hz) assignable to C(4)- and C(5)-H, whereas **27** has two singlets (7.30 and 7.40 ppm) due to C(4)- and C(10)-H.

Compound **14** gave the cyclization product (**28**) though in very poor yield (7.8%) with **29** (2.3%) and recovery of **14** (3.9%).

Finally, **15** gave **30** (37.8%) and **31** (5.2%), with recovery of **15** (9%). Again, no cyclization product at the indolic N position was observed.

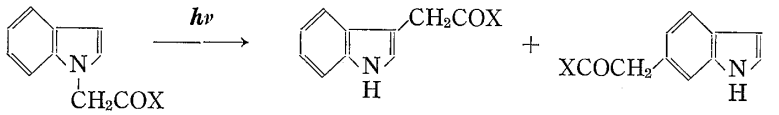


32 **33** **34** **35**

Chart 3

Although the yields were unsatisfactory, these photocyclizations are potentially useful because of the direct formation of novel ring systems.[18] No traces of the expected four compounds (**32**—**35**) were detected even by high-speed liquid chromatography (HSLC).

On irradiation, methyl indole-1-acetate (**36**) and indole-1-acetamide (**37**) are known to rearrange mainly to the corresponding 3- (**38**, **39**) and 6-substituted compounds (**40**, **41**).[19] This type of photorearrangement appeared to be responsible for the failure to detect **32** and **35**. However, this is not the case, because the observed quantum yield for the disappearance of **37** (ϕ=0.053) is too small to remove completely the initially formed **32** and **35** through absorption of the second proton, and hence the indolic N position must have no reactivity in these photocyclizations.



36: X=OMe
37: X=NH_2

38: X=OMe
39: X=NH_2

40: X=OMe
41: X=NH_2

Chart 4

Based on the above data, the relative order of reactivity of each position on the indole ring can be roughly expressed as 3, 4, 6>2, 5, 7>1.

16) HSLC analysis: **24** (70%), **25** (0.5%), and **12** (1%).
17) HSLC analysis: **26** (24.2%), **27** (39.2%), and **13** (24.9%).
18) Better results were obtained in the quantitative analyses by HSLC; for example, the analytical yield of **24** was 70%, though the isolation yield was only 33%.
19) S. Naruto and O. Yonemitsu, *Chem. Pharm. Bull.*, **20**, 2272 (1972).

Table I. Quantitative Reeults of Photocyclization of N-Chloroacetylindolylethylamines and Quantum Yields for Disappearance of the Starting Materials and for Formation of the Cyclizationo Prducts[a]

Compound	Concentration[b] mM	Yield, % 4 min	8 min	12 min	Quantum yield	Cyclization position[c]
9	1.964	73.0	57.1	44.8	0.233	
16		6.2	9.3	10.2	0.062[d]	2
17		10.7	18.9	23.3	0.108	7
10	1.920	73.8	55.2	36.5	0.253	
32		0	0	0	0	1
19		25.4	41.5	55.6	0.250	3
11	1.768	74.6	55.2	35.0	0.230	
21		2.7	5.5	7.2	0.025	2
22		16.5	33.1	40.7	0.150	4
12	1.902	74.7	51.9	34.0	0.277	
24		27.8	48.6	59.9	0.271	3
33		0	0	0	0	5
13	2.050	76.4	52.1	24.9	0.274	
26		8.4	13.6	15.2	0.088	4
27		17.1	30.2	34.2	0.180	6
14	1.931	59.8	46.0	38.7	0.270	
28		5.1	8.6	10.5	0.051	5
34		0	0	0	0	7
15	1.910	69.7	49.2	34.4	0.293	
30		12.5	23.4	27.3	0.122	6
35		0	0	0	0	1

a) The average light intensity at 253.7 nm was 8.1×10^{-9} einstein/sec.
b) Initial concentration of the starting materials.
c) Position of bond formation on the indole ring in the process of photocyclization.
d) This result is unreliable because of the instability of **16**.

