Drugs: Photochemistry and Photostability

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Edited by

A. Albini
Dell' Università Di Pavia, Italy

E. Fasani
Dell' Università Di Pavia, Italy

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Preface

That many drugs, just as non-pharmaceutically active compounds, are photoreactive has been long known. As an example, Pasteur noticed the photolability of quinine in 1846[1] and industry-sponsored studies on the photochemistry of drugs were already systematically carried out in the twenties.[2] However, until recently the matter has received only limited attention, mainly on the assumption that by using the appropriate opaque container no significant decomposition could have taken place.

As a result, the available knowledge is quite sparse. All Pharmacopoeias mention that some drugs have to be protected from light, but one cannot rely upon such qualitative (and incomplete) information. The number of reports in specialised journals is growing, but remains low.

The situation has changed recently, however, and this is due to several causes.

First, more sensitive analytical methods are now available and the standard of purity required has become more and more stringent. Thus, even traces of (photochemically formed) impurities must be revealed. This has led to the formulation by ICH of internationally accepted Guidelines for Drug Photostability (see p. 66), which have been implemented since January 1998.

Second, there have been cases of promising drugs which have been discarded late in the development process due to a too high photolability. The development of a new drug is very expensive and this calls for more attention to the photochemical properties of a molecule early in the development, or for a way to predict the photostability of a new molecule.

Third, significant phototoxic effects have been ascertained for several drugs in common clinically, and in general there is now more attention to the phototoxic effects of drugs (as well as of cosmetic products and sunscreens). Here again, control of the photobiological effects demands that the photohemistry of the active molecule is known.

The awareness of this situation has led to the organisation of two international meetings, the first one in Oslo in June 1995, the latter in Pavia in September 1997. Both have been attended by scientists of different affiliations (industries, regulatory agencies, universities) and of different specialisations (pharmaceutical techniques, pharmaceutical chemistry, photochemistry, photophysics, biology, toxicology). The need for a close collaboration between such different areas has been recognised.

This book is based on the communications presented at the Pavia meeting, and is organised as follows.

1. Introductory part. This includes an overview on the photochemistry of drugs and on some related problems (dependence on conditions, protection of photolabile drugs) by the editors, the text of the ICH Guidelines on Photostability, and an introduction to medicinal chemistry with attention to the kinetics of photochemical processes by *Beijerbergen van Henegouwen.*

2. Photochemistry of drugs. Photochemistry of drug families, *viz.* antimalarials (*Tønnesen*), diuretic drugs (*Moore*), antimycotics (*Thoma*), phenothiazines (*Glass*), anti-inflammatory drugs (*Monti*), coumarins (*Zobel*), sunscreens (*Allen*), Leukotriene B4 antagonists (*Webb*). The photosensitising properties by some drugs are treated by *De Guidi* and *Tronchin.*

3. Photostability of drugs. Methods for implementing the ICH guidelines (*Drew*) and a discussion of their application (*Helboe*); the choice of lamps (*Piechocki*) and in general of the appropriate conditions for carrying out photostability studies (*Boxhammer* and *Forbes*); the choice of the actinometer (*Favaro* and *Bovina*).

It is hoped that these contributions may help to determine on a sound basis the significance of drug photostability for the pharmaceutical industry and also help to serve as support for phototoxicity studies.

Thanks are due to Mr F. Barberis and Misses M. Di Muri, M. Parente and F. Stomeo for their help in preparing the manuscripts.

A. Albini and E. Fasani Pavia, March 1998

1. L. Pasteur, *Comp. Rend.*, 1853, **37**, 110.
2. J. Piechocki, p. 247.

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Photochemistry of Drugs: An Overview and Practical Problems

Angelo Albini and Elisa Fasani
Department of Organic Chemistry
University of Pavia
v.le Taramelli 10, I-27100 Pavia, Italy

1 INTRODUCTION

Absorption of light (UV or visible) by the ground state of a molecule (S_0) generates electronically excited states, either directly (the singlet states) or after intersystem crossing from the singlet manifold (the triplet states). Alternatively, triplet states may be generated by energy transfer from another excited state (a sensitiser). In both multiplicities, very fast internal conversion leads to the lowest states (S_1 and T_1 respectively). These states, although still quite short lived (typical lifetime $\tau<10^{-8}$ s for S_1 and $<10^{-6}$ s for T_1) live long enough that a chemical reaction competes with decay to the ground state.

