Photochemical Reaction of α-Alkyl-β-oxoamides. Competitive γ- and δ-Hydrogen Abstraction by Excited Ketone Carbonyl Groups

Tadashi Hasegawa,* Yoshiaki Arata, Kouichi Mizuno, Kenji Masuda, and Nobutoshi Yoshihara
Department of Chemistry, Tokyo Gakugei University, Nukuikitamachi, Koganeishi, Tokyo 184, Japan

The α-alkyl-β-oxoamides (**1a**—i) undergo the Norrish Type II photoreaction. The excited ketone carbonyl group in the β-oxoamides (**1c**, **1f**—i) abstracts γ- and δ-hydrogen competitively from the n,π^* triplet state. The regioselectivity of the hydrogen abstraction is affected by both the γ- and the δ-substituents. The presence of γ- or δ-substitution increases the γ- or the δ-hydrogen abstraction, respectively. The δ-hydrogen abstraction greatly predominates over the γ-hydrogen abstraction in the photolyses of the α-ethyl-β-oxoamides (**1f**) and (**1i**).

Intramolecular hydrogen abstraction by an excited carbonyl group is very specific in that γ-hydrogen abstraction involving a six-membered cyclic transition state generally predominates over δ-hydrogen abstraction and other possible modes.[1] Aryl alkyl ketones undergo γ-hydrogen abstraction from their n,π^* triplet states with nearly 100% efficiency.[2] The great facility of γ-hydrogen abstraction is due to stereoelectronic[3] or geometric requirements[4] for the abstraction. Hydrogen abstraction involving a seven-membered cyclic transition state takes place only when γ-hydrogens are absent or when δ-hydrogens are activated by substituents. Ketones bearing both γ- and activated δ-hydrogens undergo competitive γ- and δ-hydrogen abstraction by the excited carbonyl oxygen;[4,5] however, in general the quantum yields for the product formation through γ-hydrogen abstraction greatly surpass those through δ-hydrogen abstraction.[5a] We have previously reported that *NN*-dialkyl-β-oxoamides underwent photocyclization *via* δ-hydrogen abstraction to give pyrrolidin-2-ones in high yields.[6] We report here the completing γ- and δ-hydrogen abstractions by a ketone carbonyl group in photolyses of α-alkyl-β-oxoamides.[7]