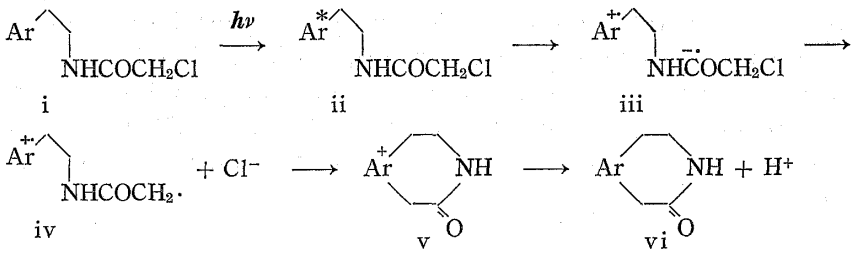


Chart 5

Table II. Frontier Electron Densities of Several Species of Indole

Position	Indole[a]	SOMO of radical cation[b] Indole	1-Methylindole	SOMO of indole-1-radical[b]
1	0.2066	0.0058	0.0126	0.1062(0, 0)
2	0.3510	0.2004	0.2016(0.062)[c]	0.1258(0.025)
3	0.3007	0.1176	0.1334	0.2818(0.250, 0.271)
4	0.3300	0.0642	0.0750(0.088)	0.1200(0.150)
5	0.0129	0.0468	0.0330(0.051)	0.0004(0)
6	0.3322	0.2196	0.2122(0.180)	0.1636(0.122)
7	0.3031	0.0396	0.0516(0.108, 0)	0.0686

a) Reactivity index[21] calculated by CNDO/2.[22]
b) Calculated by INDO.[24]
c) This result is unreliable because of the instability of **16**.
d) Values in parentheses are the quantum yields taken from the data in Table I.

Correlation between Quantum Yields and Calculated Electron Densities. A Mechanistic Study

In order to clarify the mechanism, quantum yields for the disappearance of the starting materials and for the formation of the cyclization products were first meausred using a ferrioxalate actinometer[20] with 253.7 nm monochromatic light (Table I).

The quantum yields for product formation can be considered to reflect the reactivity of each position on the indole ring in bond formation in the photocyclization, and accordingly a more accurate estimate of the relative order of reactivity is 3>6, 4>7, 2>5>1 on the basis of the data in Table I.

A common mechanism in these type of photocyclizations involves intramolecular electron transfer from the excited singlet state of an aromatic chromophore to the chloroacetyl moiety, cleavage of the C-Cl bond, and radical coupling between the aromatic radical cation and the methylene radical with loss of a proton, as shown in the following scheme.[5,6,7,8]

The reactivity of the position on the aromatic ring to which the methylene radical couples is determined in the step from iv to v, and may correspond to the old electron density. In order to confirm whether the above mechanism is operative in the photocyclizations presented here or not and to narrow down the real reactive intermediary species, the frontier electron densities of several species of indole in relation to radical reactions were calculated (Table II).

The reactivity index [$fr=(LV)^2+(HO)^2$] of the ground state molecule of indole for radical reactions[21] was first calculated by CNDO/2,[22] but the calculated values (the second column of Table II) did not show a satisfactory correlation with the quantum yields for the products (correlation coefficient $r=0.45$). Therefore, indole in its ground state appears not to be the reactive species, as expected from the proposed mechanism.

In view of the proposed mechanism, electron densities (ED) of singly occupied molecular orbitals (SOMO)[23] were next calculated by INDO.[24] ED values of radical cations of indole and 1-methylindole were calculated, since the calculation for substituted indoles was quite difficult. The results are listed in the third and forth columns in Table II. A very close correlation ($r=0.99$) between the values in the two columns was observed.[25] Again, the ED values showed no simple relation with the quantum yields. However, the quantum yields for the products (**17**, **26**, **27**, **28**, **34**) derived from 1-substituted starting materials (**9**, **13**, **14**) correlated fairly well ($r=0.82$) with the SOMO-ED values of the 1-methylindole radical cation (Fig. 1).