Electronically excited states are electronic isomers of the ground state, and not surprisingly show a different chemistry. These, however, can be understood with the same kind of reasoning that is used for ground state chemistry, taking into account that the very large energy accumulated in excited states makes their reactions much faster (in the contrary case, there would be no photochemistry at all, in view of the short lifetime of the key intermediates). As an example, ketones are electrophiles in the ground state due to the partial positive charge on the carbon atom. The reaction with nucleophiles occurs. In the $n\pi^*$ triplet excited state electrons are differently distributed, and the important thing is now the presence of an unpaired electron on the non-bonding orbital localised on the oxygen atom. This makes atom transfer to that atom so fast a process ($k\approx10^6 s^{-1}$, many orders of magnitude faster than any reaction of ground state molecules) that it competes efficiently with the decay of such a state.

On the basis of such principles, the many photochemical reactions now known have been rationalised. This is shown in many fine books of photochemistry,[1-5] which demonstrate both the dramatic development of this science in the last decades and the high degree of rationalisation that has been reached. The photoreactions of drugs[6] obviously can be discussed in the same way, and G. M. J. Beijersbergen van Henegouwen (p. 74) pointed out some key points that one should take into account. It is therefore generally possible to predict

the photochemical behaviour of a new drug, as of any other molecule, or at least to point out the most likely alternatives.

More exactly, as it has been pointed out by Grenhill in a recent review,[7] it is possible to indicate some molecular features that are likely to make a molecule liable to photodecomposition, even if it is difficult to predict the exact photochemical behaviour of a specific molecule. This is due to the fact that competition between the chemical reaction(s) and physical decay to the ground state depends in a complex way on the structure (and on conditions). Thus both the efficiency of a photochemical reaction and product distribution may vary significantly even among closely related compounds and further depend on conditions.

At any rate, several chemical functions are expected to introduce photoreactivity (see Scheme 1). These are:

a. The carbonyl group. This behaves as an electrophilic radical in the $n\pi^*$ excited state. Typical reactions are reduction via intermolecular hydrogen abstraction and fragmentation either via α-cleavage ("Norrish Type I") or via intramolecular γ-hydrogen abstraction followed by C_α-C_β cleavage ("Norrish Type II").

b. The nitroaromatic group, also behaving as a radical, and undergoing intermolecular hydrogen abstraction or rearrangement to a nitrite ester.

c. The *N*-oxide function. This rearranges easily to an oxaziridine and the final products often result from further reaction of this intermediate.

