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A SYNTHETIC APPROACH TO MACROLIDE MODELS BY THE REMOTE PHOTOCYCLIZATION WITH A PAIR SYSTEM OF PHTHALIMIDE AND METHYLTHIO GROUPS1)

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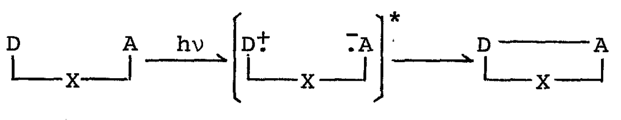
Upon irradiation a homologous series of N-substituted phthalimides (2, 3) possessing a terminal sulfide function in their side chain undergo regioselective remote photocyclization affording nine to twenty-seven membered macrolide analogs (4, 7) in moderate yields.

KEYWORDS—— phthalimide derivative; remote photocyclization; donor-acceptor pair system; extensive Norrish type II process; macrolide derivative; X-ray diffraction analysis

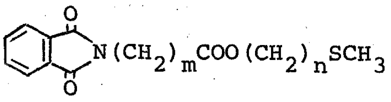
During the course of our systematic studies on imide photochemistry,2) we have found that phthalimides possessing a terminal sulfide function in their N-side chain undergo photocyclization to give azathiacyclols.3) This finding led us to novel photochemical syntheses of medium- to large-sized ring compounds.4,5a) We are now extending this type of reaction to a general synthesis of macrocycles on the basis of regioselective remote photocyclization of a pair system which consists of, in this case, a phthalimide group (electron acceptor; A) and a sulfide group (donor; D) (eq. 1).



(1)

1 X = a : [-CONH-] b : [-O-] c : [$-CO_2-$]

In photoprocesses the reactivities often seem to be more sensitive to the structural and environmental factors than in thermal processes.5b) Therefore, to see the scope and limitation of the above synthetic approach, careful examination of a structural variation in the connecting part (X), which combines the donor and the acceptor, was needed. We have already investigated the photocyclization of the phthalimides containing amide4,5a) and ether bonds1a) in their long side chain (1a, 1b). In the present paper, we wish to report the results of the photolysis of such a pair system with an ester bond (1c) in their side chain as a connecting part.



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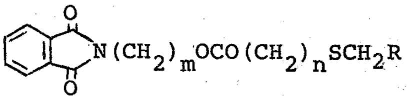

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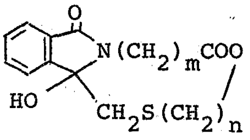

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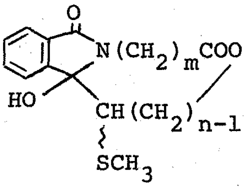

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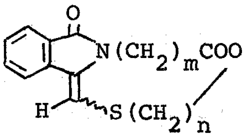

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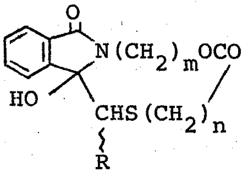

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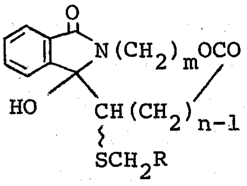

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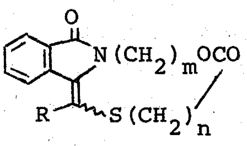

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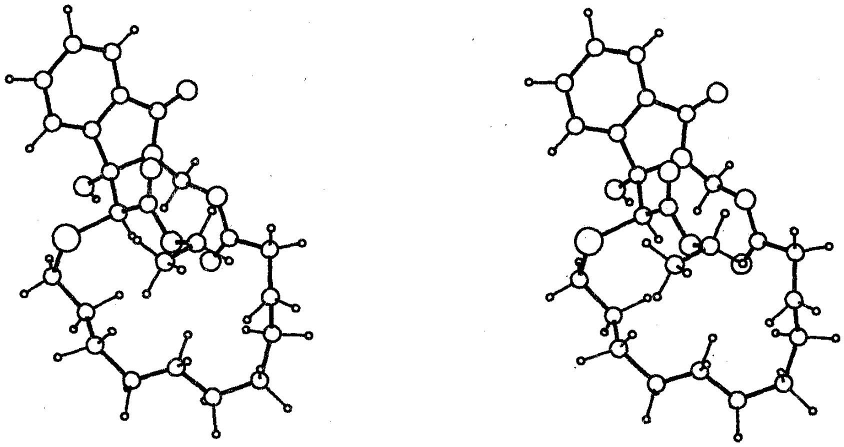
Table I. Photoproducts from the Substrates (2, 3)[6)]

Substrates				Photoproducts					
	2 m	3 n	R	4(7) %	Ring size	mp(°C)	5(8)* %	Ring size	mp(°C)
2a	1	2	-	80	9	187-189(dec.)	-		
2b	5	2	-	36	13	171-172	9	11	166-167(dec)
3a	1	10	H	(45)	17	126-128	(7)	15	141-142
3b	1	10	COOEt	(58)	17	121-123(trans) 111-112(cis)	-		
2c	10	2	-	35	18	109-111	5	16	168-169
2d	5	11	-	34	22	oil	3	20	158-159
2e	10	11	-	48	27	125-127	10	25	143-145

*) A single product was isolated, but its stereochemistry is undetermined.

