

SYNTHESES OF MEDIUM-SIZED KETO-LACTAM SYSTEMS
 BY THE PHOTO-RING-ENLARGEMENT OF N-SUBSTITUTED ALICYCLIC IMIDES¹

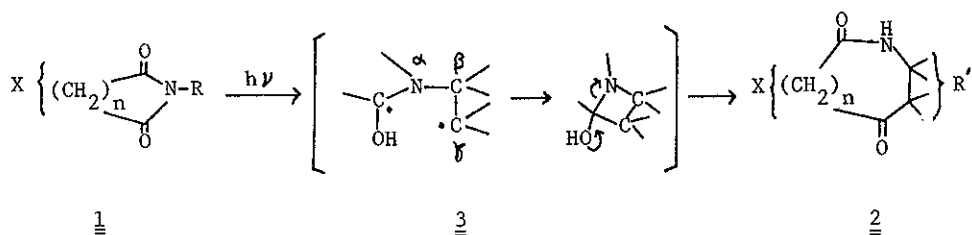
Yuichi Kanaoka^{*}, Haruo Okajima and Yasumaru Hatanaka

Faculty of Pharmaceutical Sciences, Hokkaido University

Sapporo 060, Japan

Synthetic application of the photo-ring-expansion reaction of N-substituted alicyclic imides 1 was studied and a variety of seven- and eight-membered keto-lactam systems 2 were photo-chemically synthesized from succinimides and glutarimides.

Our interest in the complex photochemical behavior of cyclic imide systems² has generated efforts to harness their diverse photoreactions to synthetic designs.¹⁻³ Properly designed molecular segments could, for example, be used as latent functional groups, capable of rearranging to the desired functionality under the mild conditions of photolysis. Thus, we have recently found that alicyclic imides 1 such as N-substituted succinimides and glutarimides undergo photocyclization, to afford keto-lactams 2, with ring-enlargement by the two carbon unit derived from the side chain.^{1a} As a first extensive application of this new ring-expansion reaction, we now wish to report easy syntheses of a series of seven- and eight-membered lactam derivatives including various di- and tri-cyclic systems.



A solution of substituted succinimides and glutarimides (1a-o) in acetonitrile (10 mM) was irradiated with a 60-W low-pressure mercury lamp for 40 min and the results are tabulated in Table I. Major photoproducts were purified by column-chromatography (silica gel) and identified by their spectra and elemental analyses.⁴ In a representative example, the structural assignment for 2g was based on (i) the presence of a carbonyl [uv 283 nm (ϵ 25); ir 1690cm⁻¹] and an amide (ir 1650cm⁻¹); (ii) the presence of the β [¹H NMR 3.6ppm (C₆H₂m)] and the γ [¹H NMR 2.5ppm (C₇H₂m)] carbons, and NH (7.50ppm); (iii) the molecular composition, C₈H₁₁NO₂ (mass m/e 153; elemental analysis). In several cases approximately 1:1 mixture of stereoisomers were obtained which are separable by analytical gas-liquid- but not by preparative column-chromatography at present.

In all cases keto-lactams having two additional carbons in their rings were readily obtained in moderate isolated yields, accompanied by some amount of the elimination products [N-unsubstituted succinimides or glutarimides 1(R=H) ; 4-28 %]. Thus the principal feature of the Norrish type II processes of the alicyclic imides is again not the elimination but rather the cyclization forming the keto-lactams with ring enlargement by the two-carbon unit most probably by way of γ -hydrogen abstraction 3. In the pre-

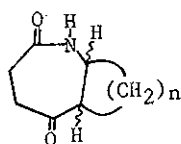
Table I Products of Photolysis of the Cyclic Imides 1

Compounds	<u>1</u>			<u>2</u>	<u>1</u> (R=H)	<u>1</u>	
	n	X	R	% ^{a)}	mp °C	% recovered %	
<u>a</u>	2	-	cyclooctyl	42 ^{b)}	191-203	12	14
<u>b</u>	2	-	cyclododecyl	39 ^{b)}	221-8	15	18
<u>c</u>	2	3-Me	Et	15 ^{b)}	139-44	14	42
<u>d</u>	2	3,3-diMe	Et	17 ^{b)}	155-66	12	46
<u>e</u>	3	4,4-diMe	isobutyl	33	203-4	18	11
<u>f</u>	3	4,4-diMe	TEF	27	157.5-8.5	25	24
<u>g</u>	2	3,4-(CH ₂) ₂ -	Et	58	160-1	4	11
<u>h</u>	2	3,4-(CH ₂) ₂ -	isobutyl	32	195-6	8	9
<u>i</u>	2	3,4-(CH ₂) ₂ -	TEF	{ 25(α) 25(β)	{ 226-7.5 183-4	16	20
<u>j</u>	2	3,4-(CH ₂) ₂ -	cyclopentyl	55 ^{b)}	239-52	11	21
<u>k</u>	2	<u>cis</u> -3,4-(CH ₂) ₄ -	Et	17	151-3	28	24
<u>l</u>	2	<u>cis</u> -3,4-(CH ₂) ₄ -	isobutyl	28	155-6	10	16
<u>m</u>	2	<u>cis</u> -3,4-(CH ₂) ₄ -	TEF	{ 27(α) 25(β)	{ 167.5-8.5 114-5	7	18
<u>n</u>	3	4,4-(CH ₂) ₄ -	TEF	26	152-4	16	21
<u>o</u>		<u>d</u> -camphoric	Et	c) { 23(α) ^{b)} 22(β) ^{b)}	{ 179-83 229-35	23 22	

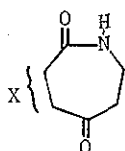
a) Recovered 1 was not calculated. b) mixture of stereoisomersc) accompanied by 2o-7. TEF = tetrahydrofurfuryl

ceding paper we have predicted general synthetic potential of this ring-expansion reaction on the basis of possible structural variation of the substrates 1.^{1a} In confirmation of part of the validity of the prediction, the results in Table I now demonstrate that the cyclic imides carrying substituents, including cycloalkanes, either on the imide ring or the N-side chain, or both, smoothly undergo the expected ring-expansion affording a variety of seven- and eight-membered keto-lactam systems: e.g., bicyclic, including a large ring 2b, tricyclic 2j, and spiro systems 2f, 1, m, n.