Although the quantum yields for the products (**19**, **21**, **22**, **24**, **30**, **32**, **33**, **35**) derived from 1-unsubstituted starting materials (**10**, **11**, **12**, **15**) cannot be explained in terms of the ED of the indole radical cation, they show a good correlation ($r=0.90$) with the SOMO-ED values of the indole-1-radical (the last column of Table II, Fig. 2). The indole radical cation is known to be quite unstable and to change rapidly to the indole radical with loss of a proton,[26] and hence it is reasonable to consider that the indole-1-radical is a reactive intermediary species. Considering that ring-size effects in product formation have been neglected in the calculations, the above correlations are satisfactory.[27]

20) C.G. Hatchard and C.A. Parker, *Pro. Roy. Soc. Ser. A*, **235**, 518 (1956).
21) K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, **22**, 1433 (1954).
22) J.A. Pople and G.A. Segal, *J. Chem. Phys.*, **44**, 3298 (1966).
23) K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, **42**, 3399 (1969).
24) J.A. Pople and D.L. Beveridge, "Approximate Molecular Orbital Theory," McGraw Hill, New York, 1970, p. 163.
25) Therefore, it may be concluded that substituents have little effect on SOMO-ED values.
26) R. Sautus and L.I. Grossweiner, *Photochem. Photobiol.*, **15**, 101 (1972); D.V. Bent and E. Hayon, *J. Am. Chem. Soc.*, **97**, 2612 (1975).
27) Electron spin densities were also calculated, but no satisfactory correlation with the quantum yields was obtained.

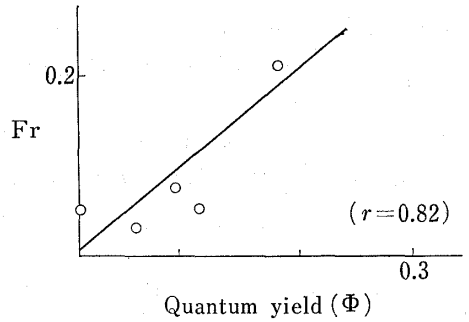


Fig. 1. Correlation (r) between Quantum Yields (Φ) for the Products (**17**, **26**, **27**, **28**, **34**) derived from 1-Substituted Starting Materials and SOMO-ED of the 1-Methylindole Radical Cation (Fr)

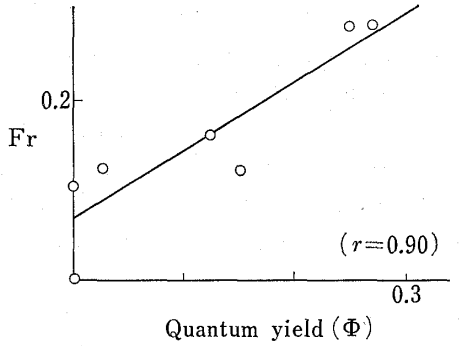


Fig. 2. Correlation (r) between Quantum Yields (Φ) for the Products (**19**, **21**, **22**, **24**, **30**, **32**, **33**, **35**) derived from 1-Unsubstituted Starting Materials and SOMO-ED of the Indole-1-radical (Fr)

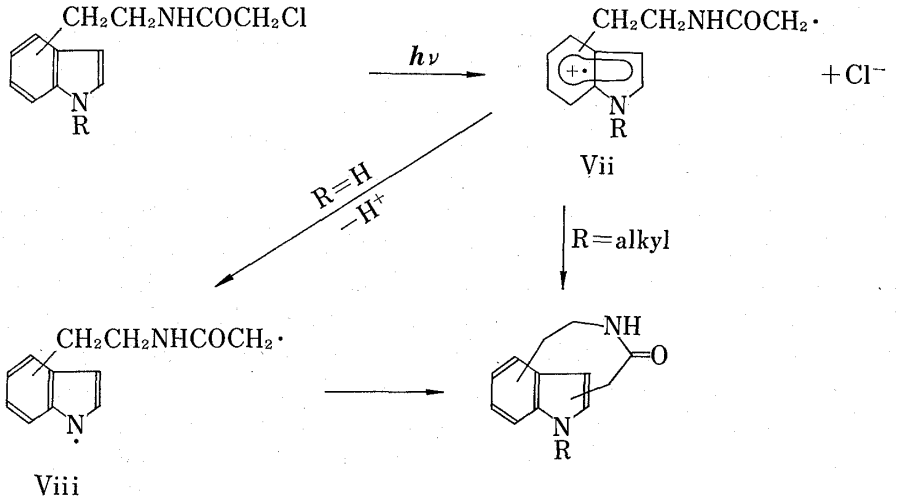


Chart 6

In conclusion, the mechanism of the photocyclizations of N-chloroacetyl-indolylethylamines can be described as follows. Excitation of the indolic chromophore leads to formation of the biradical cation intermediate (vii), which readily cyclizes to the product with loss of a proton when R is an alkyl substituent. In the case of R=H, vii rapidly loses a proton prior to the cyclization to form another intermediate (viii), which then cyclizes to the product.