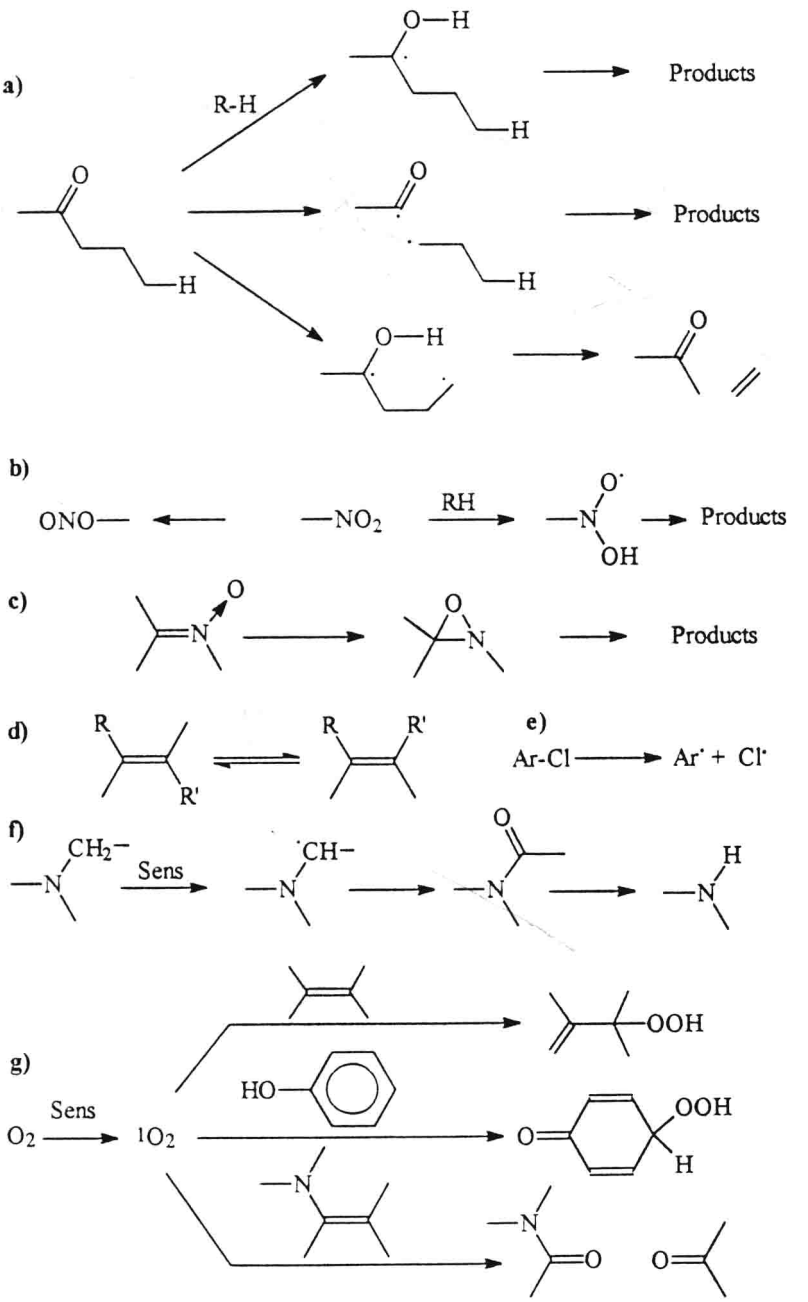
d. The C=C double bond, liable to *E/Z* isomerisation as well as to oxidation (see case g).

e. The aryl chloride, liable to homolytic and/or to heterolytic dechlorination

f. Products containing a weak C-H bond, e.g. at a benzylic position or α to an amine nitrogen. These compounds often undergo photoinduced fragmentations via hydrogen transfer or electron-proton transfer.

g. Sulphides, alkenes, polyenes and phenols. These are highly reactive with singlet oxygen, formed through photosensitisation from the relatively harmless ground state oxygen.

Such functions are present in a very large fraction, if not the majority, of commonly used drugs. Thus, many drug substances, and possibly most of them, are expected to react when absorbing light. However, photodegradation of a drug is of practical significance only when the compound absorbs significantly ambient light (λ>330 nm), and even in that case the photoreaction may be too slow to matter, particularly if concentrated solutions or solids are considered. It is important to notice that most information about photoreactions available in the literature refers to the conditions where such processes are most easily observed and studied, viz. dilute solutions in organic solvents, whereas what matters for drug photostability are (buffered) aqueous solutions or the solid state. Under such different conditions the photoreactivity of a drug may be dramatically different. To give but one example, benzophenone triplet - probably the most thoroughly investigated excited state - is a short-lived species in organic solvents, e. g. τ ca 0.3 μs in ethanol, and is quite photoreactive via hydrogen abstraction under such conditions, and in general in an organic solution. However,



Scheme 1

the lifetime of this species increases by two orders of magnitude in water, where benzophenone is almost photostable.

The present chapter has the following aims:

a. to offer an overview of reported photochemical reactions of drugs (see Sec. 2).

b. to discuss practical problems related with drug photoreactivity, such as the dependence on the physical state of the drug or drug preparation and the quantitative assessment of drug photostability (see Sec. 3).

c. to make reference to the possible ways for protecting a drug against photoreactions (see Sec. 4).

The ICH Guidelines on Drug Photostability are enclosed as an Appendix.

