PHOTOCYCLIZATION REACTION OF 5-METHYLENE-4-ACRYLOYL- AND -AROYL-4-AZATRICYCLO-[4.3.1.13,8]UNDECANES (4-AZAHOMOADAMANTANES) UNDER OXIDATIVE CONDITIONS AND A CONFORMATIONAL STUDY OF THE ACRYLOYL ENAMIDE

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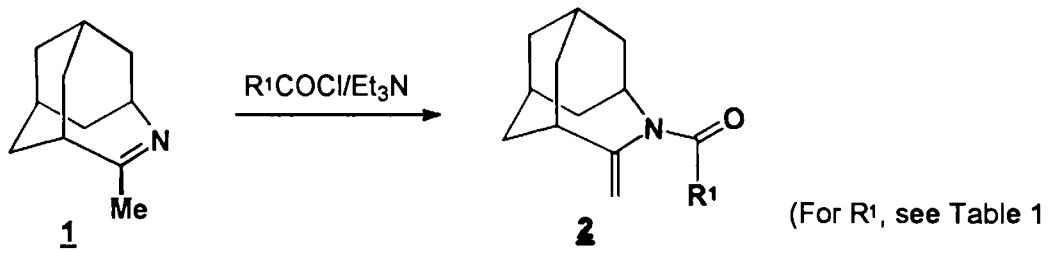
Abstract: Photocyclization studies of N-acryloyl and -aroyl derivatives of 5-methylene-4-azatricyclo[4.-3.1.1^{3,8}]undecane is reported. N-Aroyl derivatives gave isoquinolinone derivatives in good yields, while N-acryloyl derivatives yielded vinilogous amides except for methacryloyl derivative which gave cyclized product. Conformational effect to the photocyclization of the N-acryloyl enamines was discussed on the basis of MM2 calculation.