Results and Discussion

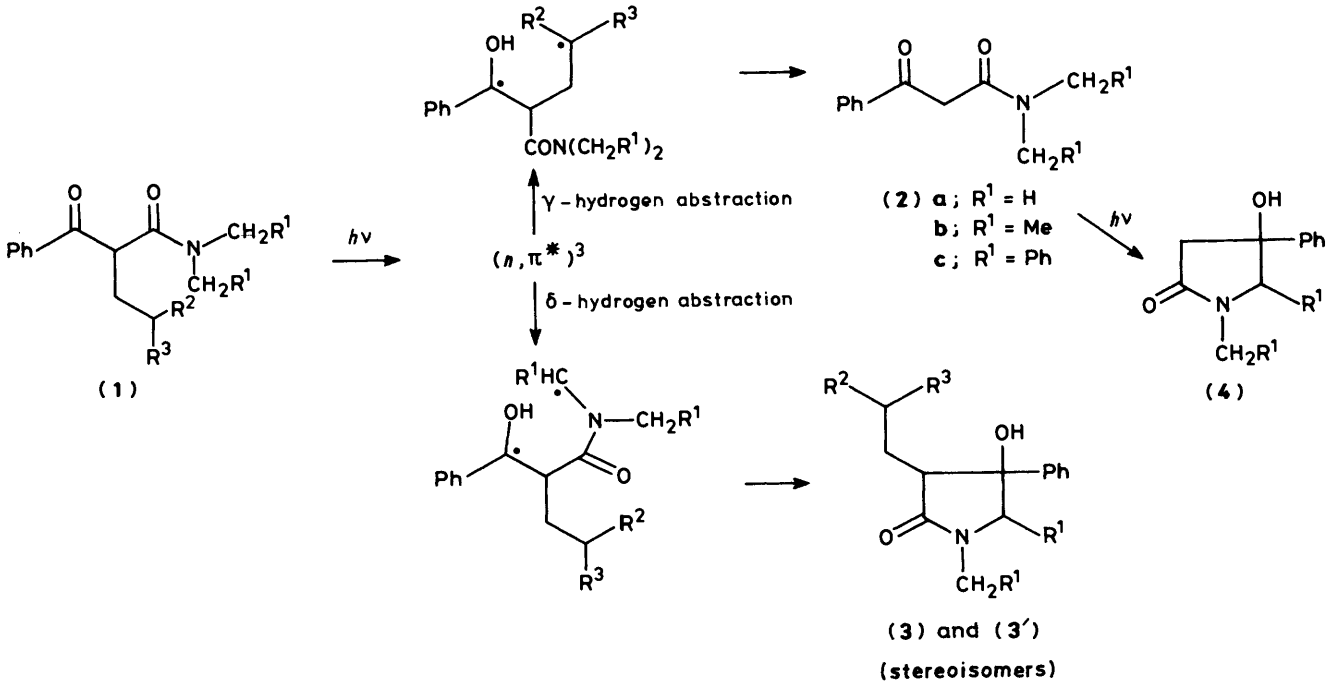
Irradiation of a methanol solution of *NN*-dimethyl-2-benzoyl-4-methylvaleramide (**1a**) under nitrogen with light from a 450 W high-pressure mercury lamp through a Pyrex filter gave *NN*-dimethylbenzoylacetamide (**2a**) quantitatively (Table 1). Similarly, irradiation of the α-alkyl-β-oxoamides (**1b**—e), (**1g**), and (**1h**) under the same conditions gave the corresponding benzoylacetamides (**2**) in high yields. In the photolysis of (**1d**), (**1g**), and (**1h**) the 3-alkylpyrrolidinones (**3d**), (**3g**), and (**3h**), respectively, were obtained as minor photoproducts. A trace of the pyrrolidinone (**4**) was also detected in each case. The ratios of the 3-alkylpyrrolidinone (**3**) to the benzoylacetamide (**2**) were quite different in photolyses of the α-alkyl-β-oxoamides (**1f**) and (**1i**). Irradiation of the *NN*-diethyl-β-oxoamide (**1f**) under the same conditions gave the benzoylacetamide (**2b**) and the 3-alkylpyrrolidinone (**3f**) in 27 and 66% yield, respectively. Similarly, irradiation of the *NN*-dibenzyl-β-oxoamide (**1i**) gave compounds (**2c**) and (**3i**) in 20 and 72% yield, respectively. The ratios of the 3-alkylpyrrolidinone (**3**) to the benzoylacetamide (**2**) are 2.44 and 3.60 in the photolysis of (**1f**) and (**1i**), respectively. In the case of the α-alkyl-β-oxoamides (**1f**—i), stereoisomers (**3f** and **f'**)—(**3i** and **i'**) were formed, whereas only one isomer could be obtained from the β-oxoamide (**1c**). We have reported that the stereoisomeric pyrrolidin-2-ones were produced from irradiation of *NN*-dibenzyl-α-methyl- and -α,α-dimethylbenzoylacetamide, and we identified the isomers from the former β-oxoamide as the *r*-4-hydroxy-*c*-3-methyl-4,*c*-5-diphenyl- and the *r*-4-hydroxy-*c*-3-methyl-4,*t*-5-diphenylpyrrolidin-2-ones on the basis of ^{1}H n.m.r. analysis.[6a] The 3-alkyl group in compounds (**3**) and (**3'**) may be located *trans* to the 4-phenyl group and the stereoisomers (**3**) and (**3'**) may be the *cis*–*trans* isomers (R^1 *cis* to 4-Ph and R^1 *trans* to 4-Ph).