2 PHOTOREACTIONS OF DRUGS

Information on drug photoreactivity is probably not sufficient among practitioners of pharmaceutical chemistry. Reports about this topic have been growing in number in the last years, but they are scattered in a variety of journals (oriented towards chemistry, pharmaceutical sciences and techniques, pharmacology, biology and medicine), thus possibly not reaching all interested readers. Furthermore, both the approach used (ranging from the simple assessment of the photolability to detailed product or mechanistic studies) and the experimental conditions used (e.g. radiation source) are quite various, and thus care is required when extending the results obtained with a drug to different conditions (let alone for predicting the reactivity of related substrates).

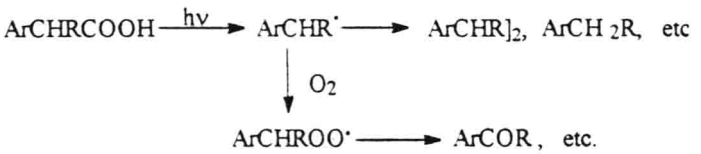
Several more or less extended reviews about the photochemistry of drugs are available in the literature,[6-16] and an extensive compilation of reference groups by compound name has been published by Tønnesen.[17]

It is hoped that the present review may help to give a better "feeling" of the type of photochemical reactions occurring with drugs. Due to limitation of the available space the overview presented here is intended to be exemplificative rather than exhaustive. The drugs are grouped according to the following broad therapeutic categories:

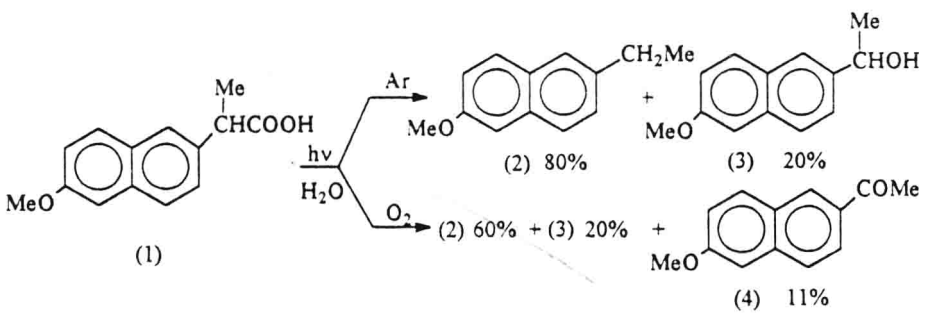
- anti-inflammatory, analgesic and immunosuppressant drugs;
- drugs acting on the central nervous system;
- cardiovascular, diuretic and hemotherapeutic drugs;
- gonadotropic steroids and synthetic estrogens;
- dermatologicals;
- chemotherapeutic agents;
- vitamins.

2.1 Anti-inflammatory, Analgesic and Immunosuppressant Drugs

2.1.1 Non-steroidal Anti-inflammatory and Analgesic Drugs. A variety of 2-aryl- (or heteroaryl-) propionic (or acetic) acid derivatives are used as anti-inflammatory agents. Most of these are photoreactive and have some phototoxic action. As a consequence, their photochemistry has been intensively investigated.[18-20] The main process in aqueous solution is decarboxylation to yield a benzyl radical, a general reaction with α-arylcarboxylic acid ("photo-Kolbe"reaction).[21] Under anaerobic conditions, benzyl radicals undergo dimerisation or reduction (and in an organic solvent abstract hydrogen).[22] In the presence of oxygen, addition to give a hydroperoxy radical and the corresponding alcohol and ketone (the latter in part from secondary oxidation of the former) takes place (Scheme 2). A further path leading to the oxidised products may involve singlet oxygen.[19, 23]