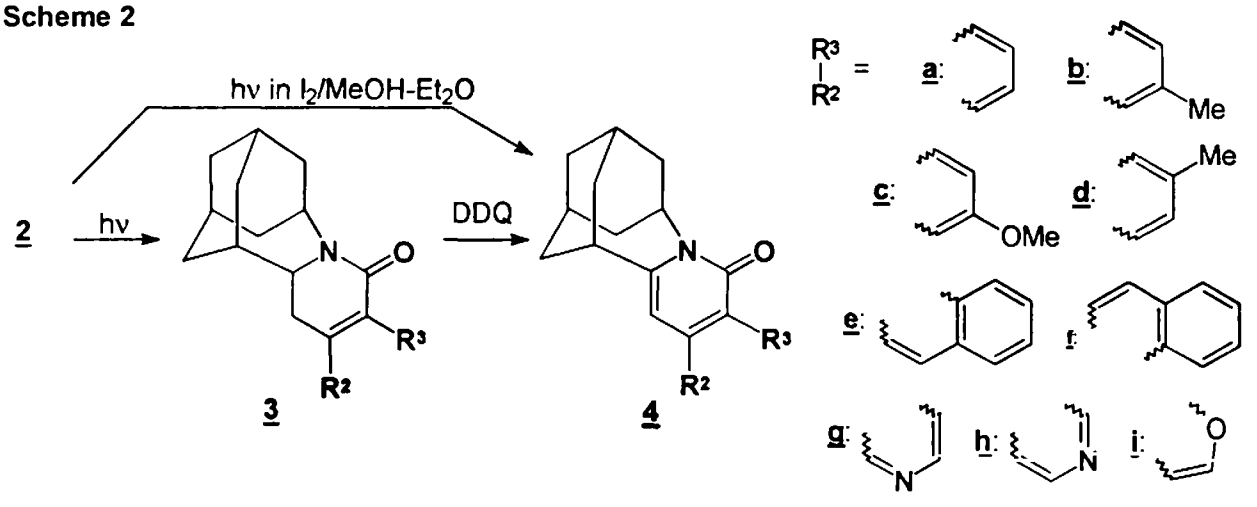
Introduction

The 6-electron thermal and photocyclizations of enamides provide a useful general synthetic tool for the construction of a variety of six-membered lactams, alkaloids, and heterocycles (2). We have reported previously synthesis of 8,9,10,11,12,13,13a,14-octahydro-7,11;9,13-dimethanoazonino[1,2-*b*]-isoquinolin-5(*7H*)-ones **3a-d** and related compounds **5a-c**. and **6** by photocyclization of 5-methylene-4-aroyl- and -acryloyl-4-azatricyclo[4.3.1.1^{3,8}]undecanes (4-azahomoadamantanes) **2** under nonoxidative conditions (Scheme 1,2) (3). In these photoreactions, the N-aroylenamines **2a-d** afforded the 6-electron cyclization products **3a-d**. which were converted to the corresponding hexahydro derivatives **4a-d** by DDQ oxidation, while among the N-acryloylenamines **2e-h**. only methacryloyl derivative **2f** yielded the cyclized product **6** in a low yield and other enamides **2e.f.h** gave the corresponding vinylogous amides **5a-c** as the 1,3-acyl rearrangement products (Scheme 3). In this paper we describe photocyclization of N-aroylenamines **2a,d,2i-m** to **4a,d,i-m** under oxidative conditions and a conformational study of N-acryloylenamines **2e** and **2g** by MM2 calculation. In particular, enamide units embeded within the rigid polycyclic frame have proved to be valuable probes for the conformational effect to electrocyclization and acyl shift as a seminal example of such compounds.

Scheme 1



Scheme 2



Scheme 3

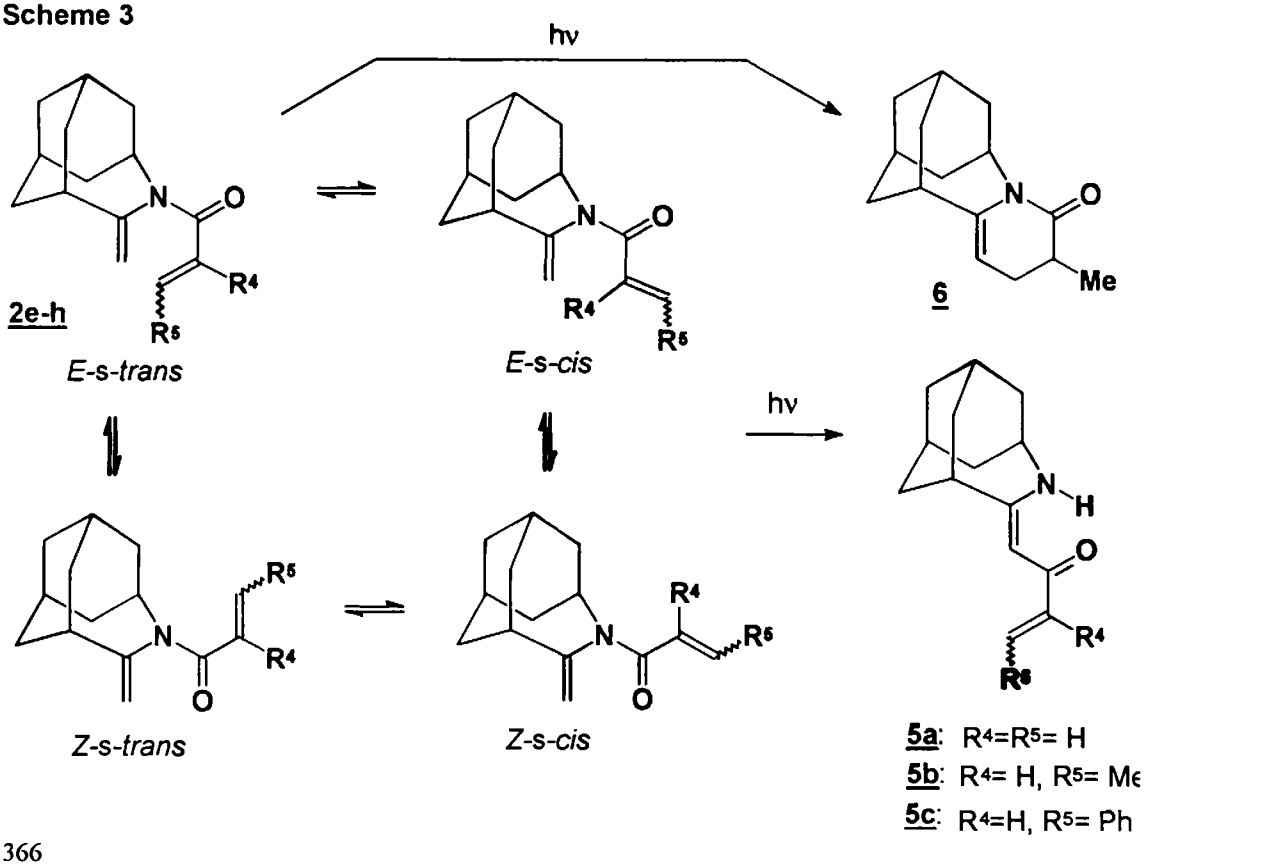
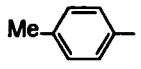
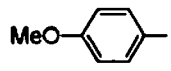
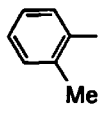
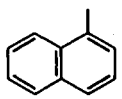
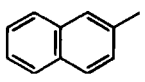
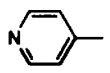