There are many reports on radical reactions of aromatic[28] and symmetrical heteroaromatic compounds[29] whose reactivities correlate well with MO data, while no similar correlations for heterocycles without symmetry such as indole have been reported.[30] Therefore, the results presented here provide an important example of the successful application of simple MO calculations to account for the radical reactivity of a rather complex molecule, indole.

28) J.K. Kochi, ed., "Free Radical," Vol. II, Wiley, New York, 1973, p. 231.
29) G.H. Williams, ed., "Advances in Free Radical Chemistry," Vol. IV, Logos Press, New York, 1972, p. 1.
30) An analysis of the reactivity of indole radical cations by MO calculations has appeared: K. Yoshida, *J.C.S. Chem. Comm.*, **1978**, 1108.

Experimental

1-Indoleethylamine (5)——N-Benzoyl-2-bromoethylamine (**2**, 34.2 g, 0.15 mol) in CH_2Cl_2 (70 ml) and benzene (200 ml) was added dropwise with stirring to a solution of indoline (**1**, 36 g, 0.3 mol) in benzene (100 ml) at room temperature. The stirring was continued at 60° for 8 hr and at 70° for 2 hr, and then the solution was cooled, washed with water several times, dried, and concentrated to leave a crude oil N-(2-indolin-1-ylethyl)benzamide (**3**, 36 g). A xylene solution (2 l) of the crude oil of **3** with 10% Pd–C (25 g) was heated under reflux for 1.5 hr. After removal of the catalyst by filtration, the solution was concentrated and passed through a silica gel column (100 g) in CH_2Cl_2–EtOAc to give N-(2-indol-1-ylethyl)benzamide (**4**, 34 g). KOH (90 g) in H_2O (200 ml) was added to an EtOH solution (400 ml) of **4**, and the solution was heated under reflux overnight, concentrated to 200 ml and extracted with CH_2Cl_2. The extract was washed with H_2O, dried and concentrated to leave a crude oil of **5** (18 g, 75% from **2**),[31] which was used in the next step without further purification.

1-Methyl-5-indoleethylamine (7)——A dispersion of 50% NaH (28 g) was added to an ice-cooled solution of N-[2-(indol-5-yl)ethyl]acetamide[12] (10 g) in DMF (70 ml) with stirring. The stirring was continued for 1 hr at room temperature, and the mixture was cooled again in an ice bath. After adding MeI (9.0 g) dropwise, the reaction mixture was stirred for 1 hr at room temperature, then poured into ice-water (500 ml), and extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated to leave a crude solid of N-[2-(1-methylindol-5-yl)ethyl]acetamide (**6**). Recrystallization from benzene gave 6.6 g (61.7%) of an amorphous solid, mp 99—100°. *Anal.* Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.58; H, 7.21; N, 12.11.

A solution of **6** (6.6 g) and KOH (2.2 g) in EtOH (90 ml) and H_2O (100 ml) was heated under reflux for 14 hr. After removal of EtOH, the mixture was saturated with NaCl and extracted with THF. The extract was washed with sat. NaCl solution, dried over K_2CO_3 and concentrated to leave 4.2 g (49% from the starting acetamide) of **7** as a crude oil, which was used in the next step without further purification.

1-Methyl-6-indoleethylamine (8)——In a similar manner, N-[2-(indol-6-yl)ethyl]acetamide[12] (3.5 g) was converted to an oil, **8** (2.2 g, 73%), which was used in the next step without further purification.