Formation of the benzoylacetamides (**2**) can be explained in terms of the Type-II photoelimination of the α-alkyl-β-oxoamides (**1**). No cyclobutanols, the Type-II cyclization products, could be obtained; however, the possibility of their presence in small amounts cannot be eliminated. Formation of the pyrrolidinone (**4**) can be rationalized in terms of the secondary photoreaction of the benzoylacetamide (**2**).[6a] Therefore, both the benzoylacetamide (**2**) and the pyrrolidinone (**4**) are derived from the Type-II photoreaction of the α-alkyl-β-oxoamide (**1**). Although the yields of compounds (**2**) and (**4**) from (**1**) were dependent on the irradiation time, the ratios of the 3-alkylpyrrolidinone (**3**) to the sum of compounds (**2**) and (**4**) were nearly constant (Table 2). These results indicate that the secondary photoreaction of compounds (**2**) competes with the primary photoreaction of compounds (**1**). Formation of the 3-alkylpyrrolidinone (**3**) can be explained in terms of photocyclization *via* δ-hydrogen abstraction by the ketone carbonyl oxygen. The δ-hydrogen abstraction competed comparably with the stereoelectronically favoured γ-hydrogen abstraction in the photolysis of compounds (**1c**), (**1g**), and (**1h**), and predominated greatly over γ-hydrogen abstraction in the photolysis of compounds (**1f**) and (**1i**). These results indicate that the amide nitrogen in the α-alkyl-β-oxoamides effectively activates the δ-hydrogen atoms. Formation of both the benzoylacetamide (**2**) and the 3-alkylpyrrolidinone (**3**) from the β-oxoamide (**1i**) were effectively quenched with penta-1,3-diene, indicating that the reactions proceed from the n,π^* triplet state of the α-alkyl-β-oxoamide (**1**). Production of the 3-alkylpyrrolidinone (**3**) *via* δ-hydrogen abstraction may be considered to proceed from the charge-transfer state of the α-alkyl-β-oxoamide (**1**).[6] Electron transfer from the amide nitrogen to the excited carbonyl group may occur prior to hydrogen transfer. However, it is quite improbable that the rate of bimolecular quenching with penta-1,3-diene greatly surpasses the rate of intramolecular charge-transfer quenching. Therefore, the 3-alkylpyrrolidinones (**3**) are presumed to be formed *via* direct δ-hydrogen abstraction from the n,π^* triplet state of the α-alkyl-β-oxoamides (**1**). This is supported by the results of substituent effects studies on the regioselectivity in the photoreaction of compounds (**1**). The regioselectivity for the intramolecular hydrogen abstraction was affected by both the γ- and the δ-substituents. The ratios of the 3-alkylpyrrolidinone (**3**) to the sum of the benzolyacetamide (**2**) and the pyrrolidinone (**4**) give the relative quantum yields for the δ-

Table 1. Irradiation of the α-alkyl-β-oxoamides (1)

	Compound			% Yield of			% Yield of			%Yield of	Ratio
	R^1	R^2	R^3	(2a),	(2b), or (2c)		(3)	or	(3′)	(4)	(3)/(2) + (4)
(1a)	H	Me	Me	100				0		*	0
(1b)	H	Me	H	83				0		*	0
(1c)	H	H	H	57				29		*	0.51
(1d)	Me	Me	Me		93			0		*	0
(1e)	Me	Me	H		83			0		2	0
(1f)	Me	H	H		27		22		44	*	2.44
(1g)	Ph	Me	Me			86	4		7	*	0.13
(1h)	Ph	Me	H			71	10		18	*	0.39
(1i)	Ph	H	H			20	24		48	*	3.60

* A trace of compound (4) was detected.



hydrogen abstraction compared with the γ-hydrogen abstraction. The ratios decrease upon γ-methyl substitution [*e.g.*, (1i) > (1h) > (1g)] and increase upon δ-substitution [*e.g.*, (1c) < (1f) < (1i)]. These results can be reasonably explained in terms of bond-dissociation energy of the γ- and the δ-C–H bonds revealed by the order primary < secondary < tertiary, and support the mechanism involving direct δ-hydrogen abstraction.

Experimental

All m.p.s were uncorrected. The i.r. spectra were recorded with a JASCO A-3 spectrometer, and ^{1}H n.m.r. spectra with a JEOL FX-90Q spectrometer using $SiMe_4$ as an internal standard. An Ushio 450 W high-pressure mercury lamp was used as irradiation source.

The α-alkyl-β-oxoamides were prepared according to the literature method.[8]

General Procedure for Photoreactions of α-Alkyl-β-oxoamides.—A solution of the α-alkyl-β-oxoamide (1) (*ca.* 1 mmol) in methanol (50 cm^3) was irradiated for 1—6 h under nitrogen with light from a 450 W high-pressure mercury lamp through a Pyrex filter. After removal of the solvent, the residue was chromatographed on silica gel. Elution with a mixture of benzene–ethyl acetate gave the unchanged amide (1), the benzoylacetamide (2), the 3-alkylpyrrolidin-2-one (3), and/or the pyrrolidin-2-one (4). The structures of compounds (2) and (4) were determined by direct comparison with authentic samples.[6a,9] The structure of compounds (3) was deduced by the spectroscopic data and by elemental analysis.

3-Ethyl-4-hydroxy-1-methyl-4-phenylpyrrolidin-2-one (3c) had m.p. 142—143 °C; $\nu_{max.}$ (KBr) 3 300 and 1 660 cm^{-1}; δ($CDCl_3$) 0.85 (3 H, t, *J* 7.3 Hz, CH_2Me), 1.73 (2 H, dq, *J* 7.2 and 7.3 Hz, CH_2Me), 2.64 (1 H, brs, OH), 2.76 (1 H, t, *J* 7.2 Hz, 3-H), 2.90 (3 H, s, NMe), 3.50 (2 H, ABq, *J* 11.0 Hz, 5-H_2), and 7.2—7.6 (5 H, m, ArH) (Found: C, 71.1; H, 7.9; N, 6.3. $C_{13}H_{17}NO_2$ requires C, 71.20; H, 7.82; N, 6.39%).

