The Photochemistry of Metyrapone in the Solid State

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Metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone) undergoes α-cleavage upon irradiation in the solid state. The reaction occurs at the crystal surface, and the radicals formed in part recombine to give dipyridylketones, and in part add oxygen to give nicotinic acid and 3-(1-hydroxymethylethyl)pyridine. The crystals partially melt and the reaction continues until complete decomposition of the starting material.

Key words metyrapone; photolability; drug; solid state

The photolability of drugs is a matter of increasing concern. Indeed, many active principles of drugs substances absorb significantly the UV-A light and their reaction when a drug preparation is exposed to ambient (outdoor or indoor) light is sufficient to cause serious activity loss or the formation of significant amounts of potentially toxic by-products.[1-3] From the practical point of view, it is important that the photochemical behavior of a drug is studied under conditions as near as possible to those of its application, thus usually as a solid or as a concentrated aqueous solution or suspension. On the other hand, a mechanistic study is usually much better carried out in various dilute organic solutions. Therefore, extension of mechanistic data to the conditions of actual use is suspect. A detailed comparison of the photoreactivity of drugs under different conditions would be valuable.

We conducted irradiation in the solid state of metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone, **1**), a heterocyclic ketone used in therapy as a diagnostic agent for pituitary function.[4,5] This molecule is a good model for a photolabile drug since it is expected to undergo a facile photoinduced α-cleavage from the triplet state, the mechanism in solution has been recently clarified,[6] and absorbance of this compound tails up to 360 nm and thus it is sensitive to the UV-A light.

Results

Metyrapone was exposed to a light source as a thin layer of finely ground powder. Both a germicidal lamp (emission at 254 nm) and a "black-light" phosphor-coated lamp (emission centered at 360 nm) were used. When the crystals were irradiated in an argon atmosphere, photodecomposition of compound **1** was slow, *i.e.* $\leq 10\%$ after 6 h with the 360 nm irradiation. On the other hand, when the crystals were exposed to air, decomposition under the same conditions amounted to *ca.* 20% after 1 h and was complete after 6 h. Decomposition with the 254 nm irradiation was similar (30% after 1 h in air). With both wavelengths, partial melting of the sample took place after 1 h and gave a viscous oil.

Preparative photolysis led to a mixture, which was washed with acetone. A precipitate was filtered off and shown to consist of nicotinic acid (**2**). The remaining material was chromatographed on silica gel, affording several compounds (see Table 1 and Chart 1). The main product was 3-(1-hydroxy-1-methylethylpyridine), **3**. The most abundant of the minor products was a dipyridyl ketone, to which structure **4** was assigned mainly on the basis of the ^{1}H- and ^{13}C-NMR spectra, which identified a pyridine ring substituted by a 3-pyridylcarbonyl group at position 2 and by an isopropyl group at position 5. Next in order of abundance, a further dipyridyl ketone was obtained. This was a more polar compound, which contained the same skeleton as compound **4**, as indicated by the closely similar NMR signals, but had an α-hydroxyl group in the chain (formula **5**). Finally, a minor fraction contained two further unseparated compounds. The most prominent signals in the NMR spectrum were in good accord with structure **6**, an isomer of **4**, although the small quantity precluded a more detailed examination.

Discussion

A study in solution had previously shown that the triplet state of **1** is an n_O–π^* state similar to that of other ketones and that it undergoes α-cleavage in 12—14 ns, practically independently of the solvent.[6] Further transients in the microsecond domain were detected, and were suggested to be due to the acyl and benzyl radicals (**7**, **8**) formed in the initial fragmentation. The end products could be rationalized as arising from coupling or disproportionation of such radicals (to give the alkylpyridines **9**, **10**, and

Table 1. Products Formed by Irradiation of Metyrapone in the Solid State and in Solution

	Products (% yield)								
	2	**3**	**4**	**5**	**6**	**9**	**10**	**11**	**12**
Solid	30	11	6	4	3	—	—	—	—
Solution (MeCN)	—	2	—	—	—	3	2	30	50

