

INTRAMOLECULAR EXCIPLEX FORMATION AND PHOTOCHEMICAL SYNTHESIS OF
1,2,3,4-TETRAHYDROISOQUINOLIN-3-ONES AND OXINDOLES FROM N-CHLOROACETYL
DERIVATIVES OF BENZYLAMINES AND ANILINES

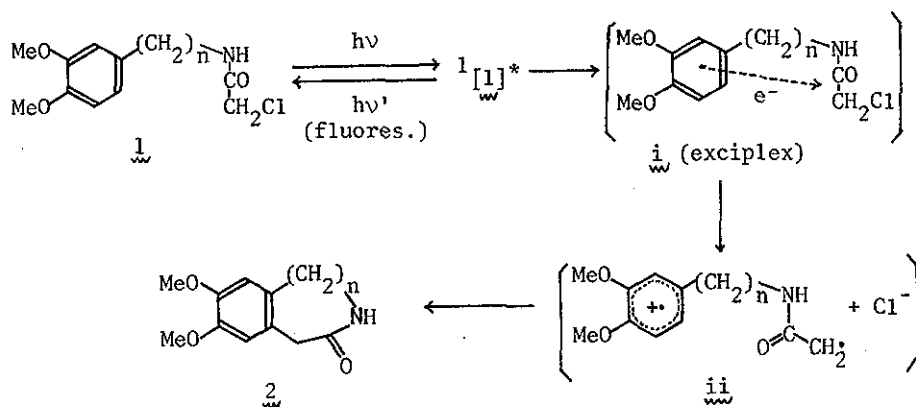
Tatsuo Hamada, Yohmei Okuno, Masayuki Ohmori, Takao Nishi,

and Osamu Yonemitsu

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

On the basis of fluorescence quenching and disappearance quantum yield measurements, the efficiency of exciplex formation and photochemical reaction of N-chloroacetyl-(3,4-dimethoxyphenyl)-alkylamines (1) was clarified to be dependent on the length of alkyl chain. The apparent unreactivity of benzylamine derivatives (1a, 4) for photocyclization, therefore, is attributable to the trans form of the amide groups. Since introduction of N-alkyl groups increases the stability of the cis isomers, on irradiation N-alkylbenzylamine derivatives (7, 8, 9) gave the corresponding isoquinolin-3-ones (10, 11, 12). This photocyclization was further extended to the synthesis of oxindoles (16, 17, 18) from N-alkylaniline derivatives (13, 14, 15).

On irradiation, N-chloroacetyl derivatives of phenethylamines with electron-donating substituents readily cyclize to many heterocycles including mainly 7 membered lactams, benzazepinones.¹ Homologous compounds, that is,



phenylpropylamine, phenylbutylamine, and phenylpentylamine derivatives also afford the corresponding photocyclization products, mainly 8, 9, and 10 membered lactams (2, $n = 3, 4, 5$).² On the other hand, benzylamine and aniline derivatives strangely give no 6 and 5 membered lactams, except for the photocyclizations of phenolic benzylamine derivatives.³ Since this type of photocyclizations usually proceeds via an intramolecular exciplex between an electron-rich aromatic ring and an electron-deficient chloroacetamide group,⁴ no cyclization of benzylamine and aniline derivatives has been assumed to be caused by the inefficient formation of exciplex, whose preferred geometry requires a perfectly overlapping sandwich conformation. In order to confirm this assumption, we have now examined intramolecular fluorescence quenching and disappearance quantum yields of various amine derivatives (1, $n = 1 \sim 5$), and the assumption has been found to be incorrect.

Fluorescence Quenching and Disappearance Quantum Yield

A 50% aqueous MeCN solution of the N-acetylbzylamine (3a, $n = 1$) emits a fluorescence spectrum with a maximum at 310 nm (excitation at 286 nm), and the corresponding N-chloroacetyl derivative (1a) also has the same spectrum, but its intensity is quite low (less than 1/20). This intramolecular