1,3-Diethyl-4-hydroxy-5-methyl-4-phenylpyrrolidin-2-ones (3f and f′) could not be separated. The mixture did not crystallize; $\nu_{max.}$(neat) 3 350 and 1 670 cm^{-1}. The isomer (3f) showed δ($CDCl_3$) 0.68 (3 H, d, *J* 6.5 Hz, 5-Me), 1.08 (3 H, t, *J* 7.2 Hz, 3-CH_2Me), 1.16 (3 H, t, *J* 8.3 Hz, NCH_2Me), 1.5—2.0 (2 H, m,

Table 2. Dependence of the ratio (3)/(2) + (4) on conversion of (1)

Compound	Conversion %	% Yield of (2)	% Yield of (3)	% Yield of (4)	Ratio (3)/(2) + (4)
(1c)	28	57	29	trace	0.51
	59	42	30	16	0.52
(1e)	64	83	0	2	0
	85	72	0	10	0
	~100	57	0	25	0

3-CH_2), 2.18 (1 H, br s, OH), 2.7—3.2 (1 H, m, 3-H), 3.5—3.9 (3 H, m, NCH_2 and 5-H), and 7.2—7.6 (5 H, m, ArH). The isomer (**3f'**) showed δ($CDCl_3$) 0.77 (3 H, t, *J* 7.7 Hz, 3-CH_2*Me*), 1.09 (3 H, d, *J* 6.4 Hz, 5-Me), 1.11 (3 H, t, *J* 7.3 Hz, NCH_2*Me*), 1.5—2.0 (2 H, m, 3-CH_2), 2.18 (1 H, br s, OH), 2.7—3.2 (1 H, m, 3-H), 3.5—3.9 (3 H, m, NCH_2 and 5-H), and 7.2—7.6 (5 H, m, ArH) [Found (for mixture): C, 73.2; H, 8.8; N, 5.5. $C_{15}H_{21}NO_2$ requires C, 72.84; H, 8.56; N, 5.66%].

1-*Benzyl*-4-*hydroxy*-3-*isobutyl*-4,5-*diphenylpyrrolidin*-2-*ones* (**3g** and **g'**) were obtained in 11% yield (ratio 2:3). The pyrrolidin-2-one (**3g'**) was isolated by fractional recrystallization, but complete purification of compound (**3g**) could not be achieved; the latter showed δ($CDCl_3$) 0.61 (3 H, d, *J* 5.1 Hz, Me), 0.74 (3 H, d, *J* 5.1 Hz, Me), 1.1—1.4 (1 H, m, C*H*Me_2), 1.7—2.0 (2 H, m, 3-CH_2), 2.19 (1 H, br s, OH), 2.86 (1 H, t, *J* 6.1 Hz, 3-H), 3.68 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.64 (1 H, s, 5-H), 5.26 (1 H, d, *J* 14.8 Hz, NCH*H*Ph), and 6.7—7.5 (15 H, m, ArH). The isomer (**3g'**) had m.p. 194—195 °C; $\nu_{max.}$(KBr) 3 350 and 1 680 cm^{-1}; δ($CDCl_3$) 0.86 (3 H, d, *J* 6.1 Hz, Me), 0.87 (3 H, d, *J* 6.1 Hz, Me), 1.1—1.4 (1 H, m, C*H*Me_2), 1.7—2.0 (2 H, m, 3-CH_2), 2.19 (1 H, br s, OH), 3.28 (1 H, t, *J* 6.1 Hz, 3-H), 3.71 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.40 (1 H, s, 5-H), 5.37 (1 H, d, *J* 14.8 Hz, NCHHPh), and 6.7—7.5 (15 H, m, ArH) (Found: C, 81.1; H, 7.4; N, 3.4. $C_{27}H_{29}NO_2$ requires C, 81.17; H, 7.32; N, 3.51%).

