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Photoreactions of Succinimides with an N-Acyl Group in the Side Chain. Synthesis and Stereochemistry of Tricyclic Pyrrolo[1,2-*a*]pyrazine Ring Systems[1]

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Photocyclization of succinimides with an N-acyl group in the side chain gave bi- and tricyclic pyrrolo[1,2-*a*]pyrazines, some of which were converted to tricyclic amines by reduction. The stereochemistry of pyrrolo[1,2-*a*]pyrazine derivatives is discussed on the basis of the results of X-ray analysis and carbon-13 nuclear magnetic resonance spectroscopy.

Keywords——succinimide; photocyclization; pyrrolo-pyrazine; hydrogen abstraction; X-ray analysis; ^{13}C-NMR spectrum; tricyclic diamine

Photoreactions of phthalimides **1** possessing a hetero atom in the side chain have given rise to a variety of new heterocycles including large-sized ring systems.[2] As regards the synthesis of various multicyclic fused heterocycles with two nitrogen atoms, the efficiency of photocyclization in phthalimide systems was greatly improved by incorporating an acyl group on nitrogen in the N-alkyl side chain (**2a**, **b** in Chart 1).[3] Further, this reaction was applied to alicyclic imide systems (**3** and **5**) with an N-acyl group.[4] The present report is a full account of this work on the synthesis and the stereochemistry of tricyclic pyrrolo[1,2-*a*]pyrazines and their reduction products.

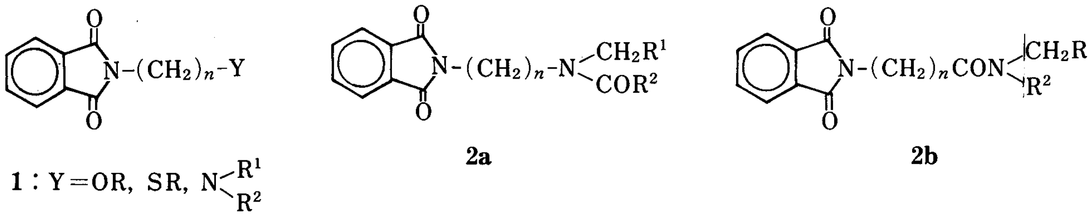


Chart 1

Succinimides **3a**—**e** were prepared from succinimidoacetyl chloride and the appropriate secondary amines, or from succinimidoacetic acid and the corresponding amines. Succinimides **5a**—**c** were prepared from succinimide and the corresponding ω-amidoalkyl acetates as reported,[5] and succinimides **5d**, **e** were obtained from succinic anhydride and *N*-acyl-*N*-methyl-1,3-diaminopropanes. Melting points and analytical data of these imides **3**, **5**, and **8** are listed in Table I.

Photolysis of **3**, **5**, and **8** was carried out in acetonitrile (10—24 mM) using 60 and 120 W low-pressure mercury lamps in an atmosphere of nitrogen at room temperature for 1.5—5 h.

Table I. Physicochemical Properties of Succinimide Derivatives **3**, **5**, and **8**

Compd.	mp (°C) (Lit.)	IR $\nu_{\mathrm{max}}^{\mathrm{Nujol}}$ (cm^{-1})	MS m/z (M$^+$)	^{1}H-NMR (in CDCl$_3$, δ)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
3a	95.5—98	1775, 1700, 1650	184	2.77 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 2.83 (3H, s, $\mathrm{N{-}CH_3}$), 3.05 (3H, s, $\mathrm{N{-}CH_3}$), 4.30 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)	$C_8H_{12}N_2O_3$	52.16 (52.14	6.57 6.55	15.21 15.39)
3b	141—142 (139—142)[9]	1780, 1710, 1650		1.7—2.3 (4H, m, $\mathrm{NCH_2{-}(C\underline{H}_2)_2{-}CH_2}$), 2.75 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.2—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2{-}(CH_2)_2{-}C\underline{H}_2{-}N}$), 4.18 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)				
3c	120—122.5	1785, 1710	224	1.3—1.9 (6H, m, $\mathrm{N{-}CH_2{-}(C\underline{H}_2)_3{-}CH_2}$), 2.80 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.2—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2{-}(CH_2)_3{-}C\underline{H}_2{-}N}$), 4.3 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)	$C_{11}H_{16}N_2O_3$	58.91 (59.19	7.19 7.21	12.49 12.67)
3d	88.5—91	1775, 1700, 1640	238	1.4—2.0 (8H, m, $\mathrm{N{-}CH_2{-}(C\underline{H}_2)_4{-}CH_2}$), 2.75 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.3—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2{-}(CH_2)_4{-}C\underline{H}_2{-}N}$), 4.26 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)	$C_{12}H_{18}N_2O_3$	60.48 (60.57	7.61 7.59	11.76 11.83)
3e	185.5—186.5	1780, 1700	226	2.81 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.4—4.8 (8H, m, $\mathrm{N{-}(CH_2CH_2)_2{-}O}$), 4.22 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)	$C_{10}H_{14}N_2O_3$	53.09 (53.03	6.24 6.25	12.38 12.54)
5a	138.5—140	1770, 1700	196	1.8—2.6 (4H, m, $\mathrm{CO{-}C\underline{H}_2C\underline{H}_2{-}CH_2}$), 2.75 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.45 (2H, t, $J=7$ Hz, $\mathrm{N{-}C\underline{H}_2{-}CH_2}$), 5.07 (2H, s, $\mathrm{N{-}CH_2{-}CO}$)	$C_9H_{12}N_2O_3$	55.09 (55.14	6.17 6.15	14.28 14.18)
5b	100—101.5	1765, 1700, 1660	210	1.8—2.4 (4H, m, $\mathrm{CO{-}C\underline{H}_2C\underline{H}_2{-}CH_2}$), 2.63 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.2—3.8 (6H, m, $\mathrm{N{-}CH_2CH_2{-}N}$, $\mathrm{N{-}C\underline{H}_2{-}CH_2}$)	$C_{10}H_{14}N_2O_3$	57.13 (57.12	6.71 6.79	13.33 13.44)
5c	87—87.5 (72)[5]	1760, 1690, 1630		1.94 (3H, s, $\mathrm{NCO{-}CH_3}$), 2.61 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 2.99 (3H, s, $\mathrm{N{-}CH_3}$), 3.59 (4H, m, $\mathrm{N{-}CH_2CH_2{-}N}$)				
5d	Oil	1765,[a] 1690, 1630	212	1.7—2.1 (2H, m, $\mathrm{N{-}CH_2C\underline{H}_2CH_2{-}N}$), 2.08 (3H, s, $\mathrm{NCO{-}CH_3}$), 2.71 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.00 (3H, s, $\mathrm{N{-}CH_3}$), 3.2—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2CH_2C\underline{H}_2{-}N}$)	$C_{10}H_{16}N_2O_3$	212.1160[b] (212.1154)		
5e	bp$_{0.6}$ 165	1770,[a] 1710, 1690	242	1.23 (3H, t, $J=7$ Hz, $\mathrm{O{-}CH_2C\underline{H}_3}$), 1.5—2.0 (2H, m, $\mathrm{N{-}CH_2C\underline{H}_2CH_2{-}N}$), 2.68 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 2.86 (3H, s, $\mathrm{N{-}CH_3}$), 3.0—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2CH_2C\underline{H}_2{-}N}$), 4.08 (2H, q, $J=7$ Hz, $\mathrm{O{-}C\underline{H}_2CH_3}$)	$C_{11}H_{18}N_2O_4$	54.53 (54.33	7.49 7.71	11.56 11.66)
8a	76—78	1770, 1710, 1645	224	1.59 (3H, d, $J=7$ Hz, $\mathrm{C{-}CH_3}$), 1.8—2.1 (4H, m, $\mathrm{NCH_2{-}(C\underline{H}_2)_2{-}CH_2}$), 2.68 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.1—3.7 (4H, m, $\mathrm{N{-}C\underline{H}_2{-}(CH_2)_2{-}C\underline{H}_2{-}N}$), 4.5—5.0 (1H, q, $J=7$ Hz, $\mathrm{{-}C\underline{H}_2CH_3}$)	$C_{11}H_{16}N_2O_3$	224.1160[b] (224.1163)		
8b	Oil	1770,[a] 1700, 1640	252	0.83 (3H, d, $J=7$ Hz, $\mathrm{{-}CH{-}C\underline{H}_3}$), 1.01 (3H, d, $J=7$ Hz, $\mathrm{{-}CH{-}C\underline{H}_3}$), 1.7—2.1 (5H, m, $\mathrm{{-}C\underline{H}(CH_3)_2}$, $\mathrm{NCH_2{-}(C\underline{H}_2)_2{-}CH_2}$), 2.7 (4H, s, $\mathrm{CO{-}CH_2CH_2{-}CO}$), 3.2—3.6 (4H, m, $\mathrm{N{-}C\underline{H}_2{-}(CH_2)_2{-}C\underline{H}_2{-}N}$), 4.38 (1H, d, $J=10$ Hz, $\mathrm{N{-}CH{-}CO}$)	$C_{13}H_{20}N_2O_3$	61.88 (61.95	7.99 8.01	11.10 11.19)