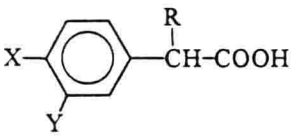


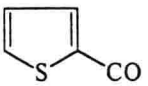
Scheme 2

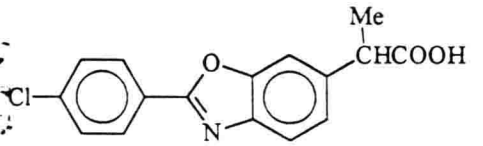


Scheme 3

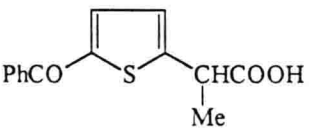
The results from the irradiation of naproxen (1) in water are shown in Scheme 3,[111, 83] and a related chemical course is followed with several drugs pertaining to this group, such as ibuprofen (5),[24] butibufen (6),[25] flurbiprofen (7),[24] ketoprofen (8),[20, 26, 27] suprofen (9),[28] benoxaprofen (10),[19, 22, 25, 29] tiaprofenic acid (11)[30] (Scheme 4) and ketorolac tromethamine (12) (Scheme 5).[31] The triplet state is responsible for initial decarboxylation. Some detailed mechanistic studies have been carried out;[26, 29] in the case of ketoprofen, as an example, it has been shown that the fast decarboxylation of the triplet in water (τ_T 250 ps, quantum yield 0.75) may involve an adiabatic mechanism via internal charge transfer and, in part, ionisation.[26]



	X	Y	R
(5)	Me_2CHCH_2	H	Me
(6)	Me_2CHCH_2	H	Et
(7)	Ph	F	Me
(8)	H	PhCO	Me
(9)		H	Me

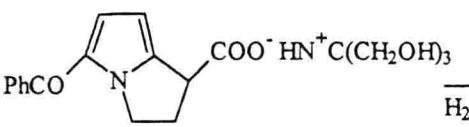


(10)



(11)

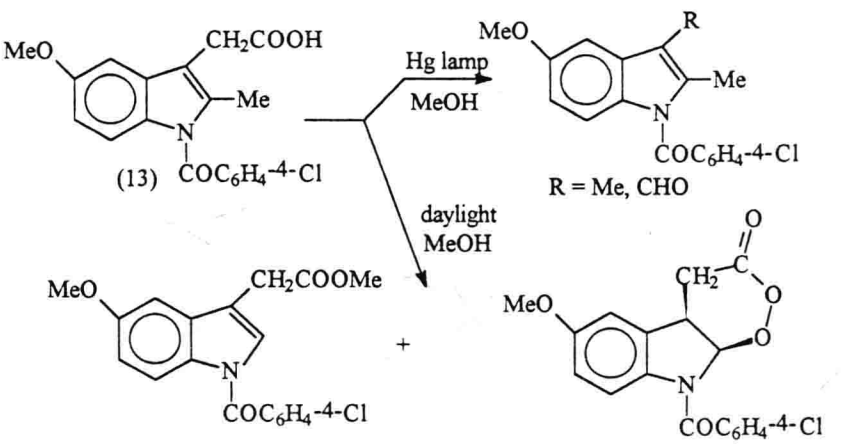
Scheme 4



(12)

X = CH_2, CHOH, CHO_2H, CO

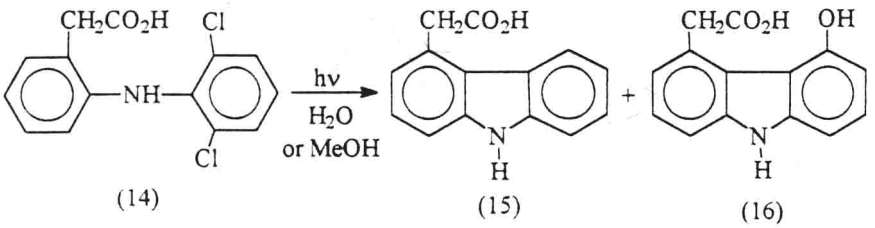
Scheme 5



(13)

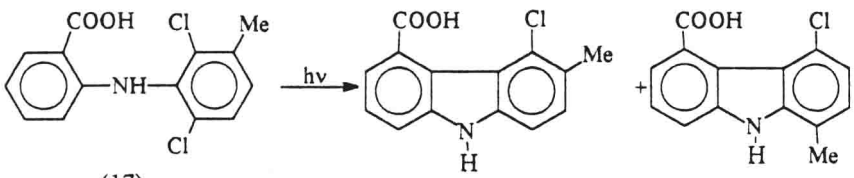
Scheme 6

Indomethacin (13) is quite photostable in the solid state (7.5% decomposition after 72 h irradiation)[32] but reacts in solution.[18] In methanol the usual decarboxylation is the main process[33, 34] when mercury lamps are used, while daylight irradiation leads to products conserving the carboxyl group which have been rationalised as arising via the acyl radical (Scheme 6).[35]