Table 1: Photolysis products of enamides **2**

Enamide		Photolysis products (yield,%)[a]	
2	R^1	hv in Et_2O or MeCN [b]	hv in I_2-MeOH-Et_2O [c]
a		**3a** (66)(Et_2O) [d]	**4a** (63)
b		**3b** (75)(Et_2O) [d]	-
c		**3c** (83)(Et_2O)[d]	-
d		**3d** (29) + **4d**(36)(Et_2O)[d]	**4d** (86)
e	CH_2=CH–	**5a** (40)(Et_2O)[d]	-
f	MeCH=CH–	**5b** (44)(Et_2O)[d]	-
g	CH_2=CMe–	**6** (25)(Et_2O)[d] (38)(Et_2O)[e]	-
h	PhCH=CH–	**5c** (61)(Et_2O)[d]	-
i		**4e** (45)(MeCN)	**4e** (56)
j		**4f** (18)(MeCN)	**4f** (69)
k		**4j** (12)(MeOH)	**4j** (40)
l		-	**4h** (35)
m		**4i** (30)(MeCN)	**4i** (76)

[a] Isolated yields. [b] A 0.17-1.5 mM solution was irradiated with a 60w low-pressure mercury lamp for 0.5-1.5 h (see ref. 3). [c] A *ca.* 0.6 mM solution was irradiated in I_2 (*ca.* 0.3 mM)/MeOH-Et_2O (1:1) similarly for 0.5-1.4 h. [d] See ref. 3. [e] Et_2O/hexane (10:4) was used.

Enamides **2a-h** were reported previously (3) and **2e-l** were prepared from 5-methyl-4-azatetracyclo[4.-3.1.$1^{3,6}$]undec-4-ene **1** (4) with R^1COCl similarly. These structures were confirmed by analytical and spectral data.