a) Neat. *b*) High-resolution MS.

TABLE II. Photoproducts from **3**, **5**, and **8**

Compd.	Irradiation time (h)	Product	Yield (%) (SM)[b]	Appearance (Recryst. solv.)	mp (°C)	IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm^{-1})	MS m/z M^+ (M^+-18)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
3a	1.5	**4a**	60 (10)	Plates (AcOEt)	110.5—112	3250, 1670, 1650	184 (166)	$C_{18}H_{12}N_2O_3$	52.16 (52.17	6.57 6.55	15.21 15.33)
3b	1.5	**4b**-i	43 (10)	Powders (AcOEt)	81 (dec.)	3550, 1675, 1660, 1642	210 (192)	$C_{10}H_{14}N_2O_3 \cdot H_2O$	52.62 (52.97	7.07 7.15	12.27 12.27)
		4b-ii	11	Prisms (EtOH)	135—138	3320, 1700, 1642	210 (192)	$C_{10}H_{14}N_2O_3$	57.13 (56.99	6.71 6.65	13.33 13.42)
3c	5	**4c**-i	13 (25)	Plates (AcOEt)	143 (dec.)	3200, 1675, 1650	224 (206)	$C_{11}H_{16}N_2O_3$	58.91 (58.88	7.19 7.20	12.49 12.31)
		4c-ii	9	Prisms (AcOEt)	102.5—104.5	3400, 1680, 1625	224 (206)	$C_{11}H_{16}N_2O_3$	58.91 (58.83	7.19 7.22	12.49 12.47)
3d	2	**4d**-i	43 (7)	Prisms (EtOH)	160—163	3240, 1660, 1640	238 (220)	$C_{12}H_{18}N_2O_3$	60.48 (60.48	7.61 7.68	11.76 11.86)
		4d-ii	32	Plates (AcOEt)	142—144	3200, 1670, 1650	238 (220)	$C_{12}H_{18}N_2O_3$	60.48 (60.49	7.61 7.69	11.76 11.62)
3e	4	**4e**	26 (9)	Plates (AcOEt)	200 (dec.)	3340, 1690, 1658	266 (208)	$C_{10}H_{14}N_2O_4$	53.09 (53.09	6.24 6.23	12.38 12.35)
5a[a]	1.5	**6**	51 (3)	Plates (AcOEt)	131—133	3280, 1690, 1660	196 (178)	$C_9H_{12}N_2O_3$	55.09 (55.18	6.17 6.06	14.28 14.49)
5b	1.5	**7b**	41 (29)	Needles (AcOEt)	154—156	3360, 1720, 1660	210	$C_{10}H_{16}N_2O_3$	57.13 (57.13	6.71 6.68	13.33 13.27)
5c	1.5	**7c**	31 (29) (16)[c]	Plates (AcOEt)	115.5—117.5	3250, 1710, 1640	198	$C_9H_{14}N_2O_3$	54.53 (54.42	7.12 7.16	14.13 14.13)
5d	3.5	**7d**	23 (7) (18)[c]	Plates (AcOEt)	115.5—117	3275, 1695, 1665	212	$C_{10}H_{16}N_2O_3$	56.59 (56.52	7.60 7.69	13.20 13.13)
5e	2	**7e**	25 (10)	Plates (Benzene)	78—81	3180, 1700, 1665	242	$C_{11}H_{18}N_2O_4 \cdot 1/2\,H_2O$	52.57 (52.52	7.62 7.50	11.15 11.11)
8a	1.5	**9a**	33 (25)	Plates (AcOEt)	136—140	3350, 1660, 1630	224	$C_{11}H_{16}N_2O_3$	58.91 (58.94	7.19 7.15	12.49 12.49)
8b	1.5	**9b**	28 (39)	Needles (AcOEt)	203—204.5	3260, 1695, 1660	252	$C_{13}H_{20}N_2O_3$	61.88 (61.80	7.99 7.97	11.10 11.04)

a) Irradiation was carried out in methanol. *b*) Recovery of starting material. *c*) Yields of simple succinimide.

The results are collected in Table II.

The photolysis of **3**, which lacks γ- and δ-hydrogens relative to the imide carbonyl group, was initiated by ε-hydrogen abstraction reaction to give bi- and tricyclic pyrrolo[1,2-*a*]pyrazine derivatives **4a**—**e** in moderate yields (Chart 2). In the cases of **4b**—**d**, two stereoisomers were produced, and they were separated by column chromatography on silica gel. The structures were assigned on the basis of spectral data (Table III). In the infrared (IR) spectra of **4a**—**e**, the bands in the regions of 3200—3500 and 1625—1700 cm^{-1} indicated the presence of the cyclol and lactam moieties, respectively.[6] In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **4a**—**e**, two doublets with the large coupling constant of 18—19 Hz appeared at 3.46—3.72 and 3.97—4.95 ppm, indicating the presence of geminal methylene protons on the newly formed pyrazine ring. In the carbon nuclear magnetic resonance (^{13}C-NMR) spectra of tricyclic **4b**—**e**, singlets at 83.9—89.3 and doublets at 60.8—65.8 ppm indicated the presence of a quaternary carbon and a tertiary carbon, suggesting that a new carbon–carbon bond had been formed between the imide carbonyl group and the carbon adjacent to the amide nitrogen in the N-side chain.