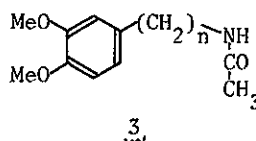
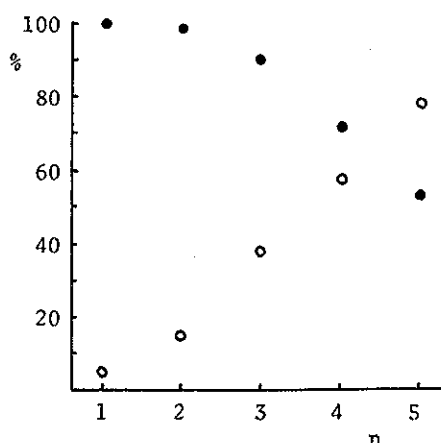
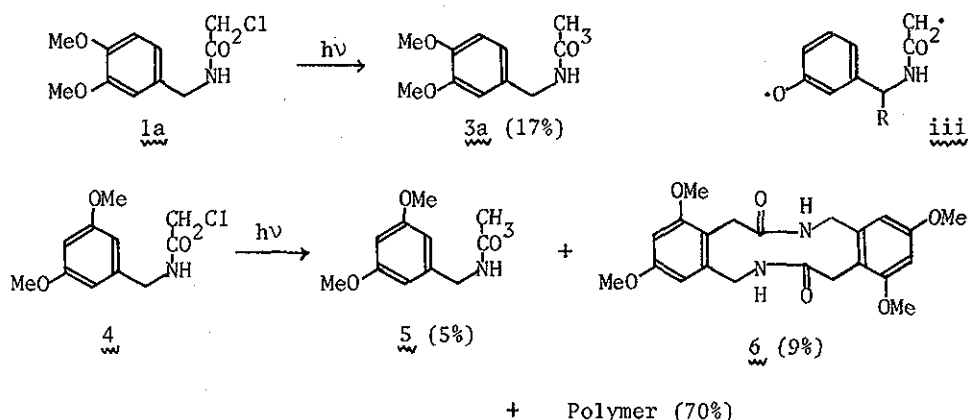


Fig 1. a) The ratio (%) of fluorescence intensities of 1 ($n = 1 \sim 5$) to those of the corresponding 3 vs. n (○ ○); b) The ratio (%) of quantum yields for disappearance of 1 to that of 1a vs. n (● ●).

quenching is clearly attributable to the exciplex formation.^{4,5} The homologous derivatives (1, $n = 2 \sim 5$) exhibit similar behavior. The ratios of the fluorescence intensities of 1 relative to those of the corresponding 3 are plotted against n in Fig 1a, indicating that the efficiency of exciplex formation depends apparently on the distance between the aromatic ring and the chloroacetamide, and not on their geometrical restriction.⁶

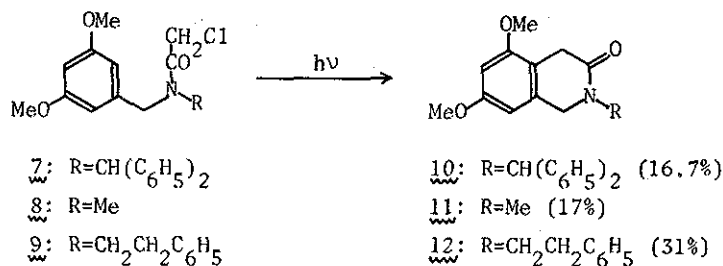
This conclusion has been supported on the basis of quantum yield measurements for disappearance of 1. Aqueous MeCN (50%) solutions of 1 ($n = 1 \sim 5$; 10 mM) and the 1,3-dimethyluracil actinometer⁷ in quartz test tubes were placed on a merry-go-round apparatus and irradiated with a 60 W low pressure mercury lamp. The percentage disappearance of 1 was determined gas chromatographically and the ratios of the disappearance quantum yields of 1 relative to that of 1a are also plotted in Fig 1b, indicating again that 1a is the most reactive, though no cyclization product has been isolated. Actually, when 1a in aqueous EtOH was irradiated, only 3a was an isolable product. Similarly, 4 gave 5, a dimer [mp > 320°; ν 3260, 1650 cm^{-1} ; m/e 414 (M^+), 207, 164 (base)], and a polymeric product.



Synthesis of 1,2,3,4-Tetrahydroisoquinolin-3-ones

Since N-monosubstituted amides in solution are present predominantly in their trans forms,⁸ it is almost impossible that the chloromethyl groups in the benzylamine derivatives (**1a**, **4**) come close to the aromatic ring, though possible in the homologous compounds (**1**, $n = 2 \sim 5$).⁹

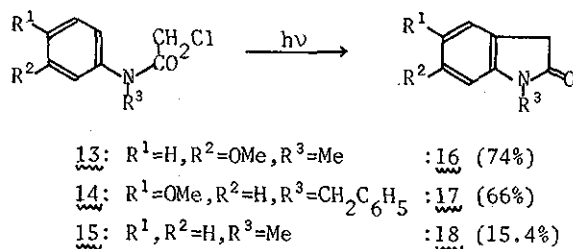
The introduction of a bulky substituent at the N atom, therefore, may lead to fixation of the amide group in its cis isomer, and then to photocyclization to an isoquinoline. In fact, when a 50% aqueous MeCN solution of the benzhydryl derivative (**7**) was irradiated with a 100 W high pressure lamp for 1 hr, the expected cyclization occurred to give the isoquinolin-3-one (**10**) [mp 77-78°; ν 1660 cm^{-1} ; m/e 373 (M^+), 208, 206, 182, 165 (base); δ (CDCl_3) 3.62 (2H, s), 3.74 (3H, s), 3.81 (3H, s), 4.12 (2H, s), 6.17 (1H, d, $J = 2$ Hz), 6.38 (1H, d, $J = 2$ Hz), 7.0-7.6 (10H, m)], though in less satisfactory yield. Under similar conditions, the N-methyl compound (**8**), which might be present in both the cis and trans forms, gave also the cyclization product (**11**) [mp 100-101°; ν 1660 cm^{-1} ; m/e 221 (M^+), 164 (base); δ (CDCl_3) 3.10 (3H, s), 3.48 (2H, s), 3.80 (6H, s), 4.46 (2H, s), 6.26 (1H, d,