Irradiation of **2a** in ether-methanol (1:1) involving iodine (0.5 mol equiv.) with a low pressure mercury lamp through a quartz filter for 1.5 h afforded a cyclization product **4a** (63%), which was identical with an authentic sample prepared by DDQ oxidation of **3a** (3) by spectral data (IR, ^1H NMR) and TLC *Rf* values. Irradiation of **2d** for 1.5 h under similar conditions afforded **4d** in 86% yield. Thus, photocyclization of **2a** and **2d** under the oxidative conditions provides a better route to hexahydrodimethanoazonino[1,2-*b*]isoquinolinones **4a** and **4d** than the stepwise method reported previously (3). We applied this method to synthesis of 4-azahomoadamantane fused heterocycles **4e-l** by irradiation of naphthoyl, pyridinoyl and furoyl enamides **2e-l** as summarized in Table 1. Novel heterocycles **4e-l** were obtained in moderate to good yields and given structures were evidenced by spectral and analytical data (see Experimental). For example, compound **4e** had characteristic ^1H NMR signals at δ 10.17 (dm), 6.45 (s), 6.25 (br t), and 3.17 (br s) assignable to C1-H, C7-H, C14-H (a bridgehead proton adjacent to nitrogen), and C8-H (a bridgehead proton) respectively. The appearance of C1-H at very lower field could be rationalyzed by anisotropic effect of the peripheral carbonyl group. These enamides yielded oxidized products **4** in lower yields even irradiation under nonoxidative conditions as observed for **2d** previously (Table 1).

On the other hand, irradiation of N-acryloylenamine derivatives **2e,f,g,h** under nonoxidative conditions gave vinylogous amides, photo-Fries rearrangement products, **5a,b,c** except **2g** which gave photocyclized product **6** in 25% yield (Scheme 3) (3). The yield of **6** was improved to 38% by irradiation in Et_2O/hexane (10:4) for 1 h but the reaction was not clean being accompanied with side-products. Irradiation under the oxidative conditions gave only intractable complex mixture.

In the photocyclization of N-acryloyl enamines and -anilides, the α-substituent of the acyl moiety is known to assist the cyclization by the steric effect that favors the requisite s-*trans* conformation of the α,β-unsaturated carbonyl group (2b,c,5-7). For the present N-acryloylenamines **2e-h**. the observed photochemical results were rationalyzed in terms of conformatioanl effects (3), *i.e.*, assuming the importance of *E* isomers compared to *Z* isomers, concerning the amide bond, among the four possible conformers, *E*-s-*cis* form may be the most populated one for R^4 = H derivatives, **2e, f, h** but the presence of an α-substituent like **2g** (R^4= Me) permits the *E*-s-*cis* confomer to equilibrate with *E*-s-*trans*, the prerequisite conformation for the cyclization as depicted in Scheme 3. For more quantitative rationalization, relative energies and populations of the confomers were calculated by MM2 program for **2e** and **2g** as summarized in Table 2. The ORTEP diagrams of the corresponding conformers are depicted in Figure 1. Surprisingly the most stable conformer of **2e** was not *E*-s-*cis* but *Z*-s-*cis*. The total

Table 2: Relative energies and populations of **2e**- and **2g**-conformers based on MM2 calculations

	2e E-s-trans	**2e** E-s-cis	**2e** Z-s-trans	**2e** Z-s-cis	**2g** E-s-trans	**2g** E-s-cis	**2g** Z-s-trans	**2g** Z-s-cis
Total energy kcal/mol	34.24	30.25	38.71	29.29	33.76	32.77	36.92	34.70
Relative population % (27 °C)	0.0	16.9	0.0	83.1	15.5	81.2	0.1	3.3