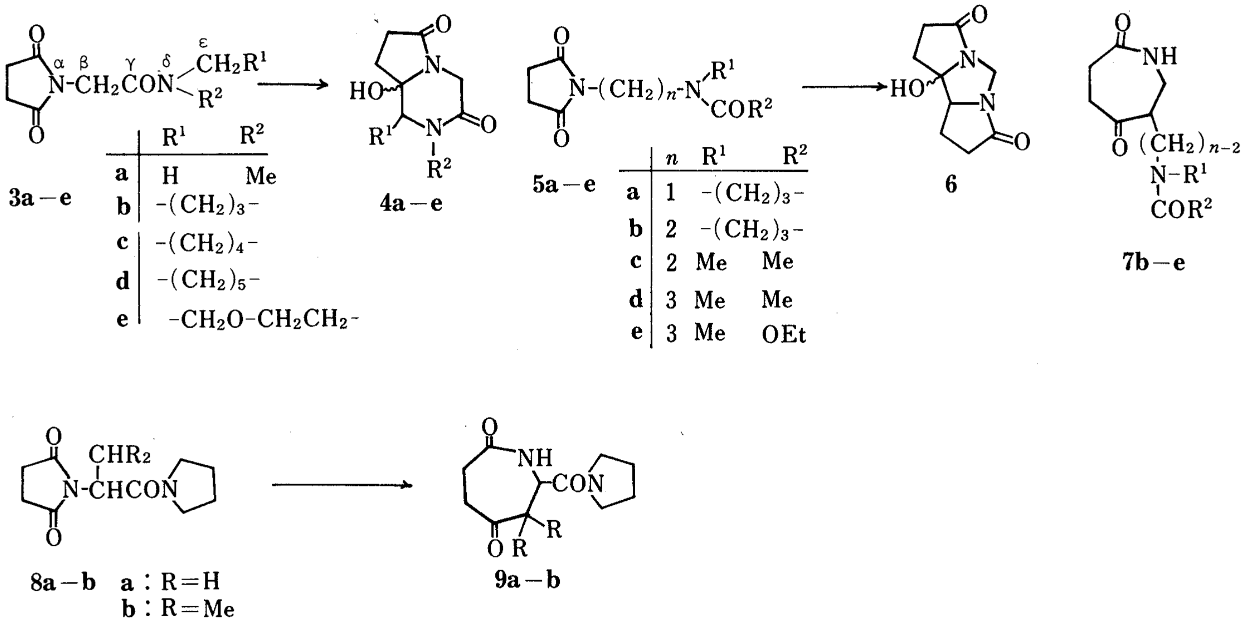


Chart 2

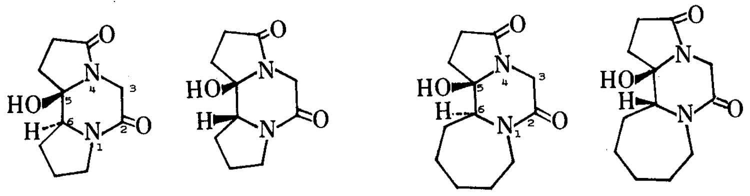
However, since it was difficult to confirm the stereochemistry of three pairs of pyrrolo[1,2-*a*]pyrazine derivatives **4b**—**d** by nuclear magnetic resonance (NMR) spectroscopy, X-ray structure analyses of **4b**-ii and **4d**-i were carried out. From the results of X-ray analyses, the configurations of the hydroxy group at C_5 and the methine proton at C_6 were assigned as *cis* for **4b**-ii and *trans* for **4d**-i (Chart 3). Perspective drawings of compounds **4b**-ii and **4d**-i are shown in Fig. 1, and the bond lengths and angles in Fig. 2.

In the ^{13}C-NMR spectra of a series of **4b**—**d**, where small chemical shift differences between stereoisomers of **4**-i (*trans*) and **4**-ii (*cis*) were observed, the chemical shifts were correlated with those of the analogous compounds **10b**—**d**, whose stereochemistry was previously determined on the basis of the ^{1}H-NMR spectra.[3b)] For example, the signals due to C_3 (*) in **4d**-i and **10d**-i showed upfield shifts compared with those of **4d**-ii (*cis*) and **10d**-ii (*cis*), suggestive of *trans* configuration (Chart 4). As shown in Fig. 3, all signals of methylene carbons (C_3) on the pyrazine ring of **4b**—**d** appeared at 42.0—47.3 ppm, and their chemical shifts are analogous to those of **10b**—**d** (41.5—47.2 ppm). Similarly, the stereochemistry of a pair of stereoisomers (**4c**-i and **4c**-ii) was inferred to be *trans* and *cis*, respectively, from the