$J = 2$ Hz), 6.35 (1H, d, $J = 2$ Hz)]. N-Phenethyl compound (9) cyclized more smoothly to the expected product (12) [mp 115–116°; ν 1650 cm^{-1} ; m/e 311 (M^+), 192 (base); δ (CDCl_3) 2.94 (2H, t, $J = 8$ Hz), 3.30 (2H, s), 3.72 (2H, t, $J = 8$ Hz), 3.76 (3H, s), 3.78 (3H, s), 4.27 (2H, s), 6.16 (1H, d, $J = 2$ Hz), 6.34 (1H, d, $J = 2$ Hz), 7.25 (5H, s)] in a fair yield.

Synthesis of Oxindoles

Further, these photocyclizations have been extended to the synthesis of oxindoles. In analogy with 1a and 4, aniline derivatives gave only substitution products of side chains, not cyclization products. Recently Kumar isolated rearrangement products, also not cyclization products.¹⁰ However, N-alkyl derivatives of anisidines were expected to cyclize to oxindoles. When a 30% aqueous MeCN solution of the N-methyl compound 13 was irradiated with the 100 W lamp for 45 min, the photocyclization proceeded quite smoothly and the oxindole (16) was isolated in 74% yield.¹¹ The photocyclization of the p-anisidine derivative (14) also proceeded, though somewhat slowly,



at the meta position with reference to the methoxy group to afford only the expected product (17) [ν 1710 cm^{-1} ; m/e 253 (M^+), 162, 91 (base); δ (CDCl_3) 3.44 (2H, s), 3.60 (3H, s), 4.74 (2H, s), 6.44 (1H, d, $J = 8$ Hz), 6.54 (1H, dd, $J = 8, 2.5$ Hz), 6.73 (1H, broad)]. Catalytic hydrogenation of 17 with Pd-C gave 5-methoxyoxindole.¹² Finally, even the aniline derivative (15) bearing no methoxy group gave N-methyloxindole (18), though in poor yield.

REFERENCES AND NOTES

- 1) Y. Okuno, M. Kawamori, K. Hirao, and O. Yonemitsu, Chem. Pharm. Bull., 23, 2584 (1975); Y. Okuno and O. Yonemitsu, Heterocycles, 4, 1371 (1976), and references cited therein.
- 2) Y. Okuno, K. Hemmi, and O. Yonemitsu, Chem. Commun., 745 (1971); T. Hamada, M. Ohmori, and O. Yonemitsu, Tetrahedron Lett., 1519 (1977).
- 3) M. Ikeda, K. Hirao, Y. Okuno, N. Numao, and O. Yonemitsu, Tetrahedron, 33, 489 (1977).
- 4) S. Naruto and O. Yonemitsu, Tetrahedron Lett., 3399 (1975).
- 5) M. T. McCall, G. S. Hammond, O. Yonemitsu, and B. Witkop, J. Am. Chem. Soc., 92, 6991 (1970).
- 6) Cf. T. Okada, T. Fujita, M. Kubota, S. Masaki, and N. Mataga, Chem. Phys. Lett., 14, 563 (1972).
- 7) N. Numao, T. Hamada, and O. Yonemitsu, Tetrahedron Lett., 1661 (1977).
- 8) W. E. Stewart and T. H. Sidall, III, Chem. Rev., 70, 517 (1970).
- 9) Phenolic benzylamine derivatives cyclized to the corresponding isoquinolines in good yield,³ probably because the life-times of intermediary phenoxy radical (iii), compared with those of the cation radicals (ii), are long enough for the cis-trans isomerization of the amide portion.
- 10) B. Kumar, R. M. Mehta, S. C. Kalra, and G. S. Manku, J. C. S. Chem. Comm., 971 (1976).
- 11) The Friedel-Crafts reaction of 13 with AlCl_3 gave 6-hydroxy-1-methyloxindole, which was methylated with Me_2SO_4 to afford 16 in 61% overall yield.¹²
- 12) A. H. Beckett, R. W. Daisley, and J. Walker, Tetrahedron, 24, 6093 (1968).

Received, 26th July, 1977