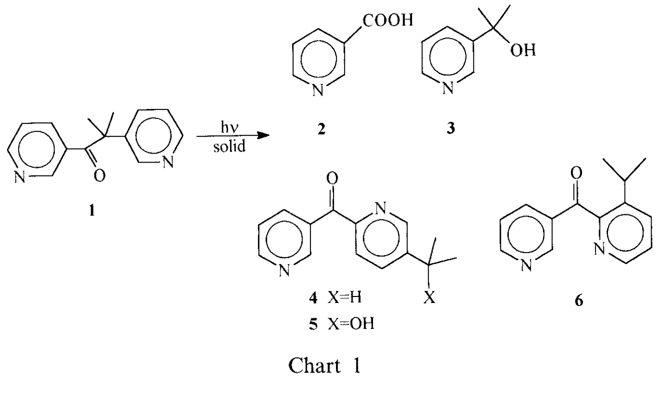

Chart 1

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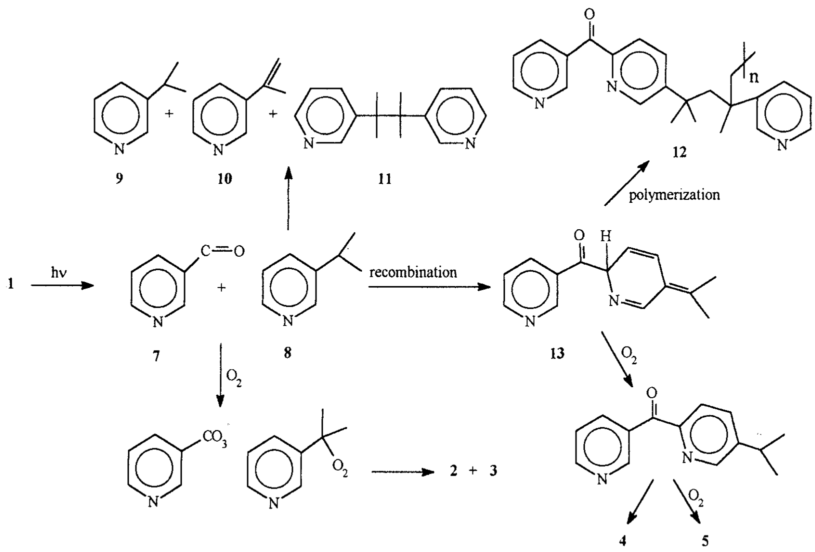

Chart 2

11 from 8) or from a polymerization process (indeed, the major part of the substrate was converted to a polymer of formula **12**, see Chart 2, upper part).

There is no reason to expect that the fragmentation of the triplet state of **1** is less efficient in the solid state than in solution, and thus it can be assumed that the primary step remains the same and radicals **7** and **8** are generated (see Chart 2, central part). Comparing the results under the two conditions (see Table 1) shows, however, that there are important differences in the distribution of the final products. While solution photochemistry leads mainly to polymerization, in the solid state this process is virtually absent. On the other hand, a large amount of nicotinic acid (not obtained by irradiation in organic solvents) is formed, and among the other products the main one is a pyridine bearing an α-hydroxyalkyl chain (compound **3**) whereas in solution only non hydroxylated pyridines are obtained (compounds **9** to **11**, Chart 2, lower part). Furthermore, in the solid state, some dipyridylketones not formed in solution are obtained, and one of them, the ketone **5**, again has a hydroxylated chain.

Thus, the reactions of radicals **7** and **8** are strongly affected by the environment in which they are generated. The products observed arise either by coupling of the radicals or by their interception by oxygen. As for coupling of radicals **7** and **8**, this either leads back to the starting material or, if the acyl radical attacks the pyridine ring rather than the side chain, leads to the alkene **13** (Chart 2, central part). The latter coupling also occurs in solution6) though under that condition the alkene **13** has not been isolated, but undergoes a radical-initiated polymerization to give the polymer **12**. In the solid state, it appears likely that **13** is formed again, but rather than being consumed in a polymerization process, this alkene rearomatizes through a hydrogen transfer process involving oxygen, leading to the isopropyl ketone **4** and the hydroxyisopropyl ketone **5**. Similar coupling at the 2 rather than at the 6 position of the pyridine ring eventually leads to the ketone **6**.

Interception by oxygen leads to the alcohol **3** and nicotinic acid (**2**). Indeed, these are the main products of the photolysis of solid metyrapone when the crystals are exposed to air, and arise from oxygen addition to the radicals **7** and **8** and decay of the peroxy radicals thus formed. This is in accord with the expectation that the photochemical reaction occurs only at the crystal surface, since light penetration is limited to a few molecular layers. Thus, the radicals are generated at the surface in contact with atmospheric oxygen, and trapping by oxygen competes efficiently with radical recombination. While the reaction proceeds, the crystals fragment and partially melt, thus exposing new surfaces to light and air. This allows further molecules to absorb and eventually all of the starting material is consumed.