TABLE III. ^{1}H-NMR and ^{13}C-NMR Spectral Data for Products

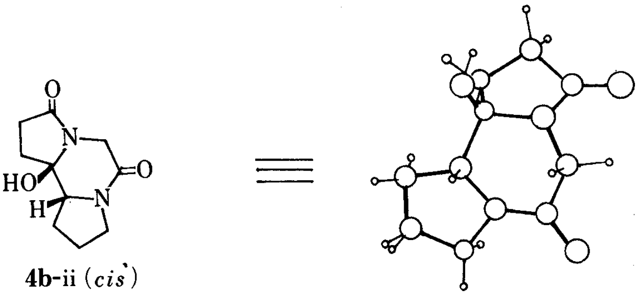
Product	^{1}H-NMR (in CDCl$_3$, δ)	^{13}C-NMR (in CDCl$_3$, δ)
4a	2.0—2.9 (4H, m, CO–C$\underline{H}_2$C$\underline{H}_2$–COH), 2.96 (3H, s, N–CH$_3$), 3.50 (2H, s, N–C$\underline{H}_2$–COH), 3.67(1H, d, J=18 Hz, N–CH$_2$–CO), 4.25 (1H, d, J=18 Hz, N–CH$_2$–CO), 5.77 (1H, s, OH)	29.4 (t), 31.4 (t), 35.2 (q), 41.7 (t), 58.9 (t), 84.5 (s), 164.7 (s), 172.8 (s)
4b-i[a]	1.7—2.7 (8H, m, CO–C$\underline{H}_2$C$\underline{H}_2$–COH, N–CH$_2$C$\underline{H}_2$C$\underline{H}_2$–C), 3.3—3.9 (3H, m, N–C$\underline{H}_2$–CH$_2$, CON–CH–), 3.54 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.20 (1H, d, J=18 Hz, N–CH$_2$–CO), 6.50 (1H, s, OH)	21.6 (t), 26.1 (t), 29.3 (t), 30.0 (t), 41.7 (t), 45.5 (t), 64.5 (d), 85.4 (s), 162.9 (s), 171.8 (s)
4b-ii[a]	1.7—3.0 (8H, m, CO–C$\underline{H}_2$C$\underline{H}_2$–COH, N–CH$_2$C$\underline{H}_2$C$\underline{H}_2$–C), 3.3—3.6 (2H, m, N–C$\underline{H}_2$–CH$_2$), 3.68 (1H, d, J=18 Hz, N–CH$_2$–CO), 3.8—4.1 (1H, m, CON–CH–), 4.27 (1H, d, J=18 Hz, N–C$\underline{H}_2$–CO), 6.49 (1H, s, OH)	22.8 (t), 25.9 (t), 29.3 (t), 30.3 (t), 42.0 (t), 43.8 (t), 62.9 (d), 89.4 (s), 167.6 (s), 174.6 (s)
4c-i	1.2—2.7 (11H, m), 3.1—3.4 (1H, m), 3.72 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.28 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.4—4.7 (1H, m), 5.33 (1H, s, OH)	22.6 (t), 24.1 (t), 25.1 (t), 29.2 (t), 31.1 (t), 41.4 (t), 42.0 (t), 63.7 (d), 85.8 (s), 164.8 (s), 172.8 (s)
4c-ii	1.0—2.7 (11H, m), 3.4—3.7 (1H, m), 3.65 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.28 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.5—4.8 (1H, m), 5.50 (1H, s, OH)	24.6 (t), 25.3 (t), 28.8 (t), 29.5 (t), 29.9 (t), 41.3 (t), 45.4 (t), 65.8 (d), 86.9 (s), 163.2 (s), 172.6 (s)
4d-i[a]	1.2—2.6 (12H, m, CO–C$\underline{H}_2$C$\underline{H}_2$–COH, N–CH$_2$–(C$\underline{H}_2$)$_4$–C), 3.3—3.7 (3H, m, N–C$\underline{H}_2$–CH$_2$, CON–CH–), 3.52 (1H, d, J=18 Hz, N–CH$_2$–CO), 3.97 (1H, d, J=18 Hz, N–CH$_2$–CO), 6.05 (1H, s, OH)	25.5 (t), 27.4 (t), 27.7 (t), 28.7 (t), 29.2 (t), 31.1 (t), 41.2 (t), 43.5 (t), 63.9 (d), 86.7 (s), 163.9 (s), 171.5 (s)
4d-ii[a]	1.0—2.9 (13H, m), 3.4—3.7 (1H, m), 3.46 (1H, d, J=18 Hz, N–CH$_2$–CO), 4.1—4.4 (1H, m), 4.95 (1H, d, J=18 Hz, N–CH$_2$–CO), 6.16 (1H, s, OH)	25.1 (t), 25.4 (t), 26.6 (t), 29.4 (t), 29.6 (t), 30.9 (t), 41.9 (t), 47.3 (t), 65.2 (d), 87.3 (s), 163.5 (s), 172.5 (s)
4e	1.7—3.0 (5H, m), 3.2—4.3 (8H, m), 6.37 (1H, s, OH)	29.0 (t), 30.1 (t), 40.0 (t), 40.8 (t), 60.0 (d), 65.4 (t), 65.7 (t), 83.9 (s), 163.1 (s), 171.3 (s)
6	2.0—3.3 (8H, m, CO–C$\underline{H}_2$C$\underline{H}_2$–C–OH, CO–C$\underline{H}_2$C$\underline{H}_2$–CH), 3.6—3.9 (1H, m, N–CH–), 4.57 (1H, d, J=9 Hz, N–CH$_2$–N), 4.78 (1H, d, J=9 Hz, N–CH$_2$–N), 5.35 (1H, s, OH)	17.5 (t), 30.6 (t), 33.1 (t), 33.3 (t), 55.0 (t), 68.3 (d), 93.9 (s), 175.0 (s), 178.9 (s)
7b	1.9—2.6 (4H, m), 2.6—3.0 (4H, m), 3.2—4.0 (4H, m, NH–C$\underline{H}_2$–C, N–C$\underline{H}_2$–CH$_2$), 4.59 (1H, dd, J=9, 5 Hz, N–CH–CO), 7.2—7.5 (1H, m, NH)	18.7 (t), 30.1 (t), 30.3 (t), 38.7 (t), 42.0 (t), 45.8 (t), 62.3 (d), 175.9 (s), 202.9 (s)
7c	2.1 (3H, s, NCO–CH$_3$), 2.3—2.9 (4H, m, CO–CH$_2$CH$_2$–CO), 3.06 (3H, s, N–CH$_3$), 3.4—4.2 (2H, m, NH–C$\underline{H}_2$–), 4.3 (1H, dd, J=9, 5 Hz, N–CH–CO), 7.6—8.0 (1H, m, NH)	21.3 (q), 29.8 (t), 36.6 (q), 38.9 (t), 41.0 (t), 66.5 (d), 171.2 (s), 176.8 (s), 203.3 (s)
7d	2.05 (3H, s, NCO–CH$_3$), 2.4—3.0 (5H, m), 3.03 (3H, s, N–CH$_3$), 3.1—3.9 (4H, m), 6.7 (1H, m, NH)	21.8 (q), 30.7 (t), 37.0 (q), 38.5 (t), 41.1 (t), 46.7 (t), 52.5 (d), 171.5 (s), 175.6 (s), 208.7 (s)
7e	1.26 (3H, t, J=7 Hz, O–CH$_2$C$\underline{H}_3$), 2.65 (4H, br s, CO–CH$_2$CH$_2$–CO), 2.89 (3H, s, N–CH$_3$), 3.1—3.7 (5H, m), 4.1 (2H, q, J=7 Hz, O–C$\underline{H}_2$CH$_3$), 6.6—7.0 (1H, m, NH)	14.6 (q), 30.7 (t), 35.0 (q), 38.6 (t), 40.8 (t), 47.6 (t), 52.6 (d), 61.8 (t), 156.9 (s), 175.8 (s), 208.4 (s)
9a	1.8—2.2 (4H, m, N–CH$_2$–(C$\underline{H}_2$)$_2$–CH$_2$), 2.6—2.9 (6H, m, CO–CH$_2$CH$_2$–CO, CO–C$\underline{H}_2$–CH), 3.3—3.7 (4H, m, N–C$\underline{H}_2$–(CH$_2$)$_2$–C$\underline{H}_2$–N), 4.1—4.5 (1H, m, NH–C$\underline{H}$–CO), 6.8—7.1 (1H, m, NH)	23.9 (t), 26.0 (t), 31.9 (t), 39.6 (t), 46.5 (t), 46.7 (t), 48.7 (t), 50.7 (d), 166.4 (s), 178.1 (s), 205.8 (s)
9b	1.16 (3H, s, C–CH$_3$), 1.26 (3H, s, C–CH$_3$), 1.7—2.1 (4H, m, N–CH$_2$–(C$\underline{H}_2$)$_2$–CH$_2$), 2.5—2.9 (4H, m, CO–CH$_2$CH$_2$–CO), 3.4—3.6 (4H, m, N–C$\underline{H}_2$–(CH$_2$)$_2$–C$\underline{H}_2$–N), 3.98 (1H, d, J=8 Hz, NH–C$\underline{H}$–CO), 6.8—7.1 (1H, m, NH)	21.0, 22.0, 24.1, 26.1, 32.2, 35.8, 46.3, 47.3, 47.3, 51.0, 59.1, 166.5, 174.7, 209.9

a) In DMSO-d_6.