2-Chloro-N-[2-(1-methylindol-5-yl)ethyl]acetamide (13)——DCC was added to an ice-cooled solution of chloroacetic acid (3.0 g) in THF (150 ml) with stirring, followed by the addition of **7** (5.2 g) in small portions. The mixture was stirred for a further 1 hr at room temperature then filtered, and the filtrate was concentrated to leave **14** as an oil, which was purified by passage through a short column of silica gel in CH_2Cl_2–EtOAc followed by recrystallization from benzene to give 6.2 g (83%) of colorless prisms, mp 110—111°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1640. UV λ_{max}^{EtOH} nm (ε): 274 (6500), 283 (6750), 293 (5450). NMR ($CDCl_3$) δ: 2.90 (2H, t, J=7 Hz), 3.55 (2H, q, J=7 Hz), 3.66 (3H, s), 3.91 (2H, s), 6.34 (1H, d, J=3 Hz), 6.60 (1H, br s), 6.83 (1H, dd, J=2, 9 Hz), 6.90 (1H, d, J=3 Hz), 7.03 (1H, d, J=2 Hz), 7.45 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{15}ClN_2O$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.37; H, 6.01; N, 11.12.

The following chloroacetyl derivatives were synthesized from the corresponding indole-ethanamines under similar conditions.

2-Chloro-N-[2-(indol-1-yl)ethyl]acetamide (9)——mp 81—82°. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1655. UV λ_{max}^{EtOH} nm (ε): 273 (6000), 280 (6000), 293 (4600). NMR ($CDCl_3$) δ: 3.50 (2H, q, J=7 Hz), 3.75 (2H, s), 4.16 (2H, t, J=7 Hz), 6.41 (1H, d, J=3 Hz), 6.65 (1H, br s), 6.80—7.60 (5H, m). *Anal.* Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.87; H, 5.54; N, 11.86.

2-Chloro-N-[2-(indol-2-yl)ethyl]acetamide (10)——mp 143—145°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3300, 1680. UV λ_{max}^{EtOH} nm (ε): 271 (7800), 277 (7050), 288 (6050). NMR ($CDCl_3$) δ: 2.93 (2H, t, J=7 Hz), 3.56 (2H, q, J=7 Hz), 3.91 (2H, s), 6.16 (1H, s), 6.80—7.40 (5H, m), 9.64 (1H, br s). *Anal.* Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 61.16; H, 5.69; N, 11.85.

2-Chloro-N-[2-(indol-4-yl)ethyl]acetamide (12)——mp 106—108°. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3280, 1660. UV λ_{max}^{EtOH} nm (ε): 271 (7800), 277 (7600), 288 (5650). NMR ($CDCl_3$) δ: 3.15 (2H, t, J=7 Hz), 3.70 (2H, q, J=7 Hz), 3.97 (2H, s), 6.65 (1H, m), 6.70 (1H, br s), 6.93 (1H, dd, J=2, 7 Hz), 7.21 (1H, t, J=7 Hz), 7.27 (1H, m), 7.36 (1H, dd, J=2, 7 Hz), 8.50 (1H, broad s). *Anal.* Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.91; H, 5.49; N, 11.83.

2-Chloro-N-[2-(1-methylindol-6-yl)ethyl]acetamide (14)——mp 96—97°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1650. UV λ_{max}^{EtOH} nm (ε): 275 (5850), 287 (5500), 298 (3800). NMR ($CDCl_3$) δ: 3.00 (2H, t, J=7 Hz), 3.63 (2H, q, J=7 Hz), 3.76 (3H, s), 4.02 (2H, s), 6.50 (1H, d, J=4 Hz), 6.60 (1H, br s), 6.97 (1H, dd, J=1, 9 Hz), 7.06 (1H, d, J=4 Hz), 7.10 (1H, d, J=1 Hz), 7.63 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{15}ClN_2O$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.51; H, 5.85; N, 11.30.

2-Chloro-N-[2-(indol-7-yl)ethyl]acetamide (15)——Oil. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1660. UV λ_{max}^{EtOH} nm (ε): 270 (6550), 279 (6250); 289 (4670). NMR ($CDCl_3$) δ: 2.83 (2H, t, J=7 Hz), 3.33 (2H, q, J=7 Hz), 3.76 (2H, s), 6.40 (1H, m), 6.60—7.50 (4H, m), 9.50 (1H, br s). *Anal.* Calcd for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.54; N, 11.83. Found: C, 60.96; H, 5.70; N, 11.56.