(14) (15) (16)

Scheme 7



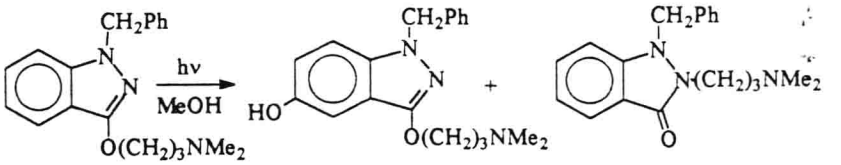
(17) (18) (19)

Scheme 8

In the case of the related drug 2-(2,6-dichlorophenylamino)phenylacetic acid (diclofenac, 14), on the other hand, dechlorination - as stated above, one of the general photochemical reaction of aromatics - is the dominant process. Sequential loss of both chlorine atoms is followed by ring closure, reasonably via radical addition, to yield the carbazole-1-acetic acids (15) and (16) as the main products (Scheme 7).[36] It may be noticed that 2-(2,6-dichloro-3-methylphenylamino)benzoic acid, also an anti-inflammatory agent (meclofenamic acid, 17), likewise undergoes photochemical dechlorination and ring closure to the carbazoles (18) and (19) (Scheme 8).[37]

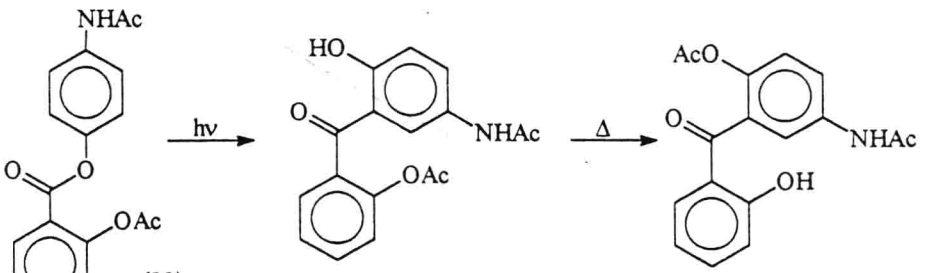
Photoreactivity has been reported also for some anti-inflammatory and analgesic drugs different from arylacetic acids. Thus, benzydamine (20) (irradiation of the hydrochloride in methanol leads to hydroxylation in position 5 as well as well as to Fries type *O-N(2)* chain migration, to yield products (21) and (22) respectively, see Scheme 9).[38] Benorylate (23) likewise undergoes a Fries rearrangement to give (24) which then further rearranges thermally to product (25) (see Scheme 10).[39] The photo-Fries rearrangement is a general reaction with aromatic esters and amides, and occurs via a radical mechanism, rather than via the ionic mechanism of the thermal reaction. 5-Aminosalicylic acid (26), used for the treatment of

chronic inflammatory bowel diseases, undergoes light-accelerated oxidation and polymerisation (Scheme 11).[40]



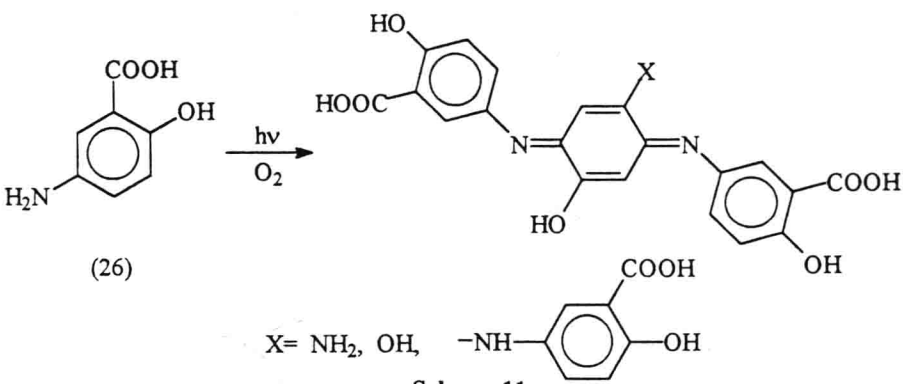
(20) (21) (22)