Figure 1. Stereoscopic View of the Compound 7b(trans)



A series of N-substituted phthalimides (2, 3) containing an ester bond and a ω-methylthio group were prepared, and the photolysis was performed as follows: A solution of 2 (or 3) in acetone (3-7 mM) was irradiated with a 400W high-pressure mercury lamp in a stream of argon for 30-110 min at room temperature. As shown in Table I, in most cases a mixture of 4 (or 7) and 5 (or 8) were obtained, with the former as a major product after silica gel column chromatography in moderate yields (35-80%).6) In all examples studied, the expected macrocyclic products were obtained as a result of C-C bond formation between the imide carbonyl group and the S-methyl (or $-CH_2COOEt$) group through the extensive Norrish type II process.2,4) Some minor products, in which the S-methylene group is involved, were isolated mostly in less than 10% yields. The largest ring thus formed was a twenty-seven-membered ring in the case of compound 4e. In a representative example, the structural assignment for 4e was based on the following factors: (i) the presence of cyclol moiety was confirmed from the spectroscopic data [UV 248 nm (ε=4630, in MeOH), hydroxyl (IR 3200 cm^{-1}), amide (1680 cm^{-1}) and methylene (instead of methyl in 2e) NMR (in $CDCl_3$) 3.0 and 3.23 ppm (ABq, J=14 Hz)]; (ii) the molecular weight values determined by the vapor-pressure method7) and mass spectrometry were 532 and 531, respectively, both in agreement with the monomeric value (531); (iii) treatment with p-toluenesulfonic acid (or thionyl chloride-pyridine) gave the dehydrated compound 6 (or 9). In a similar manner, irradiation of 3b afforded 7b, which was separated by silica gel chromatography into trans and cis isomers (with regard to a hydroxyl group and an ethoxycarbonyl group in the new ring). On treatment with acid, 7b (trans and cis) were readily converted into the same dehydrated product 9b (R=COOEt) in moderate yields, in support of the tertiary hydroxyl structure of 7b. The structure of the trans isomer of 7b was established by X-ray diffraction analysis. Stereoscopic view of the structure of 7b (trans) is illustrated in Figure 1.8)

The importance of macrocyclic compounds in biological and chemical systems has recently attracted considerable attention. A large number of macrocyclic natural products, including antibiotics such as depsipeptides and macrolides, have been isolated, and in many cases their roles as ligands in complexing various metals have been identified.9) Crown ethers and cryptands are well-known examples of synthetic macrocyclic ligands.10) Although many ground-state reactions for the construction of macrocycles have been known, much less information is available for photochemical macrocyclic syntheses.11) In view of such methodology, it seems important that the substrates (2, 3) having a functional group such as the ester bond undergo a smooth selective remote photocyclization at the terminal thiomethyl group. Usually in the photocyclization of long-chain substrates, a mixture of various products is obtained following the statistical distribution.11c-d) This pair system may provide a versatile photochemical unit for the synthesis of various macrocycle analogs. Further possible applications of this approach (D-A pair system), as well as the detailed mechanism, are under investigation.

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6) All new compounds gave satisfactory elemental analyses, and their structures were supported by spectral (UV, IR, NMR, MS) data.
7) Hitachi-Perkin molecular weight measuring apparatus Model 115: in methanol.
8) X-ray diffraction analysis of 7b: Crystal data; $C_{24}H_{33}NO_6S$ (MW 463.60), triclinic, space group; $P\bar{1}$, a=11.707(1), b=13.528(2), c=8.439(1) Å, α=103.377(6), β=86.796(7), γ=112.283(5)°, V=1202.4 $Å^3$, D_{cal}=1.280 g/cm^3, Z=2. The intensity data were collected on a Rigaku automatic four-circle diffractometer (AFC-3) using CuKα radiation monochromated by means of a graphite plate; 4081 independent reflections with 2θ less than 130° were measured and corrected for the Lorentz and polarization factors. The structure was solved by the direct method using MULTAN and was refined by the block-diagonal least-squares procedure. The final R value was 0.077, assuming anisotropic thermal parameters for the nonhydrogen atoms and isotropic ones for the hydrogen atoms.
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