31) E. Pfeil and U. Harder, *Ang. Chem. Intern. Ed. Engl.*, **6**, 178 (1967).

Photocyclization of 9——A 50% aqueous EtOH solution (300 ml) of **9** (0.9 g) and K_2CO_3 (0.4 g) was irradiated with a 400 W high-pressure mercury lamp for 1.5 hr. The solution was concentrated to *ca.* 30 ml and extracted with EtOAc. The extract was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel, eluting with CH_2Cl_2, to give the starting material (**9**, 61 mg, 6.8%). Elution with CH_2Cl_2–EtOAc gave N-[2-(indol-1-yl)ethyl]acetamide (**18**, 20 mg, 2.6%).[32] Further elution with EtOAc gave two fractions. The first fraction was 4-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]diazepino[4,5-*a*]indole (**16**, 75 mg, 9.9%), which was recrystallized from MeOH to give colorless leaflets, mp 253—254°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1680. UV λ_{max}^{EtOH} nm (ε): 275 (8700), 281 (8850), 291 (6850). NMR (DMF-d_7) δ: 3.95 (2H, s), 3.90—4.40 (4H, m), 6.30 (1H, s), 7.0—8.0 (5H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 6.00; N, 13.93.

The second fraction was 2-oxo-2,3,4,5-tetrahydro-1*H*-[1,4]-diazocino[6,5,4-*hi*]indole (**17**, 124 mg, 16.3%), which was recrystallized from MeOH to give colorless leaflets, mp 254—255°. IR ν_{max}^{Nujol} cm^{-1}: 3190, 1660. UV λ_{max}^{EtOH} nm (ε): 275 (8700), 281 (8850), 291 (6850). NMR (DMF-d_7) δ: 3.5—4.0 (2H, m), 4.03 (2H, s), 4.83 (2H, d, J=7 Hz), 6.43 (1H, d, J=3 Hz), 6.90—7.50 (4H, m), 8.00 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.91; H, 6.01; N, 14.06.

Photocyclization of 10——A 50% aqueous MeOH solution (700 ml) of **10** (3.0 g) and K_2CO_3 (1.5 g) was irradiated with the 400 W lamp for 4 hr. The solution was concentrated to *ca.* 200 ml, and the precipitated solid was collected by filtration, washed with H_2O and dried to give 2.0 g of a solid. Decolorization with C in MeOH and recrystallization from MeOH gave 1,2,3,4,5,6-hexahydro-2-oxoazepino[4,5-*b*]indole (**19**, 500 mg, 19.7%), mp 230—232°. IR ν_{max}^{Nujol} cm^{-1}: 3520, 3360, 3290, 3200, 1650. UV λ_{max}^{EtOH} nm (ε): 274 (6850), 282 (7150), 292 (6050). NMR (DMF-d_7) δ: 2.93 (2H, t, J=7 Hz), 3.60 (2H, m), 3.73 (2H, s), 7.0—7.6 (5H, m), 10.8 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2O \cdot 1/2H_2O$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.65; H, 6.25; N, 13.28.

The initial aqueous layer was extracted with EtOAc. The extract was combined with the mother liquor of **19**, dried, and concentrated, then the residue was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave 520 mg (17.3%) of the starting material. Elution with CH_2Cl_2–EtOAc gave N-[2-(indol-2-yl)-ethyl]acetamide (**20**,[32] 95 mg, 3.7%), which was recrystallized from benzene–EtOAc to give colorless prisms, mp 140—142°. Elution with EtOAc gave 290 mg of **19** (total yield; 31%).