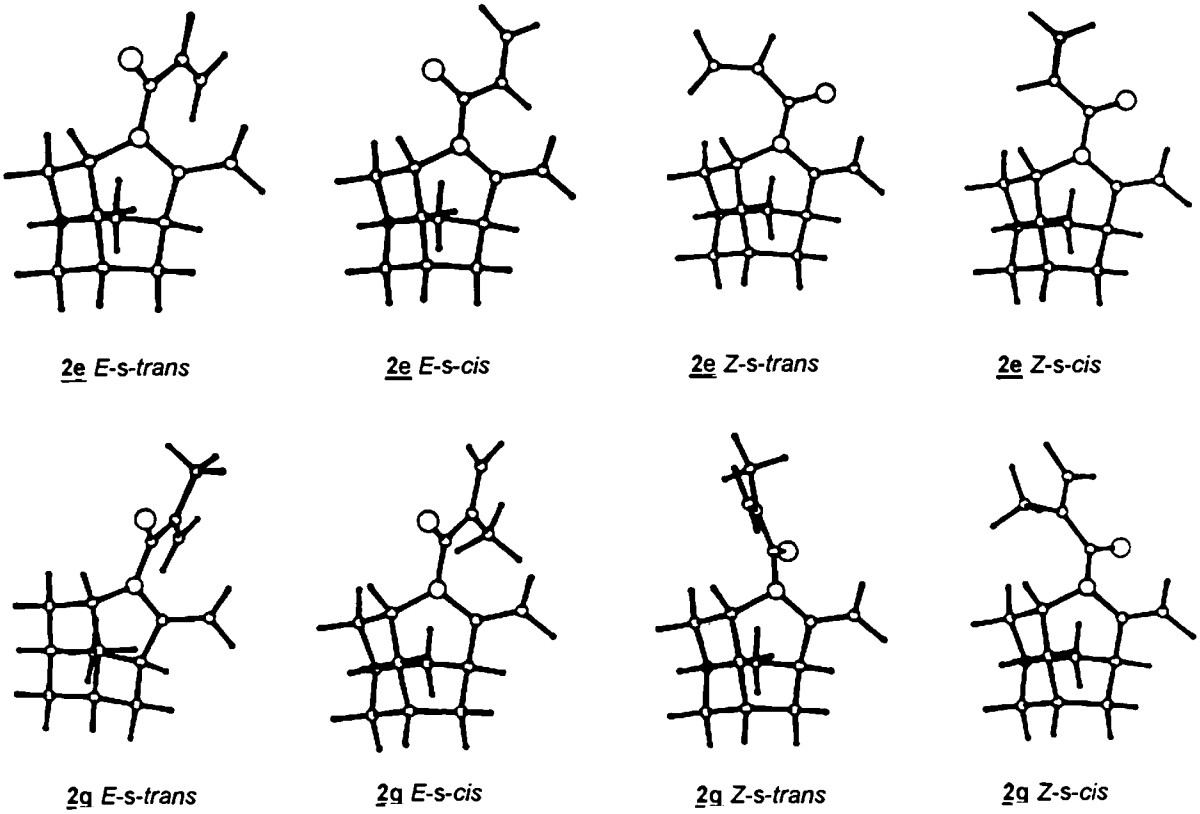


Figure 1: ORTEP Diagrams of **2e**- and **2g**-conformers

energy is 30.25 and 29.29 kcal/mol respectively, and the relative population at 27 °C is 16.9 and 83.1% respectively. The *E*-s-*trans* form requisite for electrocyclization has 34.24 kcal/mol and 0% population at 27 °C. Therefore, only photoacyl rearrangement should be possible as in fact observed. On the other hand, the most stable conformer of **2g** is *E*-s-*cis* (32.77 kcal/mol) and next one is *E*-s-*trans* (33.76 kcal/mol), and their populations at 27 °C are 81.2 and 15.5% respectively. And hence, the electrocyclization to afford **6** is possible arbite the yield was modest as observed.

Such conformational effect due to the presence of α-substituent of the acryloyl moiety is very important in the photocyclization of N-acryloyl enamine derivatives which are known as very useful building blocks for synthesis of various hydroquinolines, fused quinolines, fused quinolizines, and important alkaloid skeletons (2,8). Our results reported above provide a valuable suggestion useful for future synthetic design of 6-membered nitrogen heterocycles and related alkaloids by 6e-photocyclization.