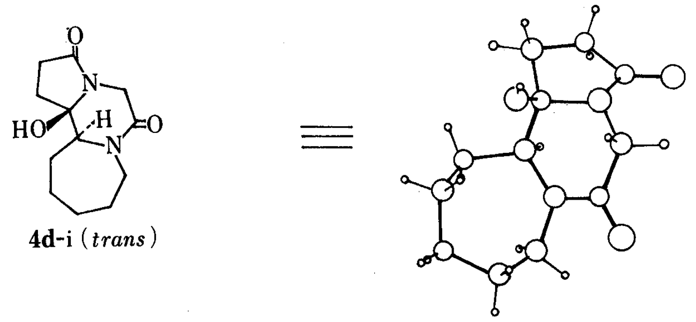


4b-i (*trans*) **4b**-ii (*cis*) **4d**-i (*trans*) **4d**-ii (*cis*)

Chart 3



4b-ii (*cis*)



4d-i (*trans*)

Fig. 1. Molecular Structures of **4b**-ii and **4d**-i

^{13}C-NMR data. Thus, the stereochemistry in the series of **4b**—**d** was determined as shown in Chart 4.

In order to investigate whether an amide nitrogen can enhance the reactivity of the C–H bond adjacent to the nitrogen or not, the photoreaction of **5** was examined. In the case of **5a** lacking γ-hydrogen, a tricyclic product **6** was obtained in 51% yield by initial δ-hydrogen abstraction. However, in all cases of **5b**—**e** having γ-hydrogen, the γ-hydrogen abstraction reaction proceeded predominantly to give ketolactams **7b**—**e** with ring expansion by a two-carbon unit derived from the N-side chain, and in the cases of **5c**, **d**, the simple succinimide was obtained in 16—18% yields together with the lactams, apparently formed by initial γ-hydrogen abstraction followed by elimination. Further, photoreaction of **8**, analogs of **3b** having both γ- and ε-hydrogens, gave the ketolactams **9a** and **9b** with ring expansion in 33 and 28% yields, respectively, but photocyclized products having a pyrazine ring such as **4** (ε-product) were not isolated. The formation of these ketolactams **7b**—**e** and **9** can be explained on the basis of the general pattern of imide photochemistry.[1a,7)]

Further, as an extension of the synthetic application of this reaction, chemical conversion of the photoproducts to tricyclic fused diamines was examined. The bicyclic lactam **4d**-i was reduced with lithium aluminum hydride to afford two tricyclic diamines **11a** and **11b** in 73 and 11% yields, respectively. When **4d**-ii was reduced, tricyclic diamines **11a** and **11b** were similarly obtained in 22 and 49% yields, respectively. These diamines were identical with the products derived from **4d**-i under similar reaction conditions (Chart 5). The resulting tricyclic diamines (**11a**, **b**) are probably *trans* and *cis* stereoisomers on the basis of the ^{13}C-NMR spectra, in which eight peaks out of twelve in **11b** showed an upfield shift compared with those

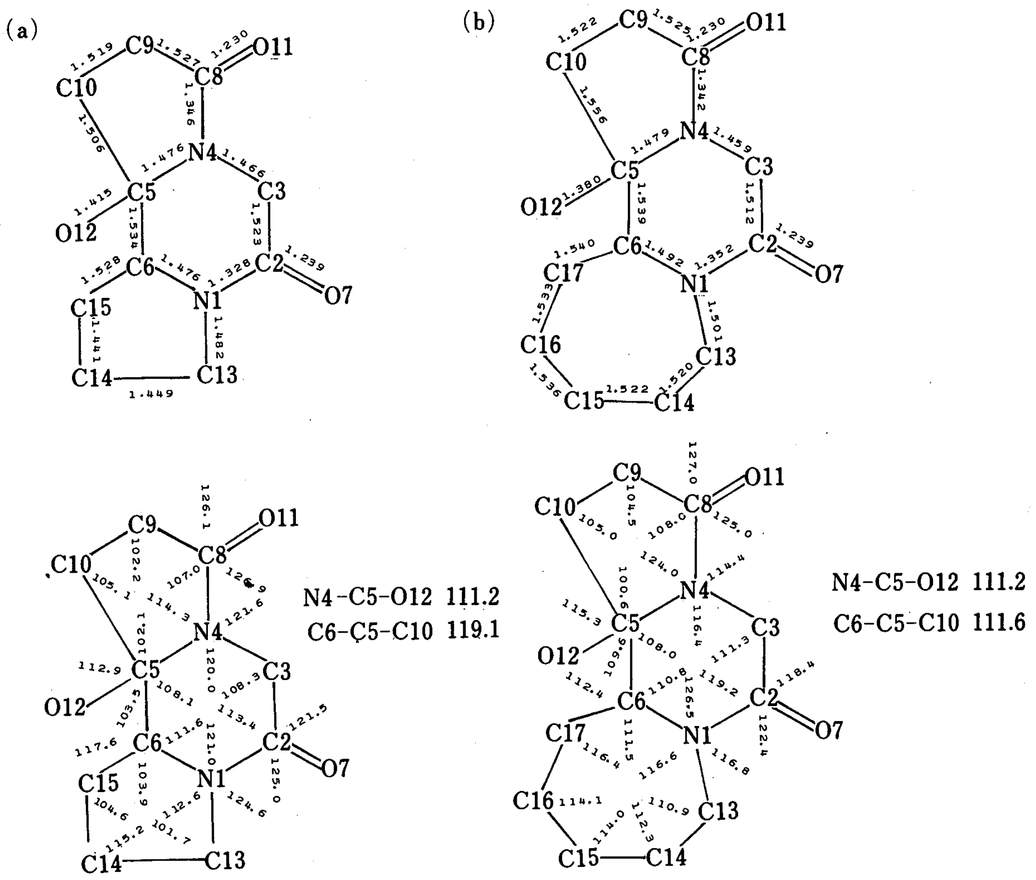
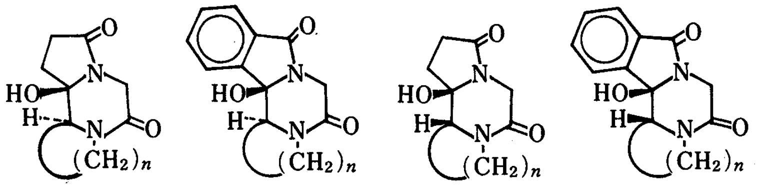


Fig. 2. Bond Lengths (Å) and Bond Angles (°) for **4b**-ii (a) and **4d**-i (b)



4-i (*trans*) **10**-i (*trans*) **4**-ii (*cis*) **10**-ii (*cis*)

$n=3$, **4b** and **10b**
$n=4$, **4c** and **10c**
$n=5$, **4d** and **10d**

Chart 4

in **11a** (Chart 5), a phenomenon which can be interpreted in terms of steric effect or γ-effect. Although further work is required to establish the stereochemistry of the diamines, the structures of **11a** and **11b** were tentatively assigned as *trans* and *cis* stereoisomers, respectively.

