PHOTOCYCLIZATION OF N-AMINOALKYLPHTHALIMIDES.

SYNTHESES OF MULTICYCLIC FUSED HEXAHYDROPYRAZINES AND HEXAHYDRO-1,4-DIAZEPINES[1]

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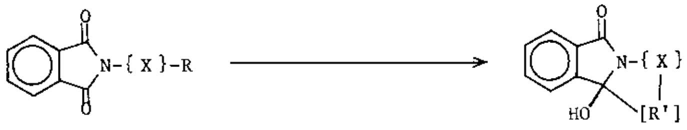
Abstract —— Photolysis of a series of N-aminoalkylphthalimides (3) afforded fused hexahydropyrazines (4a, 6a,b) and hexahydro-1,4-diazepines (4b, 6c,d).

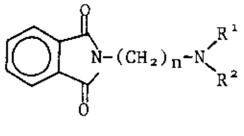
Photochemical cyclization of N-substituted phthalimides[2](1) gave rise to a number of new heterocycles (2) with either nitrogen and oxygen[3] or nitrogen and sulfur[4] in the newly formed rings (Scheme I). As to synthesizing the rings with two nitrogen atoms, we have already reported photocyclization of N-(ω-methylanilino)-alkylphthalimides, in which ring sizes up to 16-membered have been synthesized.[5] While phthalimide Mannich bases are reported to undergo similar reaction,[6] Coyle et al. have recently described the photocyclization of N-dibenzyl phthalimide Mannich bases[7] and their homologues.[7d] During the course of synthetic photochemical studies of phthalimides with nitrogen-containing substituents, we now report the synthesis of various multicyclic fused systems with two nitrogen atoms by photolysis of N-aminoalkylphthalimide derivatives (3).

Scheme I



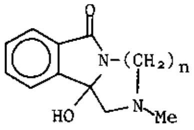
1 X = N, O, S 2

N-Dimethylaminoalkylphthalimides (3a,b) were prepared by the reaction of phthalic anhydride and the corresponding amine. The ω-pyrrolidyl (3c) and ω-piperidyl (3d,f) derivatives were synthesized by the reaction of the corresponding ω-bromoalkylphthalimides with pyrrolidine and piperidine, respectively. Compound 3e was prepared from potassium phthalimide and 3-chloropropylpyrrolidine.



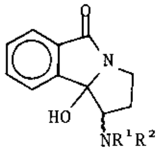
3

	n	R^1	R^2
a	2	Me	Me
b	3	Me	Me
c	2	$-(CH_2)_4-$	
d	2	$-(CH_2)_5-$	
e	3	$-(CH_2)_4-$	
f	3	$-(CH_2)_5-$	



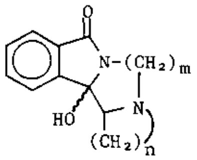
4

a n = 2
b n = 3



5

	R^1	R^2
a	Me	Me
b	$-(CH_2)_5-$	



6

	m	n
a	2	3
b	2	4
c	3	3
d	3	4

Irradiation of 2.4-2.5 X 10^{-2} M solutions of 3 in a mixture of acetone and petroleum ether (1 : 3, v/v), with a 500 W high-pressure mercury lamp in a stream of nitrogen for 30-40 min, produced cyclized photoproducts as listed in Table I. In all cases a new carbon-carbon bond was formed between the imide carbonyl and the carbon adjacent to nitrogen in the side chain. The structures of the products, which include multicyclic fused hexahydropyrazines (4a, 6a,b) and hexahydro-1,4-diazepines (4b, 6c,d), were assigned on the basis of analytical and spectral data.[8]

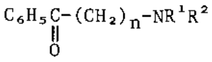
Table I Photoproducts from N-Aminoalkylphthalimides 3

Substrate	Time (min)	Product	mp °C	Yield (%)	H*
3a	30	4a	147.5 - 148	29	ε
3b	30	4b	130.5 - 131.5	13	ζ
		5a	125.5 - 127	5	δ
3c	40	6a	154.5 - 155	20	ε
3d	30	6b	180 - 181	33	ε
3e	30	6c** (i)	203.5 - 204.5	12	ζ
		(ii)	165.5 - 167		ζ
3f	30	6d	144 - 145	9	ζ
		5b	160 - 162	5	δ

* Hydrogen transferred

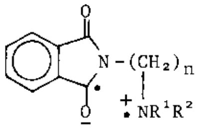
** (i) and (ii) are stereoisomers separated by silica gel TLC.

In our study on the imide photochemistry, the methodology consistently applied has been systematic comparison of the photochemical behavior of the imides with that of simple carbonyls, the parent system.[2] In the aminoketones such as 7, the parent keto system of this work, Wagner et al. found that charge transfer quenching of the ketone triplet by the remote amino group competes with type II processes.[9a] Among type II processes, the major process for 7 was photoelimination, whereas the important photoreaction for 3 was cyclization. In addition, the results in Table I show that the reaction takes place, at least formally, by transfer of a hydrogen adjacent to nitrogen which is the δ-, ε-, or/and ζ-position relative to the imide carbonyl. It is generally accepted that the γ-hydrogen abstraction is a major path for the simple carbonyl systems.[9] This behavior of 3 is self-consistent with our earlier observation of "cyclophilic" nature[2] of the phthalimide system with side chains containing hetero atoms[3,4] or aromatic substituents.[5,10] Cohen first proposed that amines reduce ketone triplets and that the resulting radical ions often collapse to radicals by a proton transfer (Scheme II).[11] Such interactions can well occur also with the phthalimide system, both in the intermolecular[2,12] and intramolecular[2,5] modes. Although further work is required for exact understanding of the photoreaction of 3, the electron transfer mechanism[2,4b,5,7b,12] involving such a radical ion intermediate (8) may tentatively explain the above reaction. This method thus provides a simple synthetic route to the multicyclic fused nitrogen heterocycles.



$C_6H_5\underset{\overset{\|}{O}}{C}-(CH_2)_n-NR^1R^2$

7



8

Scheme II

$$R_2C{=}O^* \quad + \quad R_2\ddot{N}CH_2R \longrightarrow R_2\dot{C}{-}\overset{-}{O} \quad + \quad R_2\overset{+\cdot}{N}{-}CH_2R \longrightarrow R_2\dot{C}OH \quad + \quad R_2\ddot{N}{-}\dot{C}HR$$

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