

PHOTOCHEMISTRY OF THE PHTHALIMIDE SYSTEM. V¹

PHOTOCYCLIZATION OF THE PHTHALIMIDES WITH A SULFIDE CHAIN:

SYNTHESIS OF AZA-CYCLOLS BY δ , ϵ , AND ζ HYDROGEN ABSTRACTION²

Yasuhiko Sato, Hideo Nakai, Hiroshi Ogiwara and Tomishige Mizoguchi

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda, Saitama 335 Japan

Yoshihiro Migita and Yuichi Kanaoka*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060 Japan

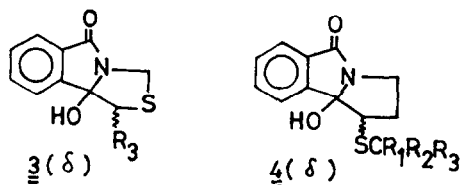
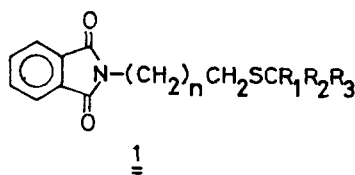
(Received in Japan 22 August 1973; received in UK for publication 5 October 1973)

Certain N-substituted phthalimides having γ or δ hydrogens³ undergo cyclization to benzazepinone lactams¹ or aza-cyclopentanols⁴ on photolysis. Some N- ω -alkoxyalkylphthalimides were also cyclized to aza-cyclopentanol derivatives with facile δ hydrogen abstraction^{4b}. In continuation of the photochemical synthetic studies of the phthalimide system, phthalimide derivatives having a sulfide moiety in the N-alkyl side chain were now prepared and their photolysis was explored.

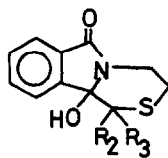
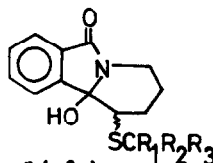
Irradiation⁵ of 1a afforded the cyclized product 3a only in a very low yield. The major product was N-methylphthalimide (30%)^{6,7}. However, 3b was obtained from 1b in a better yield as a 1 : 2 mixture of cis and trans isomers. Relatively facile δ hydrogen transfer is again realized for the photolysis of 1 (n=2; R₁=R₂=R₃=Me) giving 4 in 47 % yield. Substrates (1 ; n=1) which possess both γ and ϵ hydrogens similarly activated by the adjacent sulfur atom were then photolyzed to compare their susceptibility to the abstraction. Aza-thiacyclohexanol derivatives (5a - d) were isolated as major photoproducts, which have apparently arisen from a Norrish type II reaction with ϵ hydrogen transfer, accompanied by benzazepinone lactam, a γ hydrogen transfer product¹. Of particular interest is the observation that ϵ hydrogens are rather reactive than γ hydrogens in the photocyclization of these phthalimides⁸. The result is worthy to

note in view of that the reactivity in the order $\gamma > \delta > \epsilon$ has been well established in the conventional type II reactions of the ordinary keto system⁹. This tendency was further confirmed by the irradiation of 1 ($n=3$), which gave the aza-cyclohexanol derivatives (6a - d) in moderate to good yields.

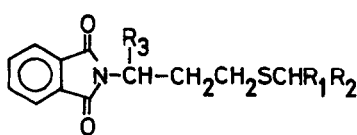
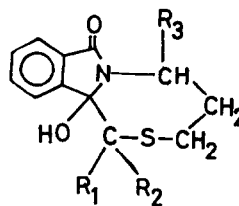
During the studies of photodecarboxylation of N-phthaloyl- α -amino acids¹⁰, an unexpected product (7a ; 38 %) was isolated on irradiation of N-phthaloylmethionine (2; $R_1=R_2=H$, $R_3=CO_2H$). The nmr spectrum of 7a showed a new peak of methylene (3.43 (d, 15 Hz), 3.01 (d, 15 Hz); δ , $CDCl_3$) in place of the original methyl in 2 clearly indicating that the cyclization has occurred at the sulfide methyl group, and all other spectral and analytical data supported the structure 7a. Irradiation of N-phthaloylmethionine methyl ester afforded 7b, and 2a was converted to 7a in a very good yield. It is remarkable that in all examples (2a - f) studied, aza-thia-cycloheptanol derivatives 7 were obtained mostly in good yields. None of γ -hydrogen transfer products were detected, while the yields of the " S " products 7 always surpassed that of the competing δ hydrogen transfer products 4 ($R_3=H$) except the case of 2d. These results represent the first examples of efficient photocyclization involving a carbonyl system to form a seven membered cyclic alcohol. Although detailed mechanisms of these reactions presented in this work are unknown^{11,12}, ϵ and S hydrogen abstractions are tentatively postulated on the basis of formal analogy with the typical Norrish type II processes^{1,4,9}. The scope and limitation as well as the mechanism of these reactions are under investigation.