From systematic studies on the photochemistry of imides with various functional groups in the N-side chain, it has become clear that there are remarkable differences in photochemical behavior between the alicyclic and the aromatic cyclic imides (phthalimides).[2)] As reported in the previous papers,[3)] in the case of the aromatic imide system having an amide group in the N-side chain, the photocyclization took place not only on the γ- and δ-carbons but also on the ε- and ζ-carbons relative to the imide carbonyl attached to the amide nitrogen (Chart 6). Namely, in substrates possessing both γ- and ζ-hydrogens, such as **2a** ($n=3$) and **2b** ($n=2$), the Norrish type II cyclization takes place on the ζ-carbons in preference to the γ-position. Thus

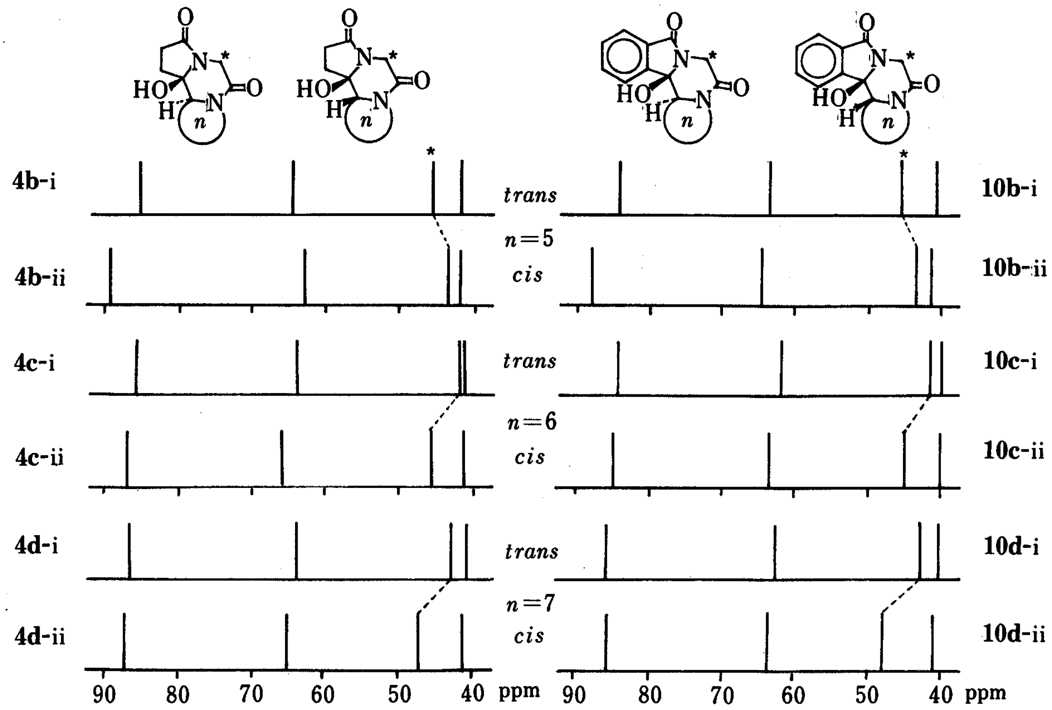


Fig. 3. ^{13}C-NMR Correlation Spectra for **4** and **10**

The symbol *n* indicates the size of the ring for cycloamines.

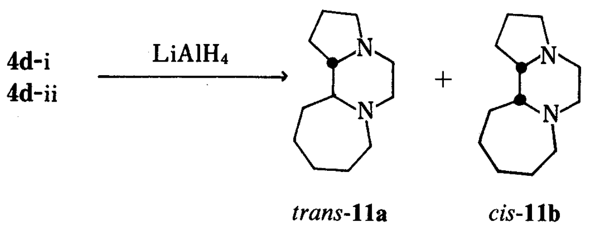


Chart 5

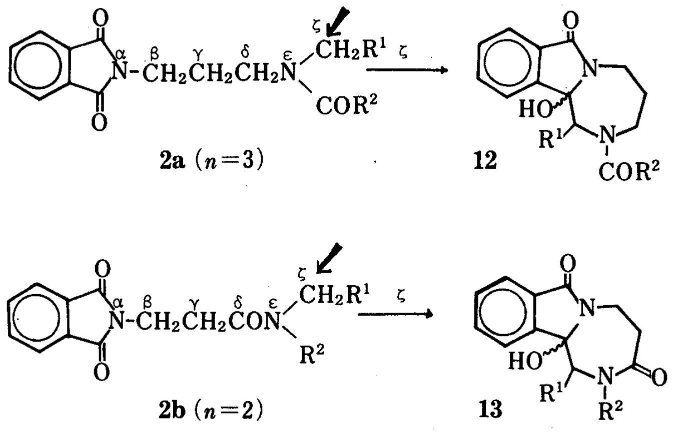


Chart 6

in the photoreaction of aromatic imide systems (**2**), an amide nitrogen at the ε-position enhances the reactivity of the ζ C–H bond adjacent to the nitrogen rather than that of the γ C–H bond. On the other hand, the alicyclic imide system having no γ-hydrogen but with ε-hydrogens underwent the type II cyclization on the ε-carbon. As observed in the present work, in the alicyclic imide system having both γ- and ε-hydrogens, the type II cyclizations are initiated predominantly by typical γ-hydrogen abstraction, in contrast with the behavior of the aromatic imides, and this abstraction is parallel to the photochemical behavior of the common carbonyl group. Therefore, it seems that these differences between the photochemical behavior of the aromatic and the alicyclic imides reflect entropy requirements (stereoelectronic requirements) for the formation of the favorable transition state necessary for the cyclization.

In the photochemistry of alicyclic imide systems with an N-acyl group in the side chain, this method provides a simple route to tricyclic nitrogen heterocycles, which may serve as convenient synthetic intermediates for alicyclic amine systems. Thus a variety of tricyclic diamine compounds are expected to be accessible by reduction of these tricyclic heterocycles, which are obtainable by photoreaction with minimal side reactions such as oxidation, polymerization, and elimination.

Experimental

All melting points were determined on a Yamato melting point apparatus, model MP-21, and are uncorrected. IR spectra were recorded on a Shimadzu IR-400 spectrometer. NMR spectra were taken on a Hitachi R-40 spectrometer and a JEOL FX 60 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS, 0.0 ppm) as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were determined with a Shimadzu-LKB 9000 gas chromatograph-mass spectrometer equipped with a direct inlet system.

Irradiations of succinimide derivatives in 10 mM solution were conducted using 60 W and 120 W low-pressure mercury lamps and a water-cooled quartz immersion well (Eikosha PIL-60 and EL-J-120). Stirring of the reaction mixture was effected by the introduction of a stream of nitrogen at the bottom of the outer jacket. All column chromatography was conducted using silica gel (Merck, Kieselgel 60, 70—230 mesh).

Succinimidoacetic Acid and Succinimidoacetyl Chloride——Succinimidoacetic acid (mp 111—115 °C, lit.,[8] mp 117—120 °C), prepared from succinic anhydride and glycine, was treated with phosphorus pentachloride to give succinimidoacetyl chloride, mp 63—66 °C (lit.,[8] mp 68—80 °C) according to the reported procedure.[8]

1-[(2,5-Dioxo-1-pyrrolidinyl)acetyl]dimethylamine (3a): Typical Procedure——A solution of dimethylamine (17.5 g, 14% (w/w)) in benzene was added dropwise to an ice-cooled solution of succinimidoacetyl chloride (28 mmol) in dry benzene (15 ml), and the mixture was stirred at room temperature for 1—2 h. After filtration, the solvent was removed *in vacuo*, and the residue was recrystallized from EtOH–Et_2O to give colorless plates (60% yield).