Experimental

Melting points were taken on a Yanagimoto micro-melting points hot-stage apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 2400S elemental analyzer. ^{1}H NMR spectra were obtained at 25 °C with a JEOL JMN-C-60 HL instrument and a Varian Gemni-200 spectrometer at 60 and 200 MHz respectively for samples in $CDCl_3$ solution with $(CH_3)_4Si$ as internal standard. IR spectra were recorded on a JASCO A-100 spectrometer. EI Mass spectra were obtained on a ESCO EMD-05B spectrometer at 70 eV. TLC (Thin layer chromatography) was performed on a Merck Kieselgel 60 F_{254} unless otherwise specified, and/or on Merck Aluminium oxide F_{254}.

General procedure for synthesis of 5-methylene-4-acryloyl- and -aroyl-4-azatricyclo[4.3.1.1^{3,8}]undecanes 2:

An appropriate acyl chloride (0.75 mmol) in anhydrous benzene (0.5 mL) was added to a stirred mixture of 5-methyl-4-azatricyclo[4311^{3,8}]undec-4-ene 1 (81 mg, 0.50 mmol)(4) and triethylamine (76 mg, 0.75 mmol) in anhydrous benzene (3 mL). The stirring was continued for 0.5 h at room temperature and for 3 h at 80 °C. The cooled mixture was diluted with ether (10 mL) and washed with water (5 mL x 3), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a solid residue which was chromatographed on a column using silicagel (Fujigel BW-300, eluted with C_6H_6-CH_2Cl_2 system) for 2i,j,m and alumina (Woelm N, eluted with CH_2Cl_2) for 2k,l. Enamides 2a-h were previously reported (3).

The yields, physical and spectral properties of newly prepared enamides 2i-m are given below.

5-Methylene-4-(1-naphthoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane 2i:

colorless crystal (97.0%), mp 150.5-152 °C (hexane); IR(KBr) 3071, 2930, 2861, 1698, 1679, 1607, 1460, 1403, 1329, 1321, 1240, 876, 800 cm^{-1}; ^{1}H NMR (60 MHz) δ 8.12-7.19 (7H, m), 5.23 (1H, br s), 4.34 (1H, s), 4.20 (1H, s), 2.83 (1H, br s), 2.24-1.49 (12 H, m); Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.40; H, 7.31; N, 4.52.

5-Methylene-4-(2-naphthoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane 2j:

colorless crystal (99.0%), mp 146-149 °C (hexane); IR(KBr) 3065, 2930, 2861, 1698, 1679, 1607, 1480, 1408, 1355, 1343, 1240, 873, 800 cm^{-1}; ^{1}H NMR (60 MHz) δ 8.13-7.12 (7H, m), 5.20 (1H, br s), 4.54 (1H, s), 4.14 (1H, s), 2.96 (1H, br s), 2.83-1.52 (12 H, m); Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H,

7.30; N, 4.41. Found: C, 83.43; H, 7.31; N, 4.26.

5-Methylene-4-(4-pyridinoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane 2k:

colorless crystal (90.0%), mp 184.6-186.0 °C (hexane); IR(KBr) 3050, 2915, 2857, 1650, 1631, 1595, 1554,1461, 1441, 1400,1339, 1280, 1238, 1216, 881, 847 cm^{-1}; ^{1}H NMR (60 MHz) δ 8.69-8.09 (2H, m), 7.21-7.36 (2H, m), 5.06 (1H, br s), 4.61 (1H, s), 4.13 (1H, s), 2.92 (1H, br s), 2.25-1.49 (12 H, m); Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.07; H, 7.53; N, 10.44. Found: C, 76.12; H, 7.42; N, 10.33.

5-Methylene-4-(3-pyridinoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane 2l:

colorless crystal (31.0%), mp 185-188 °C (hexane); IR(KBr) 3040, 2940, 2931, 2851, 1636, 1592, 1439, 1400,1340, 1155, 874, 831, 742 cm^{-1}; ^{1}H NMR (60 MHz) δ 8.58 (2H, br s), 7.90-7.68 (1H, m), 7.37-7.15 (1H, m), 5.12 (1H, br s), 4.66 (1H, s), 4.09 (1H, s), 2.94 (1H, s), 2.84-1.65 (12H, m); Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.07; H, 7.53; N, 10.44. Found: C, 76.21; H, 7.56; N, 10.31.