Photocyclization of 11——A 50% aqueous EtOH solution (800 ml) of **11** (4.0 g)[14] and K_2CO_3 (2.0 g) was irradiated with the 400 W lamp for 4 hr. The solution was concentrated to *ca.* 50 ml, then the precipitated solid was collected by filtration, and dried to give 3.3 g of crystals, which was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave 100 mg (2.5%) of the starting material (**11**) and N-[2-(indol-3-yl)ethyl]acetamide (**23**, 30 mg, 0.9%). Further elution with EtOAc gave two fractions. The first fraction was 1,2,3,4,5,6-hexahydro-4-oxoazepino[4,5-*b*]indole (**21**, 120 mg, 3.8%), which was recrystallized from MeOH to give colorless leaflets, mp 245—247°. IR ν_{max}^{Nujol} cm^{-1}: 3375, 3210, 1660. UV λ_{max}^{EtOH} nm (ε): 283 (7900), 291 (7000). NMR (MeOD-d_4) δ: 2.80 (2H, t, J=7 Hz), 3.60 (2H, t, J=7 Hz), 3.76 (2H, s), 6.80—7.40 (4H, m). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.67; H, 6.01; N, 14.20.

The second fraction was 1,3,4,5,6,7-hexahydro-6-oxoazocino[4,5,6-*cd*]indole (**22**, 750 mg, 22.2%), which was recrystallized from MeOH to give colorless prisms, mp 290—292°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1650. UV λ_{max}^{EtOH} nm (ε): 285 (6350), 292 (6100). NMR (DMF-d_7) δ: 3.13 (2H, t, J=7 Hz), 3.68 (2H, t, J=7 Hz), 3.78 (2H, s), 6.74 (1H, dd, J=3, 7 Hz), 6.89 (1H, t, J=7 Hz), 7.07 (1H, s), 7.24 (1H, dd, J=3, 7 Hz). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.64; H, 6.11; N, 14.25.

Photocyclization of 12——A 50% aqueous EtOH solution (200 ml) of **12** (1.0 g) and K_2CO_3 (0.4 g) was irradiated with a 200-W high-pressure mercury lamp for 3 hr. After concentrating the solution to *ca.* 30 ml, the precipitated brown solid was collected by filtration and chromatographed on a silica gel column (10 g). Elution with EtOAc gave a colorless solid, which was recrystallized from MeOH to give 1,3,4,5,6,7-hexahydro-4-oxoazocino[4,5,6-*cd*]indole (**24**, 290 mg, 33%), mp 222—226°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1655. UV λ_{max}^{EtOH} nm (ε): 283 (6050), 294 (4890). NMR (DMF-d_7) δ: 3.30—4.00 (4H, m), 3.75 (2H, s), 6.83 (1H, dd, J=2, 8 Hz), 7.03 (1H, t, J=8 Hz), 7.30 (1H, dd, J=2, 8 Hz), 7.33 (1H, s), 10.95 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}N_2O \cdot 1/2H_2O$: C, 68.88; H, 6.26; N, 13.39. Found: C, 69.20; H, 6.29; N, 13.28.

Photocyclization of 13——A 50% aqueous EtOH solution (800 ml) of **13** (3.5 g) and K_2CO_3 (2.0 g) was irradiated with the 400-W lamp for 4 hr. After concentrating the solution to *ca.* 50 ml, the precipitated solid was collected by filtration and passed through a short column of silica gel in EtOAc to give 2.8 g of a pale brown solid. The solid (300 mg) was separated by silica gel preparative TLC, developing with CH_2Cl_2, to give two fractions. The upper fraction was 3,6,7,8,9,10-hexahydro-3-methyl-9-oxoazepino[4,5-*e*]indole (**26**, 50 mg, 15.6%), which was recrystallized from MeOH to give colorless leaflets, mp 187—189°. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3200, 1650. UV λ_{max}^{EtOH} nm (ε): 276 (6950), 288 (6250), 300 (4830). NMR (MeOD-d_4) δ: 3.00 (2H, t, J=7 Hz), 3.45 (2H, q, J=7 Hz), 3.63 (3H, s), 3.95 (2H, s), 6.46 (1H, d, J=4 Hz), 6.85 (1H, d, J=9 Hz), 7.05 (1H, d, J=4 Hz), 7.06 (1H, s), 7.13 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{13}H_{14}N_2O \cdot 1/2H_2O$: C, 69.93; H, 6.77; N, 12.55. Found: C, 70.24; H, 6.78; N, 12.64.

32) P.H. Shirayog and G.P. Muralidhar, *Ind. J. Chem.*, **10**, 984 (1972).