<u>1</u>	<u>a</u>	<u>b</u>	
n	0	0	2
R_1	H	H	Me
R_2	H	H	Me
R_3	Me	C_6H_5	Me
yield	3	27	47
mp ($^{\circ}C$)	157.5-159.5(c) 126-128(t)	184-185(c) 154-155(t)	oil ^d

5(ϵ)6(ϵ)

<u>1</u>	<u>a</u>	<u>b</u>	<u>c</u>	<u>d</u>	<u>a</u>	<u>b</u>	<u>c</u>	<u>d</u>
n	1	1	1	1	3	3	3	3
R ₁	H	H	H	H	H	H	Me	$\left. \begin{array}{l} \text{CR}_1\text{R}_2\text{R}_3 \\ = \text{C}_6\text{H}_5 \end{array} \right\}$
R ₂	H	H	Me	H	H	Me	Me	
R ₃	H	Et	Me	C ₆ H ₅	H	Me	Me	
yield	47 (Y,6)	10 (Y,5)	16 (Y,13)	19 -	68	40	76	39
mp (°C)	162-164	170-172 (mixture)	181-182	245-247	164-165(c) 115-116(t)	128-129	191-193 o ₁₁ ^d	195-197 133-135 ^d

27(ζ)

<u>2</u>	<u>a</u>	<u>b</u>	<u>c</u>	<u>d</u>	<u>e</u>	<u>f</u>
R ₁	H	H	H	Me	H	H
R ₂	H	H	Me	Me	isopropyl	C ₆ H ₅
R ₃	H	CO ₂ Me	H	H	H	H
yield	86	64	43	17 (δ ,33)	80	54
mp (°C)	187-189	202-205(c) 121-123(t)	202-203(c) 205-207(t)	209-211	200-202 189-191	222(c) 224(t) 175-176 ^d

c, cis t, trans with respect to the hydroxy and the adjacent substituent groups in the new ring. d, the dehydrated cyclic olefin.

References

- (1) For Part IV see: Y.Kanaoka, Y.Migita, K.Koyama, Y.Sato, H.Nakai and T.Mizoguchi, Tetrahedron Letters, (1973) 1193.
- (2) Photoinduced Reactions, XI.
- (3) The N atom is regarded as a with respect to the imide carbonyl carbon.^{1,4}
- (4) (a) Y.Kanaoka and K.Koyama, Tetrahedron Letters, (1972) 4517; (b) Y.Kanaoka, Y.Migita, Y.Sato and H.Nakai, ibid., (1973) 51.
- (5) Irradiation were carried out in 15 mM acetone solution unless otherwise stated using a 400 W high pressure mercury lamp under a stream of argon at room temperature for 0.5 - 3 hr. as required. Products were purified through preparative tlc or column chromatography (silica gel). All new compounds analyzed satisfactorily. Reasonable spectral data (uv, ir, nmr and mass) were obtained for all of them.
- (6) Although photochemical behaviors of γ -keto sulfides are little known^{7a}, photoelimination of β -keto sulfides has been reported from several groups^{7b-f}.
- (7) (a) P.J.Johnson and G.A.Berchtold, J.Am.Chem.Soc., 89, 2761 (1969); (b) H.Hogeveen and P.J.Smit, Rec.Trav.Chim.France, 85, 489 (1966); (c) J.R.Collier and J.Hill, Chem.Comm., (1968) 700; (d) A.Padwa, A.Battisi and E.Shefter, J.Am.Chem.Soc., 91, 4000 (1969); (e) M.C.Caserio, W.Lauer and T.Novinson, ibid., 92, 6082 (1970); (f) A.Padwa and D.Pashayan, J.Org.Chem., 36, 3550 (1971).
- (8) There have been reported only very limited examples of ϵ hydrogen transfer for a simple ketone system; see N.C.Yang in " Reactivity of the Photoexcited Organic Molecule ", Interscience, New York, 1967, pp 145.
- (9) P.J.Wagner, Account Chem.Res., 4, 168 (1971).
- (10) Y.Sato, H.Nakai, T.Mizoguchi, M.Kawanishi and Y.Kanaoka, Chem.Pharm.Bull., 21, 1164 (1973)
- (11) Inference that there is an effective interaction favoring the reaction between the phthalimide moiety and the sulfide group is attractive. However, there is indication of neither charge-transfer complex nor other ground-state interactions^{7d,12} at least as monitored by the uv and ir spectra. Other possibilities including " intramolecular exciplex ", for example, still remain to be studied.
- (12) (a) E.A.Fehnel and M.Carmack, J.Am.Chem.Soc., 71, 84 (1949); (b) N.J.Leonard, T.W.Milligan and T.L.Brown, ibid., 82, 4075 (1960); (c) G.Bergson, G.Claeson and L.Schotte, Acta Chem.Scand., 16, 1159 (1962).

Acknowledgment Y.S., H.N., H.O. and T.M. are grateful to Mr. M.Yamazaki, Director, for his encouragement.