5-Methylene-4-(2-furoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane 2m:

colorless solid (35.0%), mp 62-64 °C (AcOEt-hexane); IR(KBr) 3120, 2932, 2865, 1632, 1574, 1401, 1338, 1184, 1016, 889, 778, 750 cm^{-1}; ^{1}H NMR (60 MHz) δ 7.36 (1H, dd, J = 1.7, 1.0 Hz), 6.86 (1H, dd, J = 3.4, 1.0 Hz), 6.37 (1H, dd, J = 3.4, 1.7 Hz), 5.04 (1H, br s), 4.67 (1H, s), 4.37 (1H, s), 3.03 (1H, br s), 2.04-1.33 (12H, m); Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.67; H, 7.46; N, 5.40. Found: C, 74.72; H, 7.21; N, 5.35.

General Procedure for Photolysis of 2.

A. Under Nonoxidative Conditions.

A 0.2-0.6 mM solution of the appropriate **2** in the solvent shown in Table 1 was deoxygenated by bubbling argon through the solution for 0.5 h and irradiated with a 60w low-pressure mercury lamp for 0.5-1.4 h. Removal of the solvent under reduced pressure gave a residue which was purified by preparative TLC (Merck Kieselgel 60 F_{254} and/or Merck aluminum oxide 60 PF_{254}, type E) by eluting with CH_2Cl_2-hexane to afford either the photocyclization or 1,3-acyl shift product. The results are summarized in Table 1.

B. Under Oxidative Conditions.

A 0.5 mM solution of appropriate **2** and iodine (0.5 equiv.) in Et_2O/MeOH (1:1) was irradiated as above for 0.5-1.4 h, and work up similarly. The results are summarized in Table 1. Compounds 4a, d, 6 were reported previously (3). Physical and analytical data of new compounds 4e-i are given below.

8,9,10,11,12,13-Hexahydro-8,12;10,14-dimethanoazonino[1,2-*b*]benzo[*h*]isoquinolin-16(14*H*)-one 4e.

colorless crystals, mp 256-258 °C (CH_2Cl_2); IR(KBr) 2913, 2834, 1643, 1610, 1581, 1440, 1439, 1256, 1153, 853 cm^{-1}; ^{1}H NMR (200 MHz) δ 10.17 (1H, dm, J = 8.6 Hz, C1-H), 7.95 (1H, d, J = 8.8 Hz), 7.86 (1H, dd, J = 7.8, 1.6 Hz), 7.71 (1H, ddd, J = 8.6, 7.0, 1.6 Hz), 7.56 (1H, ddd, J = 7.8, 7.0, 1.4 Hz), 7.40

(1H, d, J = 8.8 Hz), 6.45 (1H, s, C7-H), 6.25 (H, br t, J = 5.5 Hz, C14-bridgehead H), 3.17 (1H, br s, C8-bridgehead H), 2.31-1.74 (12H, m); MS (EI) m/z (%) 316(47), 315(M^+, 100), 223(21), 222(22), 168 (41), 149(71); Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.73; H, 6.99; N, 4.40.

10,11,12,13,14,15-Hexahydro-9,13;11,15-dimethanoazonino[1,2-*b*]benzo[*f*]isoquinolin-7(9*H*)-one 4f.

colorless crystals, mp 156-158 °C (CH_2Cl_2); IR(KBr) 3071, 2941, 2930, 2861, 1698, 1679, 1607, 1460, 1403, 1329, 1321, 1240, 876, 800 cm^{-1}; ^1H NMR (200 MHz) δ 8.42 (1H, br d, J = ca. 6.8 Hz), 8.37 (1H, d, J = 8.6 Hz), 7.95-7.85 (1H, m), 7.76 (1H, d, J = 8.8 Hz), 7.69-7.55 (2H, m), 7.11 (1H, s, C16-H), 6.12 (1H, unsym. t, J = ca. 5 Hz, C9-bridgehead H), 3.27 (1H, br s, C15-bridgehead H), 2.28-1.75 (12H, m); MS (EI) m/z (%) 316(6.7), 315(M^+, 26), 314(100), 235(11), 222(13), 221(16), 164 (11); Anal. Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 83.35; H, 7.10; N, 4.43.

