Communications to the Editor

[Chem. Pharm. Bull. 30(9)3414—3417(1982)]

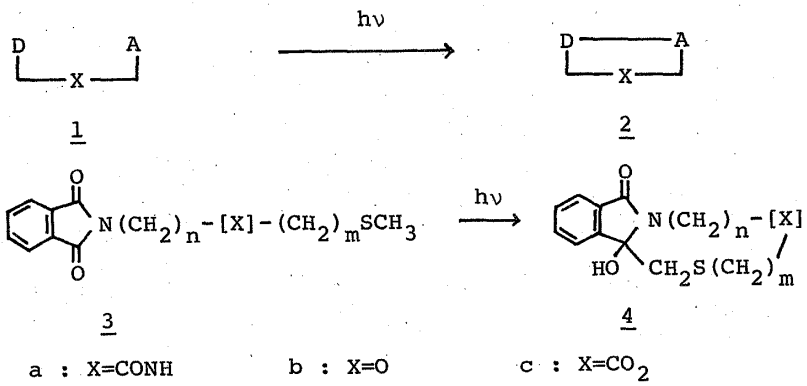
A REMOVABLE FUNCTIONAL GROUP IN A PHOTOCHEMICAL MACROCYCLIC SYNTHESIS: REMOTE PHOTOCYCLIZATION WITH A PAIR SYSTEM OF PHTHALIMIDE AND 1,3-DITHIOLANYL GROUPS[1)]

Masao Wada,[a] Hideo Nakai,[a] Yasuhiko Sato*,[a] and Yuichi Kanaoka[b]
Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.,[a]
2-2-50, Kawagishi, Toda, Saitama 335, Japan and
Faculty of Pharmaceutical Sciences, Hokkaido University,[b]
Kita-12, Nishi-6, Kitaku, Sapporo 060, Japan

Based on a regioselective remote photocyclization of a pair system consisting of a phthalimide group and a dithiolanyl group, a variety of aza-cyclic compounds with methylene, ester, or amide groups in their frameworks were synthesized. The dithiolanyl group provides a removable donor, which effects a subsequent reaction followed by removal to give a new carbon skeleton.

KEYWORDS——phthalimide derivative; regioselective remote photocyclization; macrocyclic compound; donor-acceptor pair system; electron-transfer process; desulfurization

We have been studying the application of a common working hypothesis, "photolysis of donor-acceptor pair systems" for general synthetic purposes[2)] (Scheme I). In the approach with phthalimide as a typical acceptor (A), various donors (D) have been used such as sulfides,[3a)] aromatics[3b)] anilines,[3c)] amines,[3d)] olefins,[3e)] and indene.[3f)] To see the scope and limitation of this method, a possible extent of structural variation of the substrates (3) was explored, with the phthalimide-thiomethyl pair system, by systematically changing the connector portion (X) which combines the donor and the acceptor. Thus, a series of macrocycles (4) containing amides (4a),[4-6)] ethers (4b),[5-7)] and esters (4c)[1a)] have been successfully synthesized.