1-[(2,5-Dioxo-1-pyrrolidinyl)acetyl]pyrrolidine (3b)——Triethylamine (38 mmol) and ethyl chloroformate (38 mmol) were added to an ice-cooled solution of succinimidoacetic acid (32 mmol) in tetrahydrofuran (THF) (50 ml). The mixture was stirred for 5 min and a solution of pyrrolidine (38 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred overnight, then filtered, and the solvent was evaporated off *in vacuo*. The residue was recrystallized from AcOEt–hexane to give colorless needles (64% yield), mp 141—142 °C (lit.,[9] mp 139—142 °C).

Succinimide Derivatives (3c—e)——Compound **3c** was prepared by the method described above for **3b**. Compounds **3d**—**e** were prepared according to the procedure described above for the preparation of **3a**. The melting points of these imides are listed in Table I.

1-[(2-Oxo-1-pyrrolidinyl)methyl]-2,5-pyrrolidinedione (5a)——A mixture of 2-pyrrolidone (0.24 mol) and 37% formalin (0.24 mol) was heated at 120 °C for 3 h. The water was evaporated *in vacuo*, and the residue was recrystallized from benzene, mp 77.5—80 °C (lit.,[10] mp 76—77.5 °C). The resulting *N*-hydroxymethyl-2-pyrrolidone (0.13 mol) was refluxed with acetic anhydride (0.19 mol) for 1 h. This *O*-acetate (bp 141—142 °C/8 mmHg) was heated with succinimide at 240 °C for 6 h according to the procedure of Nakajima *et al.*[5] Compound **5a** was obtained as colorless plates from EtOH–Et_2O (53% yield).

1-[2-(2-Oxo-1-pyrrolidinyl)ethyl]-2,5-pyrrolidinedione (5b)——*N*-(2-Hydroxyethyl)-2-pyrrolidone[11] prepared from γ-butyrolactone and 2-aminoethanol was acetylated and subsequently heated with succinimide according to the reported procedure[5] as described above for **5a**. Recrystallization from AcOEt gave **5b** as colorless plates (80% yield).

***N*-[2-(2,5-Dioxo-1-pyrrolidinyl)ethyl]-*N*-methylacetamide (5c)**——Compound **5c** was prepared from succinimide and the corresponding diacetate, which was prepared from 2-(methylamino)ethanol and acetic anhydride, mp 87—87.5 °C (lit.,[5] mp 72 °C).

***N*-[3-(2,5-Dioxo-1-pyrrolidinyl)propyl]-*N*-methylacetamide (5d) and Ethyl *N*-[3-(2,5-Dioxo-1-pyrrolidinyl)-propyl]-*N*-methylcarbamate (5e)**——The Schiff base, prepared from *N*-methyl-1,3-diaminopropane and benzaldehyde, was acylated with acetic anhydride or ethyl chloroformate. The resulting N-acyl compound was treated with 8% hydrochloric acid, followed by treatment with triethylamine. Subsequently the mixture of the resulting diamine and succinic anhydride was heated at 160 °C for 3 h in the usual manner. Compounds **5d** and **5e** were obtained in 66 and 61% yields, respectively, as oily products.

1-[2-(2,5-Dioxo-1-pyrrolidinyl)propionyl]pyrrolidine (8a)——2-Succinimidopropionic acid (*N*,*N*-succinylalanine), prepared from *dl*-alanine and succinic anhydride, was treated with thionyl chloride. The resulting acid chloride was coupled with pyrrolidine in the presence of triethylamine. Compound **8a** was obtained as a pale yellow oil, yield, 52%.

1-[2-(2,5-Dioxo-1-pyrrolidinyl)-3-methylbutyryl]pyrrolidine (8b)——*N*,*N*-Succinylvaline prepared from *dl*-valine and succinic anhydride was treated with thionyl chloride, and the acid chloride was reacted with pyrrolidine as described above. Recrystallization from AcOEt–Et_2O gave colorless needles (58% yield).

Photolyses of 3, 5, and 8: General Procedure——A solution of **3**, **5**, or **8** (6 mmol) in acetonitrile was irradiated with a 60 W (**3a**, **b**, **5a**—**c**, **e**, **8a**, **b**) or 120 W (**3c**—**e**, **5d**) low-pressure mercury lamp at room temperature for 1.5—5 h under a nitrogen atmosphere. After removal of the solvent *in vacuo*, the residue was chromatographed over silica gel and the products were purified by recrystallization. Column chromatography was carried out using the following solvent systems: **4a**, CH_2Cl_2 : EtOH = 7 : 1 v/v; **4b**, AcOEt : acetone = 1 : 1; **4c**, benzene : AcOEt : EtOH = 8 : 3 : 1; **4d**, benzene : EtOH = 5 : 1; **4e**, AcOEt : EtOH = 10 : 1; **6**, CH_2Cl_2 : EtOH = 40 : 1; **7b**, AcOEt : EtOH = 5 : 1; **7c**, AcOEt : EtOH = 6 : 1; 7d, $CHCl_3$: acetone = 3 : 1; **7e**, AcOEt : acetone = 1 : 1; **9a**, $CHCl_3$: AcOEt = 1 : 1; **9b**, $CHCl_3$: acetone = 3 : 1. Photoproducts: **4a**, tetrahydro-8a-hydroxy-2-methylpyrrolo[1,2-*a*]pyrazine-3,6(2*H*,4*H*)-dione; **4b**-i, *trans*-hexahydro-10b-hydroxydipyrrolo[1,2-*a* : 2′,1′-*c*]pyrazine-3,6(2*H*,5*H*)-dione; **4b**-ii, *cis*-hexahydro-10b-hydroxydipyrrolo[1,2-*a* : 2′,1′-*c*]pyrazine-3,6(2*H*,5*H*)-dione; **4c**-i, *trans*-hexahydro-11b-hydroxy-1*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-3,6-(2*H*,5*H*)-dione; **4c**-ii, *cis*-hexahydro-11b-hydroxy-1*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-3,6-(2*H*,5*H*)-dione; **4d**-i, *trans*-octahydro-12b-hydroxypyrrolo[2′,1′ : 3,4]pyrazino[1,2-*a*]azepine-3,6(2*H*,5*H*)-dione; **4d**-ii, *cis*-octahydro-12b-hydroxypyrrolo[2′,1′ : 3,4]pyrazino[1,2-*a*]azepine-3,6(2*H*,5*H*)-dione; **4e**, hexahydro-11a-hydroxypyrrolo[2′,1′ : 3,4]pyrazino[2,1-*c*][1,4]oxazine-6,9(1*H*,7*H*)-dione; **6**, perhydro-9a-hydroxy-5*H*-dipyrrolo[1,2-*c*: 2′,1′-*e*]imidazole-3,7-dione; **7b**, tetrahydro-6-[1-(2-oxopyrrolidinyl)]-1*H*-azepine-2,5-dione; **7c**, tetrahydro-6-(*N*-methylacetamido)-1*H*-azepine-2,5-dione; **7d**, tetrahydro-6-[(*N*-methylacetamido)methyl]-1*H*-azepine-2,5-dione; **7e**, tetrahydro-6-[(*N*-methyl-*N*-ethoxycarbonyl)aminomethyl]-1*H*-azepine-2,5-dione; **9a**, tetrahydro-7-pyrrolidinylcarbonyl-1*H*-azepine-2,5-dione; **9b**, tetrahydro-6,6-dimethyl-7-pyrrolidinylcarbonyl-1*H*-azepine-2,5-dione.