8,9,10,11,12,13-Hexahydro-7,11;9,13-dimethanoazonino[1,2-*b*][2,6]-naphthyridin-5(7*H*)-one 4g.

colorless crystals, mp 182-185 °C (CH_2Cl_2); IR(KBr) 3000, 2930, 2859, 1651, 1617, 1584, 1446, 1360, 1260, 1136, 1000, 848 cm^{-1}; ^1H NMR (200 MHz) δ 8.85 (1H, s), 8.59 (1H, d, J = 5.3 Hz), 8.11 (1H, d, J = 5.3 Hz), 6.39 (1H, s), 6.00 (1H, br t, J = ca. 5 Hz),), 3.16 (1H, br s), 2.27-1.65 (12H, m); MS (EI) m/z (%) 266(M^+, 32), 265(78), 183(32), 168(36), 154(50), 148 (100); Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.65; H, 6.83; N, 10.52. Found: C, 76.61; H, 6.63; N, 10.59.

8,9,10,11,12,13-Hexahydro-7,11;9,13-dimethanoazonino[1,2-*b*][3,6]-naphthyridin-5(7*H*)-one 4h.

colorless crystals, mp 174-176 °C (CH_2Cl_2); IR(KBr) 2901, 2849, 1655, 1617, 1588, 1546, 1441, 1142, 850 cm^{-1}; ^1H NMR (200 MHz) δ 8.85 (1H, s), 8.59 (1H, d, J = 5.3 Hz), 8.11 (1H, d, J = 5.3 Hz), 6.39 (1H, s), 6.00 (1H, br t, J = ca. 5 Hz), 3.16 (1H, br s), 2.27-1.45 (12H, m); MS (EI) m/z (%) 267(21), 266(M^+, 100), 265(6.1), 225(11), 223(5.6), 198(15), 197(12), 187(10), 174 (24), 173(21), 149(17); Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.65; H, 6.83; N, 10.52. Found: C, 76.49; H, 6.86; N, 10.59.

7,8,9,10,11,12-Hexahydro-6,10;8,12-dimethanoazonino[2,1-*f*]furo[2,3-c]pyridin-4(6*H*)-one 4i.

colorless crystals, mp 252-254 °C (CH_2Cl_2); IR(KBr) 3130, 2941, 2866, 1681, 1672, 1584, 1579, 1501, 1281, 1179, 852, 801 cm^{-1}; ^1H NMR (60 MHz) δ 7.67 (1H, d, J = 2.0 Hz), 6.52 (1H, d, J = 2.0 Hz), 6.25 (1H, s), 6.03 (1H, br s), 3.09 (1H, br s), 2.33-1.25 (12H, m); MS (EI) m/z (%) 255(M^+, 24), 254(100), 253(12), 214(17), 186(24), 175 (245), 162 (48), 161(48); Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.36; H, 6.77; N, 5.30.

Calculation method of relative energies and populations of 2e- and 2g-conformers.

The starting coordinates of the conformers were generated by the program COORD (9) with bond lengths, bond angles and torsion angles obtainable from Dreiding molecular models. Iterative calculations were then made to minimize the steric energy of each conformer using the program MM2 (10). The parameters for the amide moiety were obtained from J. P. Snyder (G. D. Searle) (11). Relative populations of the conformers were calculated with the energy values so far obtained, assuming that

they are in equilibrium.

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References and Notes

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