The irradiation in solution is little affected by oxygen, and the product distribution remains the same both in nitrogen-flushed and in air-equilibrated solution. Thus, in solution the radicals **7** and **8** formed in the photochemical step disproportionate or couple very rapidly, when still in the solvent cage, and are not subject to bimolecular reactions such as oxygen trapping. On the other hand, photodecomposition of the crystals is slow in an inert atmosphere. This is because radical mobility is hindered in the solid, and the radicals formed from α-cleavage mainly recombine before moving, regenerating the starting material. When oxygen is present, on the other hand, the radicals are trapped and the reaction proceeds much faster, but yields mainly oxygenated products, in contrast to the solution photochemistry. Oxygen also influences secondary reactions. Thus, the alkene **13** is formed in both cases, but in solution its main reaction is radical-initiated polymerization, whereas in the solid this alkene is formed at a low concentration and, due again to limited mobility, reacts with oxygen rather than with organic radicals to give the ketones **4** to **6** (Chart 2).

This work emphasises some key differences between mechanistic studies and photochemical studies of drugs under the conditions of use. Due to its low molecular absorptivity in the near UV, characteristic of ketones, metyrapone in dilute solutions is only slowly decomposed by ambient light, and preparative photochemistry in solution is conveniently effected by using the much more

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strongly absorbed 254 nm radiation. In the solid, on the other hand, light absorption is total, and 360 nm light is effective. However, in the latter case reaction occurs only at the surface and in the presence of oxygen. This determines the conversion of the radicals and the predominance of oxidized compounds among the end-products. Aggressive species (peroxy radicals) are formed in the process, and such species may themselves cause further decomposition of some drugs, although probably not in the present case. The partial melting of the crystals also plays a key role, since it exposes a new surface to the radiation. In another case of photochemical decomposition in the solid state, where likewise the photochemically formed radicals reacted with oxygen, it has been found that the reaction stops at a low conversion. In that case the crystals did not fragment extensively, and thus the internal part of the crystal could not absorb light or come into contact with oxygen.[7] In summary, even when the primary photochemical process remains the same in solution and in the solid state, as happens in the present case, both the rate and the mode of photodecomposition can be completely different in the two cases.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were determined on a Finnegan MAT 8222 spectrometer. NMR (^{1}H and ^{13}C) spectra were obtained on a Brucker 300 spectrometer. Chemical shifts are expressed in parts per million (δ) with tetramethylsilane as an internal standard. Thin layer chromatography was run on precoated Silica gel 60 F-254 plates (Merck) with ethyl acetate, and 254 nm light was used to detect the products. Elemental analyses were carried out on a Carlo Erba model 1106 elemental analyzer. Metyrapone (**1**) was obtained from Aldrich.

Photolability Test A test of photolability was carried out as follows. Metyrapone (10 mg) was finely ground in a mortar, spread on microscope glass (area 30 cm^2) and irradiated by means of 2×15 W lamps at a distance of 3 cm. Both low-pressure mercury arcs ("germicidal") and phosphor-coated lamps centered at 360 nm ("black light") were used (Applied Photophysics). TLC examination showed that with the 254 nm lamp 30% of **1** had been consumed after 1 h, and after 6 h only a trace was left. With the 360 nm lamp consumption was 20% after 1 h and complete after 6 h. The effect of oxygen was determined by irradiating similar samples spread on the inner face of a spectrophotometric cuvette, and comparing the results obtained in argon-flushed and in an air-equilibrated cuvettes.

Preparative Photolysis A thin layer of finely ground **1** (300 mg) was spread and irradiated by means of a 254 nm lamp for 40 h. The photolysate (a viscous oil) was washed with acetone. The residue was treated with methanol to yield 50 mg of nicotinic acid. The acetone solution was chromatographed on silica gel (TLC and column chromatography were used in different runs with similar results) with ethyl acetate and MeOH–EtOAc mixtures. The fractions isolated afforded products **3** (oil, which solidified, 18 mg), **4** (oil, 15 mg), **5** (oil, 10 mg), and **6** (oil, 8 mg, not pure).

The main spectroscopic characteristics of the compounds separated are as follows.

