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PHOTOCHEMICAL SYNTHESIS OF AN OXAZOLO[4,3-a]ISOINDOLE-1-*SPIRO* RING SYSTEM[1,2]

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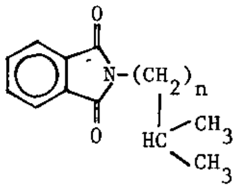
On irradiation certain N-β-*sec*-alkoxyalkyl-substituted phthalimides **6** afforded an oxazolo[4,3-a]isoindole-1-*spiro* ring system **7** in moderate yields demonstrating a photochemical synthesis of *spiro* heterocycles by utilizing the excited imide carbonyl.

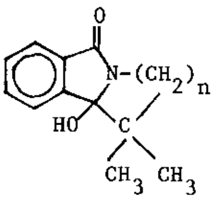
In search of biologically active substances, synthesizing new compounds, either of an entirely novel class or of a group with certain structural characteristics, forms an important approach. For example, involvement of a quaternary carbon as the central atom is known to be essential in designing synthetic narcotic analgesics[3]. For the construction of a quaternary carbon, hydrogen abstraction from a tertiary carbon followed by C-C radical coupling may be one of attractive routes. We have recently found that the imide carbonyl of N-substituted phthalimides undergoes Norrish type II photocyclization leading to a variety of ring systems[4]. This communication outlines a synthesis of a new class of heterocyclic *spiro* compounds **7** utilizing such a reactivity of appropriate phthalimide derivatives.

The simple substrates 1a-b with a tertiary carbon were thought to give, on irradiation, the cyclized products 2a-b with a quaternary carbon, respectively. In fact, either the primary photoproducts or their derivatives (1a → (2a) → 3a; 1b → 2b, 3b) were obtained but only in poor yields[5]. Apparently total efficiencies to afford the products were too low for the preparative purpose.

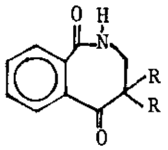
An alkoxy group enhances the reactivity of the adjacent C-H bonds for triplet carbonyl by a factor of 5.[6] Consequently, the γ (deactivated by the inductive effect of the δ-methoxy group) and δ C-H bonds of δ-methoxyvalerophenone 4 were of comparable reactivity[6]. By contrast, photolysis of 5 gave exclusively the δ hydrogen-transfered product[7] as a result of the relatively favored δ hydrogen abstraction, intrinsic to the phthalimide system, coupled with the activation due to the alkoxy group[6]. Such a consideration now points to the N-alkoxymethylphthalimides 6 as the candidate substrates for possible photocyclization because 6 have no γ hydrogen but one δ hydrogen that must be activated by the oxygen and two alkyl substituents[6]. In this regard we have already had made preliminary observations that some derivatives of 6 with a δ-methylene (R_1=H; R_2=Me, Ph) gave rise to an oxazoloisoindole system[7].



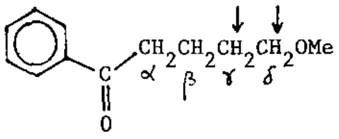
1 a : n=1 b : n=2



2 a : n=1 b : n=2



3 a : R=Me b : R=H



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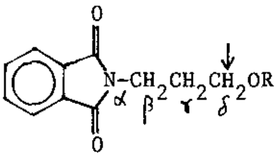

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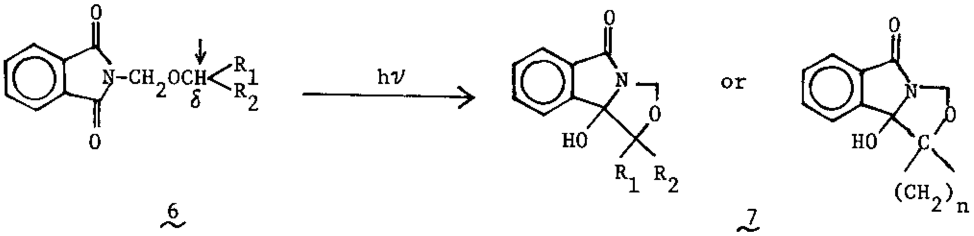

6

7

Table

6 $R_1=R_2$ or R_1-R_2		hr	7 (%)	mp°c
a	Me	2	39	123-4
b	Ph	3	39	248-9
c	$-(CH_2)_4-$	2	38	135-7
d	$-(CH_2)_5-$	2	33	185-6
e	$-(CH_2)_6-$	2	49	131-2
f	$-(CH_2)_7-$	1	53	130-1

In order to see whether a tertiary C-H can participate in the reaction, photolysis of 6a-b was first examined. The expected cyclized products 7a-b with a quaternary carbon were obtained in moderate yields. In a similar manner, the title compounds 7c-f were smoothly obtained from 6c-f, respectively. The table lists the results with varying spiro ring sizes (5-8 membered).[8]

Although the detailed nature of the excited imide carbonyl of the phthalimide is largely unknown, its photochemical behavior is, at least formally, nearly parallel to that of triplet carbonyl in many respects.[1,4,5,7] It is noteworthy that the excited cyclic imide reacts without any appreciable steric effect to form the spiro skeleton which is constructed into a multicyclic system 7. The methodology suggested in the present work could be readily extended to syntheses of related systems including other heteroatoms such as sulfur or nitrogen. In addition, this process has the advantage of permitting large-scale preparation in fairly good yields, for example, with a 2 KW mercury lamp as an energy source[9]. Systematic studies of synthesis, preparation and bioassays of these new heterocycles are under way.

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8 Photolyses were performed with a 400w high pressure mercury lamp in acetonitrile (10～15mM). All new compounds gave satisfactory analyses and their structures were supported by spectral (uv, ir, nmr, mass) data.

9 Unpublished data at Org.Chem.Res.Lab., Tanabe Seiyaku Co., Ltd.

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