1-*Benzyl*-4-*hydroxy*-4,5-*diphenyl*-3-*propylpyrrolidin*-2-*ones* (**3h** and **h'**) could not be separated. The 5:9 mixture had m.p. 185—202 °C; $\nu_{max.}$(KBr) 3 400 and 1 680 cm^{-1}. The isomer (**3h**) showed δ($CDCl_3$) 0.75 (3 H, t, *J* 6.4 Hz, Me), 1.1—2.1 (4 H, m, NCH_2CH_2Me), 2.36 (1 H, br s, OH), 3.19 (1 H, t, *J* 5.8 Hz, 3-H), 3.64 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.57 (1 H, s, 5-H), 5.27 (1 H, d, *J* 14.8 Hz, NCH*H*Ph), and 6.6—7.4 (15 H, m, ArH). The isomer (**3h'**) showed δ($CDCl_3$) 0.86 (3 H, t, *J* 6.1 Hz, Me), 1.1—2.1 (4 H, m, NCH_2CH_2Me), 2.36 (1 H, br s, OH), 3.20 (1 H, t, *J* 5.8 Hz, 3-H), 3.60 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.40 (1 H, s, 5-H), 5.34 (1 H, d, *J* 14.8 Hz, NCH*H*Ph), and 6.6—7.4 (15 H, m, ArH) [Found (for mixture): C, 81.1; H, 7.1; N, 3.6. $C_{26}H_{27}NO_2$ requires C, 81.01; H, 7.06; N, 3.63%].

1-*Benzyl*-3-*ethyl*-4-*hydroxy*-4,5-*diphenylpyrrolidin*-2-*ones* (**3i** and **i'**) could not be separated. The 1:2 mixture had m.p. 95—117 °C; $\nu_{max.}$(KBr) 3 420 and 1 680 cm^{-1}. The isomer (**3i**) showed δ($CDCl_3$) 0.81 (3 H, t, *J* 7.7 Hz, Me), 1.4—2.2 (2 H, m, 3-CH_2), 1.66 (1 H, br s, OH), 2.7—2.9 (1 H, m, 3-H), 3.69 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.61 (1 H, s, 5-H), 5.26 (1 H, d, *J* 14.8 Hz, NCH*H*Ph), and 6.5—7.4 (15 H, m, ArH). The isomer (**3i'**) showed δ($CDCl_3$) 0.99 (3 H, t, *J* 7.7 Hz, Me), 1.4—2.2 (2 H, m, 3-CH_2), 2.56 (1 H, br s, OH), 2.7—2.9 (1 H, m, 3-H), 3.67 (1 H, d, *J* 14.8 Hz, NC*H*HPh), 4.51 (1 H, s, 5-H), 5.29 (1 H, d, *J* 14.8 Hz, NCH*H*Ph), and 6.5—7.4 (15 H, m, Ar-H) [Found (for mixture): C, 80.8; H, 6.8; N, 3.7. $C_{25}H_{25}NO_2$ requires C, 80.83; H, 6.78; N, 3.77%].

References

1 P. J. Wagner, *Acc. Chem. Res.*, 1983, **16**, 461.
2 P. J. Wagner, P. A. Kelso, and R. G. Zepp, *J. Am. Chem. Soc.*, 1972, **94**, 7480.
3 N. J. Turro and D. S. Weiss, *J. Am. Chem. Soc.*, 1968, **90**, 2185.
4 P. J. Wagner, P. A. Kelson, A. E. Kemppainen, and R. G. Zepp, *J. Am. Chem. Soc.*, 1972, **94**, 7500.
5 (*a*) P. J. Wagner and R. G. Zepp, *J. Am. Chem. Soc.*, 1971, **93**, 4958; (*b*) L. M. Stephenson and J. L. Parlett, *J. Org. Chem.*, 1971, **36**, 1093; P. Yates and J. M. Pal, *Chem. Commun.*, 1970, 553; D. J. Coyle, R. V. Peterson, and J. Heicklen, *J. Am. Chem. Soc.*, 1964, **86**, 3850.
6 (*a*) T. Hasegawa, H. Aoyama, and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2054; 1979, 963; (*b*) T. Hasegawa, M. Inoue, H. Aoyama, and Y. Omote, *J. Org. Chem.*, 1978, **43**, 1005.
7 A preliminary account of this work has appeared: T. Hasegawa, Y. Arata, and K. Mizuno, *J. Chem. Soc., Chem. Commun.*, 1983, 395.
8 A. L. Searles and D. Ressler, *J. Am. Chem. Soc.*, 1958, **80**, 3656; G. E. Utzinger, *Helv. Chim. Acta*, 1952, **35**, 1359.
9 T. Oishi, M. Ochiai, M. Nagai, and Y. Ban, *Tetrahedron Lett.*, 1968, 497; M. Seefelder, Ger. P. 1 089 760 (*Chem. Abstr.*, 1962, **56**, 1326i); H. Aoyama, T. Hasegawa, T. Nishio, and Y. Omote, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1671.

Received 21*st May* 1984; *Paper* 4/823