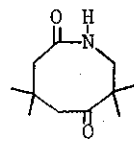
We are intrigued by the observation that a rigid imide 1o gave a product 2o-γ of a different pattern, as well as the expected bicyclic bridged keto-lactams (2o-α, β). The structures 2o-α and β were assigned on the basis of their ¹³C NMR spectra (DMSO-d₆) [α: C₁55.2, C₂176.0, C₆212.0, C₇



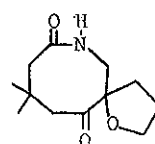
2 a : n = 6
b : n = 10



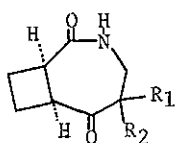
2 c : X = CH₃
d : X = (CH₃)₂



2 e



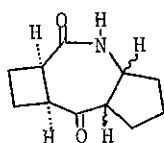
2 f



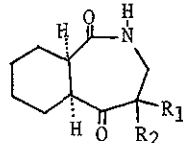
2 g : R₁=R₂= H

h : R₁=R₂= CH₃

i : R₁-R₂=



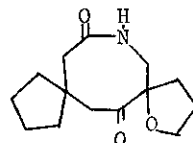
2 j



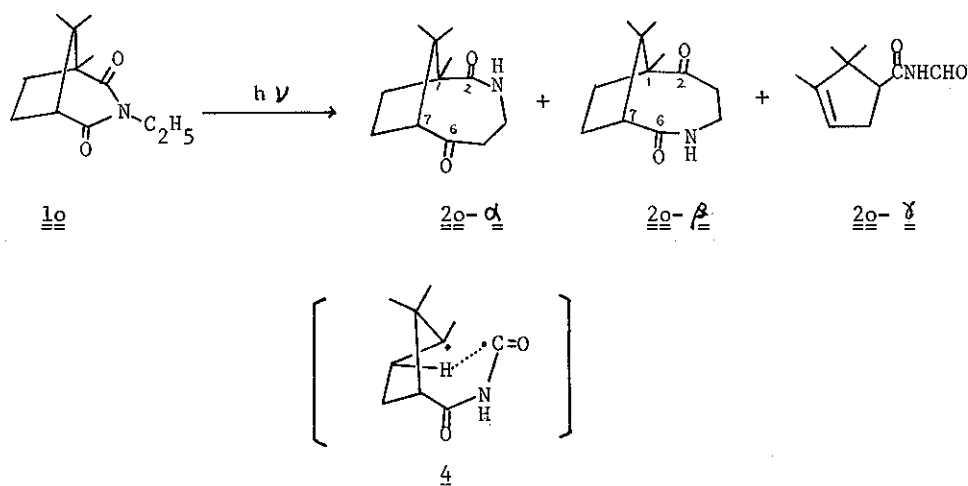
2 k : R₁=R₂= H

1 : R₁=R₂= CH₃

m : R₁-R₂=



2 n



65.0ppm; $\underline{\beta}$: C_1 59.7, C_2 214.0, C_6 173.9, C_7 60.7ppm]. It appears that partial isomerization including photoracemization takes place in the course of the photolysis in view of the too broad mps of $\underline{20-\alpha}$ and $\underline{-\beta}$ for their clear ^1H - and ^{13}C -NMR spectra. The pathway leading to the third compound $\underline{20-\gamma}$, which was a monocyclic unsaturated formimide, may involve type I cleavage of the photo-elimination product followed by hydrogen transfer as visualized in the postulated intermediate biradical $\underline{4}$. This is the first case of type I process reported in the photochemistry of cyclic imides,² a fact which may be attributed to better stabilization of a radical generated on the tertiary carbon of the intermediate $\underline{4}$.

Medium-sized lactams are often difficult of access by conventional cyclization reactions. In addition, while these keto-lactams will further be used as synthetic intermediates by virtue of their multifunctionality, cyclic imides are starting materials which can be relatively easily prepared. In conclusion, this photo-ring-expansion reaction provides a versatile synthetic entry to otherwise rather inaccessible type of heterocyclic systems.

ACKNOWLEDGEMENTS One of the author (Y.K.) wishes to express deep gratitude to Professor Shigehiko Sugasawa, on the occasion of his 80th birthday, for the guidance which directed him to the fascinating research field of heterocyclic chemistry.

This work was supported in part by grants from the Ministry to Education, Science and Culture.

REFERENCES

- 1 a) Photochemistry of the Imide System.II. For Part I: Y. Kanaoka and Y. Hatanaka, J.Org.Chem., 1976, 41, 400.
b) Photoinduced Reactions.XXXII. For Part XXXI: M. Machida, H. Takechi, and Y. Kanaoka, submitted.
- 2 For a review see: Y. Kanaoka, J.Soc.Org.Synth.Chem.Tokyo, (in Japanese) 1975, 33, 949.
- 3 Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka and Y. Kanaoka, J.Am.Chem.Soc., 1976, 98, 2349; and papers cited therein.
- 4 All new compounds gave satisfactory elemental analyses and their structures were supported by spectral (uv, ir, NMR, Mass) data.

Received, 5th August, 1977