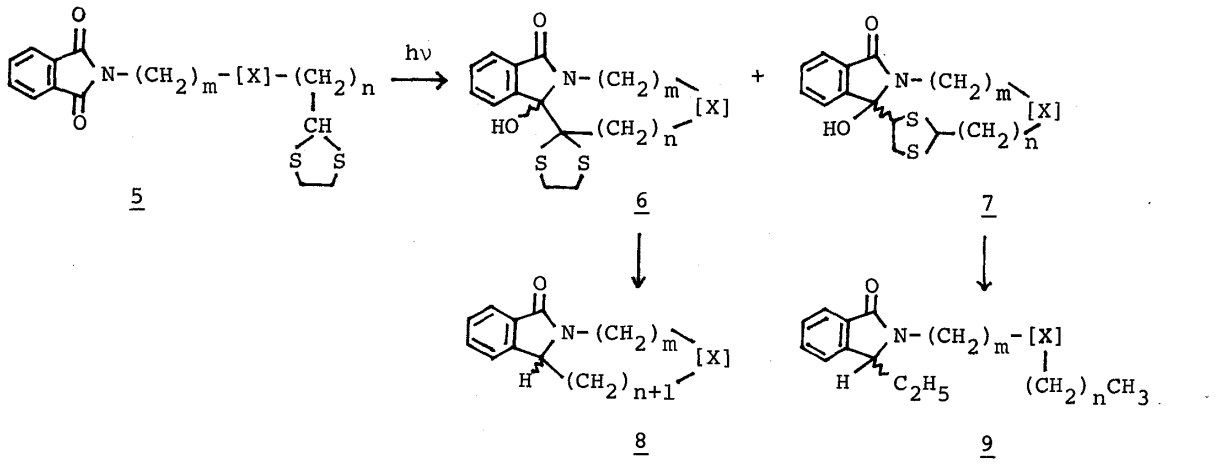


Scheme I

In this system, the imide carbonyl and the sulfide methyl groups provide the site for the formation of a new carbon-to-carbon bond, and as a result the thioether moiety is inevitably involved in the newly formed macrocyclic framework (4). In view of general synthetic methodology, it is advisable to have a functional group which effectively induces a certain desired reaction, then at a proper stage it can be removed or converted into a group needed for the following reaction steps. In the present work we wish to report that 1,3-dithiolanyl group is a candidate for such a removal functional group.

The substrates 5[8] were prepared by the following methods; N-(ω-formylalkyl)-phthalimides and N-((2,2-diethoxy)ethyl)-11-(phthalimido)-undecanamide were ketalized (or transketalized) with ethane dithiol in the presence of BF_3-etherate to afford 5a (mp 97-98°C), 5b (mp 82-83°C) and 5e (mp 124-125°C). N-Phthaloylglycine and 11-(phthalimido)-undecanoic acid were esterified with 4-(1,3-dithiolan-2-yl)butan-1-ol, 1-methyl-2-chloropyridinum iodide[9] and triethylamine to afford 5c (mp 99-100°C) and 5d (mp 45-46°C) respectively in good yields.

A solution of 5 (4-10 mM) was irradiated with a 400 W high-pressure mercury lamp in a stream of argon at room temperature for 25-360 min. As shown in Table I,[8] the cyclized product 6 was obtained in moderate yield (20-82%) as a major product (in some cases accompanied by small amounts of 7) after silica gel column chromatography. This resulted from a C-C bond formation between the imide carbonyl and the methine (and/or methylene) carbon(s) adjacent to the sulfur atom in their side chain, probably through electron transfer.[2,3] The methine group is more reactive than the methylene group, apparently due to the cumulative effects of the two adjacent sulfurs of the dithiolanyl function. In some limited cases, azathiacyclols 7 predominates, presumably due to the solvent effects and conformational factors in the excited state. In a representative example, the structural assignment for 6e was based on the following evidence: (i) the presence of the



Scheme II

Table I. Photoproducts from the Substrates (5)

Substrates 5				Conditions		Products 6			Products 7[e]		
No.	m	X	n	Solvent[a] [mM]	Time (min)	Yield (%)[b]	Ring size	mp (°C)	Yield (%)[b]	Ring size	mp (°C)
a	2	CH_2	0	A[5]	25	82	6	242-243*			
b	4	CH_2	0	A[5]	25[c]	56	8	180-182*			
c	1	CO_2	4	A[6]	85[c]	26	10	231-233*	17	13	224-226*
				M[11]	60	19	10				
				B[5]	360				12	13	
d	10	CO_2	4	A[4]	60[c]	53	19	160-161			
e	10	CONH	1	A[5]	60	20	16	178-180	12	19	185-188*
				B[6][d]	130	25	16				

a) A=acetone, M=methanol, B=benzene. b) Isolated yield. c) Irradiated with a 200 W high pressure mercury lamp. d) Irradiated through a Pyrex filter. e) A single product was isolated, but its stereochemistry is undetermined. *) Decomposed.