Reduction of *trans*-4d-i with Lithium Aluminum Hydride: *trans*-Perhydropyrrolo[2′,1′ : 3,4]pyrazino[1,2-*a*]azepine (11a) and *cis*-Perhydropyrrolo(2′,1′ : 3,4]pyrazino[1,2-*a*]azepine (11b)——A solution of **4d**-i (300 mg, 1.26 mmol) in dry THF (60 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (240 mg, 6.3 mmol) in dry THF (20 ml) at room temperature. After being refluxed for 8.5 h, the excess reagent was decomposed with water and the resulting precipitate of inorganic salt was filtered off. The filtrate was dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was subjected to column chromatography on alumina, and elution with AcOEt–hexane (1 : 3, v/v) gave **11a** (179 mg, 73%) and **11b** (27 mg, 11%) as oily products.

Similarly, **4d**-ii was reduced to give **11a** (29%) and **11b** (37%). Compound **11a**: ^{1}H-NMR ($CDCl_3$) δ: 1.1—3.2 (22H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (t), 24.6 (t), 27.3 (t), 27.4 (t), 27.9 (t), 31.1 (t), 51.8 (t), 54.1 (t), 56.1 (t), 56.3 (t), 67.5 (d), 69.1 (d). MS *m*/*z*: 194 (M^+). High-resolution MS Calcd for $C_{12}H_{22}N_2$ (M^+, *m*/*z*): 194.1778. Found: 194.1783. Picrate of **11a** was recrystallized from methanol, mp 220 °C (dec.). Compound **11b**: ^{1}H-NMR ($CDCl_3$) δ: 1.1—3.1 (22H, m). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (t), 24.8 (t), 25.7 (t), 26.0 (t), 27.6 (t), 49.3 (t), 51.8 (t), 54.4 (t), 56.3 (t), 61.9 (d), 67.1 (d). High-resolution MS Calcd for $C_{12}H_{22}N_2$ (M^+, *m*/*z*): 194.1778. Found: 194.1772. Picrate, mp 218 °C (dec.) from methanol.

Crystal Data for 4b-ii——$C_{10}H_{14}N_2O_3$, $M_r = 210.23$, monoclinic, $a = 14.793\ (5)$, $b = 7.554\ (1)$, $c = 9.479\ (4)$ Å, $\beta = 107.67\ (5)°$, $v = 1009.3\ (6)$ Å^3, $z = 4$, $D_c = 1.383$ gcm^{-3}, space group $P2_1/a$.

Crystal Data for 4d-i——$C_{12}H_{18}N_2O_3$, $M_r = 238.29$, orthorhombic, $a = 17.195\ (2)$, $b = 12.756\ (1)$, $c = 10.436\ (1)$ Å, $v = 2289.2\ (2)$ Å^3, $z = 8$, $D_c = 1.383$ gcm^{-3}, space group *Pbca*.

Crystallographic Measurements and Structure Analyses——The intensity data for both compounds were collected by the $2\theta - \omega$ scan technique using graphite-monochromated Cu-$K\alpha$ radiation on a four-circle diffractometer (Rigaku AFC-5). The total numbers of reflections collected for **4b**-ii and **4d**-i were 1938 and 2188, respectively, of which 1534 and 1654 were significant [$|F_o| \geq 3.0\sigma(|F_o|)$]. Both structures were solved by the direct method using MULTAN and were refined by the block-diagonal least-squares methods. The final *R* values were 0.079 for **4b**-ii and 0.082 for **4d**-i. The bond lengths and angles of **4b**-ii and **4d**-i are shown in Figs. 2a and 2b, respectively.

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References

1) *a*) Photochemistry of the Imide System. XII. Part XI: M. Machida, K. Oda, and Y. Kanaoka, *Chem. Pharm. Bull.*, **32**, 950 (1984); *b*) Photoinduced Reactions. LXXXVI. Part LXXXV: K. Oda, M. Machida, K. Aoe, Y. Nishibata, Y. Sato, and Y. Kanaoka, *Chem. Pharm. Bull.*, **34**, 1411 (1986).

2) *a*) Y. Kanaoka, *Acc. Chem. Res.*, **11**, 407 (1978); *b*) P. H. Mazzocchi, "Organic Photochemistry," Vol. 5, ed. by

A. Padwa, Marcel Dekker, Inc., New York, 1981, p. 421; *c*) Y. Sato, H. Nakai, M. Wada, T. Mizoguchi, Y. Hatanaka, Y. Migita, and Y. Kanaoka, *Liebigs Ann. Chem.*, **1985**, 1099 and references cited therein.

3) *a*) M. Machida, H. Takechi, Y. Shishido, and Y. Kanaoka, *Synthesis*, **1982**, 1078; *b*) H. Takechi, M. Machida, and Y. Kanaoka, *Justus Liebigs Ann. Chem.*, **1986**, 859.

4) M. Machida, S. Oyadomari, H. Takechi, K. Ohno, and Y. Kanaoka, *Heterocycles*, **19**, 2057 (1982).

5) K. Nakajima, T. Shin-uchi, and M. Tauchi, *Nippon Kagaku Zasshi*, **88**, 976 (1967).

6) *a*) M. Machida, H. Takechi, and Y. Kanaoka, *Chem. Pharm. Bull.*, **30**, 1579 (1982); *b*) M. Machida, K. Oda, and Y. Kanaoka, *Chem. Pharm. Bull.*, **32**, 75 (1984).

7) *a*) Y. Kanaoka and Y. Hatanaka, *J. Org. Chem.*, **41**, 400 (1976); *b*) Y. Kanaoka, H. Okajima, and Y. Hatanaka, *Heterocycles*, **8**, 339 (1977); *c*) H. Nakai, Y. Sato, T. Mizoguchi, M. Yamazaki, and Y. Kanaoka, *ibid.*, **8**, 345 (1977).

8) J. C. Sheehan and G. Laubach, *J. Am. Chem. Soc.*, **73**, 4376 (1951).

9) J. P. Devlin, W. D. Ollis, J. E. Thorpe, R. J. Wood, B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, and D. E. Wright, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 830.

10) F. P. Sidel'kovskaya, M. G. Zelenskaya, and M. F. Shostakovskii, *Izv. Akad. Nauk SSSR*, **1959**, 901 [*Chem. Abstr.*, **54**, 1286*e* (1960)].

11) B. Puetzer, L. Katz, and L. Horwitz, *J. Am. Chem. Soc.*, **74**, 4959 (1952).