The lower fraction was 1,5,6,7,8,9-hexahydro-1-methyl-8-oxoazepino[4,5-*f*]indole (**27**, 80 mg, 25%), which was recrystallized from MeOH, mp 203—205°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1660. UV λ_{max}^{Nujol} nm (ε): 279 (6550), 286 (6450). NMR (DMF-d_7) δ: 3.0—3.7 (4H, m), 3.81 (3H, s), 3.88 (2H, s), 6.40 (1H, d, J=3 Hz), 7.28 (1H, d, J=3 Hz), 7.30 (1H, s), 7.40 (1H, s). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.62; H, 6.38; N, 12.85.

Photocyclization of 14——A 50% aqueous EtOH solution (250 ml) of **14** (1.8 g) and K_2CO_3 (1.0 g) was irradiated with the 400-W lamp for 3 hr. After concentrating the solution, the precipitated solid was collected by filtration and chromatographed on a short column of silica gel (5 g). Elution with EtOAc–CH_2Cl_2 gave 70 mg (3.9%) of the starting material and 240 mg of a brown solid, which was subjected to silica gel preparative TLC, developing with EtOAc, to give two fractions. The upper fraction was N-[2-(1-methylindol-6-yl)ethyl]acetamide (**29**, 36 mg, 2.3%). The lower fraction was 1,5,6,7,8,9-hexahydro-1-methyl-6-oxo.azepino[4,5-*f*]indole (**28**, 120 mg, 7.8%), which was recrystallized from MeOH–hexane to give colorless prisms, mp 197—198°. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3080, 1680. UV λ_{max}^{EtOH} nm (ε): 280 (6450), 286 (6500). NMR (MeOD-d_4) δ: 3.0—3.6 (5H, m), 3.60 (3H, s), 3.71 (2H, s), 6.20 (1H, d, J=4 Hz), 6.90 (1H, d, J=4 Hz), 6.97 (1H, s), 7.16 (1H, s). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.05. Found: C, 72.60; H, 6.51; N,13.07

Photocyclization of 15——A 50% aqueous EtOH solution (250 ml) of **15** (1.0 g) and K_2CO_3(1.0 g) was irradiated with the 400-W lamp for 3 hr. After concentrating the solution, the precipitated solid was collected by filtration and chromatographed on a silica gel column. Elution with CH_2Cl_2 gave 90 mg (9.0%) of the starting material (**15**). Elution with CH_2Cl_2–EtOAc gave 1,6,7,8,9,10-hexahydro-7-oxoazepino[4,5-*g*]indole (**30**, 320 mg, 37.8%), which was recrystallized from MeOH, mp 283—285° (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1660. UV λ_{max}^{EtOH} nm (ε): 272 (6350), 281 (6250), 292 (4750). NMR (DMF-d_7) δ: 3.27 (2H, t, J=7 Hz), 3.73 (2H, t, J=7 Hz), 3.92 (2H, s), 6.50 (1H, m), 6.85 (1H, d, J=9 Hz), 7.37 (1H, m), 7.42 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.69; H, 6.21; N, 14.03.

Determination of Quantum Yields——Aqueous 50% EtOH solutions of N-chloroacetylindolylethylamines (*ca.* 2 mM, $OD_{253.7}$=*ca.* 5) and $NaHCO_3$ (3 mM) were irradiated with a 60-W low-pressure mercury lamp (253.7 nm). After 0, 4, 8, and 12 min, the amounts of starting materials and the cyclization products were determined quantitatively by high-speed liquid chromatography (Waters ALC 201: Corasil II 3 feet, 3—13% MeOH in isopropyl ether). Quantum yields for disappearance of the starting materials and formation of the products were determined relative to the formation of ferrous ions from 12 mM potassium ferrioxalate solution as an actinometer[20] which was photolyzed simultaneously. The average light intensity at 253.7 nm was 8.1×10^{-9} einstein/sec. The results are shown in Table I.

MO Calculation——Pople's CNDO/2 and INDO approximations[22,24] were employed for MO calculations on an IBM 370/125. The geometries of the indole molecules were obtained from the X-ray analytical data,[33] using the following bond lengths: 1.08 A for C–H and 1.50 A for N–C bonds.

33) I.L. Karle, K. Britts, and P. Gum, *Acta Cryst.*, **17**, 496 (1964).