Scheme 9



(23) (24) (25)

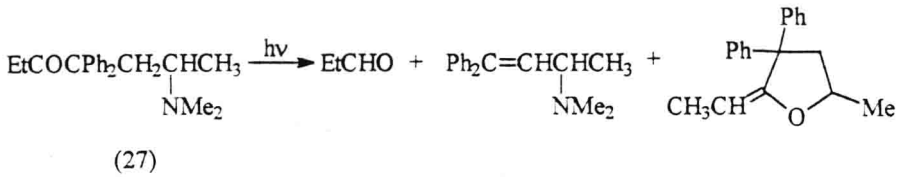
Scheme 10



(26)

Scheme 11

The narcotic analgesic methadone hydrochloride (27) reacts when irradiated by UV light both in aqueous solution[41] and in the solid state.[42] The processes observed (fragmentation and cyclisation, see Scheme 12) are a typical manifestation of the radical-like character of the $n\pi^*$ state of ketones (α- and β-cleavage, see Scheme 1, a). However, this drug is photostable in an isotonic solution when exposed to ambient light.[43]



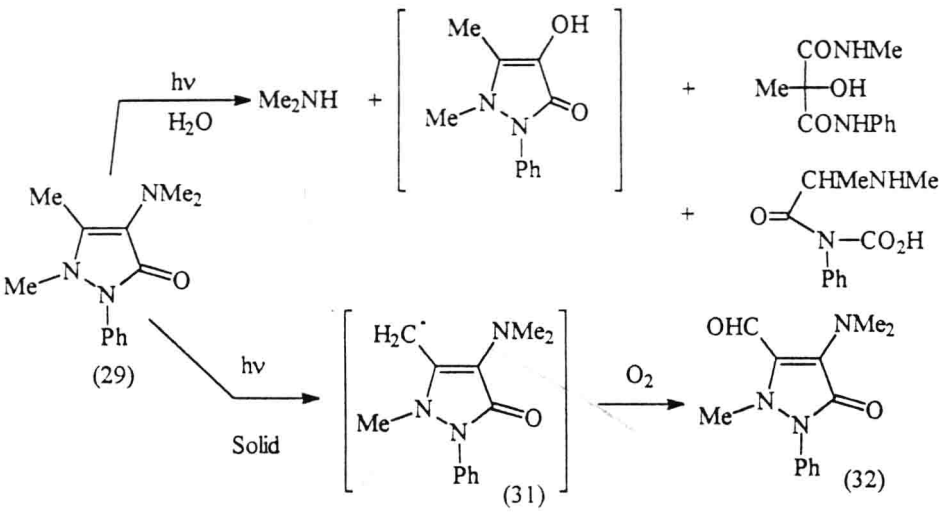
(27)

Scheme 12

The enkefalinase inhibitor thiorfan (28), a new generation analgesic, is quite sensitive to oxidation and is converted to the disulphide; this reaction is accelerated by light.[44]

$$PhCH_2CH(SH)CONHCH_2COOH \quad (28)$$

2.1.2 Pyrazolone Analgesic and Antipyretic Drugs. The largely used drugs of this structure are photoreactive, and cleavage of the pyrazole ring occurs in most cases.[45, 46] Typical reactions are shown below for the case of aminopyrine (29) (Scheme 13) and for that of phenylbutazone (30) (Scheme 14).



Scheme 13

Comparative studies in aqueous solutions[47] showed that aminopyrine is the most reactive derivative,[45] and in general 4-amino substituted pyrazolones react faster than 4-alkyl[48, 49] derivatives. In the presence of oxygen, photolysis is accompanied by a photo-oxidation reaction.[50] The above order of photoreactivity for pyrazolones remains the same in the solid state.[51] However, in the latter case different processes may be involved, as with aminopyrine for which the main reaction in the solid is type I (i.e. involving addition of ground state oxygen to a radical) photo-oxidation of the methyl group in position 5. This has been