

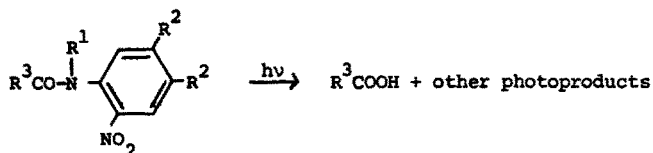
THE PHOTOREARRANGEMENT OF N-SUBSTITUTED ortho-NITROANILIDES AND NITROVERATRAMIDES.
A POTENTIAL PHOTSENSITIVE PROTECTING GROUP

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Irradiation of aliphatic amides in organic solvents leads to a variety of products due to homolytic fission of carbon-carbon and carbon-nitrogen bonds⁽¹⁾. Anilides rearrange in a mode similar to photo-Fries rearrangement; thus, photolysis of acetanilide and benzanilide leads to a mixture of aminoacetophenones and benzophenones, respectively⁽²⁾. The photolysis of an amide to yield a free carboxylic acid was observed only in a single case⁽³⁾. We have found that N-substituted-ortho-nitroanilides and nitroveratramides are light-sensitive and undergo photorearrangement to yield the appropriate free acids. To the best of our knowledge, this is the first example reported of photocleavage of amides to the free carboxylic acids in high yields (see Table). The reaction is schematically represented in the following equation:



R¹ = methyl, n-butyl, cyclohexyl, benzyl, phenyl.

R² = hydrogen, methoxy.

R³ = for acyl groups used, see Table.

The highest yields of free acids were obtained when mixtures of ethanol-water or methanol-water were used as solvents. Irradiations were carried out in a R.P.R-100 apparatus using 3500Å lamps. All the compounds were found to be sensitive to visible light as well. Thus, irradiation

of an ethanol-water solution of N-n-butyl-4',5'-dimethoxy-2'-nitro-2-naphtanilide with sunlight (40 hrs), employing a GWV filter (transmitting light of $\lambda > 370$ nm), afforded 92% of 2-naphtoic acid.

The photocleavage of the above amides formally follows the known photoredox reactions of aromatic nitro compounds bearing substituents at the ortho position, where an oxygen atom is transferred from the nitro group to the ortho substituent⁽⁴⁾. The photocleavage of DNP-aminoacids⁽⁵⁾ and photocyclization of ortho-nitro-tert-anilines⁽⁶⁾ are related examples. In the latter examples the primary photochemical reaction is probably the abstraction of a β -H atom by the excited nitro group followed by oxygen transfer.

We have found that the substituents on the amidic nitrogen are essential for the rearrangement of ortho-nitroanilides, since without such substituents these compounds are not sensitive under the irradiation conditions (see Table). Further it has been found that the free acids do not result from hydrolysis of any reaction intermediate. This was confirmed by performing the irradiations in the presence of H_2O^{18} where no O^{18} was incorporated into the liberated acids. Therefore the source of the hydroxylic oxygen must be the nitro group. This was proved by experiments with 4',N-dimethyl-2'-nitro-2-chlorobenzanilide (I), O^{18} labelled in the nitro group. This compound was synthesized, starting from para-acetotoluidide which was nitrated with HNO_3^{18} to the labelled 2-nitro-para-acetotoluidide. The nitro derivative was subsequently N-methylated, deacetylated and reacylated with 2-chlorobenzoyl chloride to give compound (I). It was observed that on irradiation of (I), an O^{18} atom was transferred from the nitro group to the 2-chlorobenzoyl moiety. According to the relative intensities of the peaks in the molecular ion region of the labelled anilide [M^+ : m.e 304 (80%), 306 (100%), 308 (42%)], its nitro group contains⁽⁷⁾ 48% $NO^{16}O^{18}$ and 10% $NO^{18}O^{18}$. The 2-chlorobenzoic acid which was released by irradiation of this anilide, was converted into its methyl ester by diazomethane. The $COO^{18}CH_3$ content of this ester was found to be 31% according to the relative intensities of its peaks in the molecular ion region⁽⁷⁾ [M^+ m/e 170 (100%), 172 (78%)]. This is in good agreement with the calculated⁽⁸⁾ value (34%).

The carboxylic hydrogen is derived from a process involving hydrogen abstraction by the excited nitro group (which is known to abstract hydrogen from solvent or intramolecularly via a cyclic intermediate^(9,10)). In the compounds studied where an N-alkyl or N-benzyl group was

present, this group was always the source of hydrogen. When such a hydrogen atom was not available from the reactant, hydrogen abstraction from the solvent took place. Thus, irradiation of N-phenyl-ortho-nitroacetanilide in 2-propanol led to the formation of two equivalents of acetone and a 90% yield of acetic acid. Irradiation of this anilide in benzene (a poor hydrogen donor) led to only 10% of acetic acid. On the other hand, irradiation of amides N-substituted with methyl, n-butyl or cyclohexyl (where an intramolecular β -H abstraction is possible) in 2-propanol, yielded no acetone, while irradiation of these compounds in benzene led to only slightly lower yields of the free acids. These results stress the importance of the hydrogen donor in the photocleavage.

The light-sensitive group described above is potentially useful for the protection of carboxylic acids due to its mild cleavage and its stability under hydrolytic conditions.

Table^a

Anilides ^b R ² = Hydrogen	M.p. °C	% Yield of free acid ^{c,d}	Veratramides ^b R ² = Methoxy	M.p. °C	% Yield of free acid ^{c,d}
R ¹ = Hydrogen ¹¹ R ³ = Phenyl	90-92	0	R ¹ = Cyclohexyl R ³ = Methyl	136-138	90
R ¹ = Benzyl ¹² R ³ = Methyl	85	90	R ¹ = n-Butyl R ³ = Methyl	81	70
R ¹ = Phenyl ¹³ R ³ = Methyl	134-135	95	R ¹ = Benzyl R ³ = Methyl	144-146	90
R ¹ = Methyl ¹⁴ R ³ = Methyl	70	95	R ¹ = Benzyl R ³ = 3,4-Dichlorophenyl	211-212	85
R ¹ = Methyl ¹² R ³ = Phenyl	83	90	R ¹ = Cyclohexyl R ³ = 3,4-Dichlorophenyl	200-201	93
R ¹ = Methyl ¹⁵ R ³ = 2-Naphthyl	124-125	90	R ¹ = Methyl R ³ = 2-Chlorophenyl	142-143	93
R ¹ = Cyclohexyl R ³ = 2-Naphthyl	236-237	80	R ¹ = n-Butyl R ³ = 2-Naphthyl	143-145	80

^aFor general formula of amides see Scheme. ^bAll compounds gave the correct elemental analysis.

^cThe above yields correspond to 10 hrs irradiations either in methanol-water or ethanol-water solutions. ^dYields were determined by gas chromatography of the methyl esters except in the case of acetic acid which was determined by distillation followed by titration.

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7. The calculation is based on the difference in the mass spectrum of the labelled and the unlabelled compounds.
8. This value is obtained by assuming that all of the molecules labelled $N^{18}O^{18}$ 10%, will produce labelled 2-chlorobenzoic acid, while only half of the molecules labelled $NO^{16}O^{18}$, i.e., 24%, will produce the labelled acid.
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