Table II. Sulfur-free Products from 6 and 7

Substrates 6 or 7				Products 8		Products 9	
No.	m	X	n	Yield (%)	mp (°C)	Yield (%)	mp (°C)
a	2	CH_2	0	58	73-74		
b	4	CH_2	0	49	oil		
c	1	CO_2	4	61	152-154	73	oil
d	10	CO_2	4	58	oil		
e	10	CONH	1	47	oil	53	94-95

cyclol moiety was confirmed by spectroscopic data [hydroxyl (IR 3290 cm^{-1}), amides (1680, 1630); the methine proton (NMR 4.45 ppm, t, J=6.5 Hz) in 5e disappeared]; (ii) the molecular weight values determined by the vapor-pressure method[10] and mass spectrometry were 440 and 448, respectively, in agreement with the monomeric value (448).

On heating with Raney Ni in ethanol or acetone, all the thioketal compounds (6) were converted to the corresponding sulfur-free products 8 (Table II). Similar treatment of the minor products (7) with the dithiolanyl group, on the other hand, afforded the open-chain sulfur-free compounds 9 [in the case of 9e: UV

247 nm (ε=6970, in $CHCl_3$); NMR 0.52 and 1.12 ppm ($-CH_2\underline{CH}_3$ × 2, t, J=8 Hz each)].

In our photochemical macrocyclic synthesis with the phthalimide-thiomethyl pair system (1,3), the feature of the C-C bond formation remains the sulfide moiety in the carbon skeleton (4). By contrast, the employment of the 1,3-dithiolanyl group as a new donor in place of a thiomethyl group, allows us to eliminate the remaining thioketal moiety after the construction of the new carbocycles, leaving little trace of the precursor group used in the cyclization stage. This example of a removable functional group in a macrocyclic synthesis may suggest a new general strategy which places less restriction on the mode of carbon skeleton syntheses.

ACKNOWLEDGEMENT: We are grateful to Drs. S. Saito and T. Mizoguchi, Organic Chemistry Research Laboratory, Tanabe Seiyaku, Co., Ltd., for their encouragement.

REFERENCES AND NOTES

1) a) Photochemistry of the phthalimide system. 27. Part 26: M. Wada, H. Nakai, K. Aoe, K. Kotera, Y. Sato and Y. Kanaoka, Chem. Pharm. Bull., 30, 2275 (1982); b) Photoinduced Reaction. 55; For Part 54, see ref. 1a).
2) Y. Kanaoka, Accounts Chem. Res., 11, 407 (1978).
3) a) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka and Y. Kanaoka, J. Am. Chem. Soc., 98, 2349 (1976); b) Y. Kanaoka and H. Migita, Tetrahedron Lett., (1974) 3693; c) M. Machida, H. Takechi and Y. Kanaoka, Heterocycles, 7, 273 (1977); Idem, Chem. Pharm. Bull., 30, 1579 (1982); d) M. Machida, H. Takechi and Y. Kanaoka, Heterocycles, 14, 1255 (1980); e) Y. Maruyama and Y. Kubo, J. Am. Chem. Soc., 100, 7772 (1978); f) M. Machida, K. Oda and Y. Kanaoka, Heterocycles, 18, 211 (1982).
4) Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi and Y. Kanaoka, Tetrahedron Lett., (1976) 1889.
5) Y. Kanaoka, Y. Hatanaka, Y. Sato, M. Wada and H. Nakai, VIII IUPAC Symposium on Photochemistry, Seefeld, July, 1980, Abstracts of Papers, p.190.
6) Y. Sato, M. Wada, H. Nakai, Y. Hatanaka and Y. Kanaoka, 12th Symposium on Heterocyclic Chemistry, Tokyo, Oct. 1979, Abstracts Papers, p.151.
7) M. Wada, H. Nakai, Y. Sato and Y. Kanaoka, Tetrahedron Lett., 23, 3077 (1982).
8) All the new compounds gave satisfactory elemental analyses and their structures were supported by spectral (UV, IR, NMR, MS) data.
9) T. Mukaiyama, M. Usui, E. Shimada and K. Saigo, Chem. Lett., (1975) 1045.
10) Hitachi-Perkin molecular weight measuring apparatus Model 115: in chloroform.

(Received June 16, 1982)