3-(1-Hydroxy-1-methylethyl)pyridine (**3**) a known compound.[8] Colorless solid, mp 50 °C. ^{1}H-NMR (CDCl$_3$) δ: 1.60 (s, 6H, CH$_3 \times 2$), 2.95 (br, 1H, OH), 7.25 (dd, $J=5$, 8 Hz, C5-H), 7.82 (dd, $J=5$, 1 Hz, C4-H), 8.42 (d, $J=2$ Hz, C6-H), 8.7 (d, $J=1$ Hz, C2-H). ^{13}C-NMR (CDCl$_3$) δ: 31.5 (CH$_3 \times 2$), 70.9 (COH), 132.4 (CH), 136.8 (CH), 146.1 (CH), 147.5 (CH).

2-[5-(1-Methylethyl)pyridyl]-3-pyridylmethanone (**4**): MS *m/z*: 226 (M$^+$). IR $\nu_{\max}$ cm^{-1}: 1660, 1600, 1305. ^{1}H-NMR δ: 1.35 (d, 6H, $J=7$ Hz, CH$_3 \times 2$), 3.10 (sept, 1H, $J=7$ Hz, C$\underline{\text{H}}$Me$_2$), 7.6 (ddd, 1H, $J=1$, 5, 8 Hz, C5′-H), 7.95 (dd, 1H, $J=2$, 8 Hz, C4-H), 8.1 (d, 1H, $J=8$ Hz, C3-H), 8.48 (dt, 1H, $J=2$, 8 Hz, C4′-H), 8.6 (d, 1H, $J=2$ Hz, C6-H), 8.73 (dd, 1H, $J=2$, 5 Hz, C6′-H), 9.18 (d, 1H, $J=2$ Hz, C2′-H). ^{13}C-NMR [(CD$_3$)$_2$CO] δ: 24.0 (CH$_3 \times 2$), 33.0 ($\underline{\text{C}}$HMe$_2$), 124.2 (CH), 125.2 (CH), 133.7, 136.3 (CH), 139.1 (CH), 148.8 (CH), 149.1, 153.0 (CH), 153.4, 153.8 (CH), 192.8 (C=O). *Anal.* Calcd for C$_{14}$H$_{14}$N$_2$O: C, 74.31; H, 6.24; N, 12.38. Found: C, 73.9; H, 6.4; N, 12.2.

2-[5-(1-Hydroxy-1-methylethyl)pyridyl]-3-pyridylmethanone (**5**): MS *m/z*: 242 (M$^+$). IR $\nu_{\max}$ cm^{-1}: 3400, 1665, 1580, 1290. ^{1}H-NMR (CD$_3$OD) δ: 1.6 (s, 6H, CH$_3$), 4.5 (br, 1H, OH), 7.6 (ddd, 1H, $J=1$, 5, 8 Hz, C5-H), 8.1 and 8.15 (AB part of an ABX system, 2H, C3′-H, C4′-H), 8.5 (dt, 1H, $J=2$, 8 Hz, C4-H), 8.73 (dd, 1H, $J=2$, 5 Hz, C6-H), 8.87 (dd, 1H, $J=1$, 2 Hz, C6′-H), 9.2 (dd, 1H, $J=1$, 2 Hz, C2-H). ^{13}C-NMR [(CD$_3$)$_2$CO] δ: 32.3 (CH$_3 \times 2$), 71.6 (COH), 124.2 (CH), 124.8 (CH), 133.7, 134.9 (CH), 139.1 (CH), 147.0 (CH), 150.5, 153.0 (CH), 153.5, 153.9 (CH), 192.9 (C=O). *Anal.* Calcd for C$_{14}$H$_{14}$N$_2$O$_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.1; H, 6.1; N, 11.3.

2-[3-(1-Methylethyl)pyridyl]-3-pyridylmethanone (**6**): MS *m/z*: 226 (M$^+$). IR $\nu_{\max}$ cm^{-1}: 1660, 1580, 1305. ^{1}H-NMR (CD$_3$OD) δ: 1.3 (d, 6H, $J=7$ Hz, CH$_3 \times 2$), 3.1 (sept, 1H, $J=7$ Hz, CH), 7.58(dd, 1H, $J=5$, 8 Hz, C5-H), 7.62 (ddd, 1H, $J=2$, 5, 8 Hz, C5′-H), 8.05 (dd, 1H, $J=1.5$, 8 Hz, C4-H), 8.48 (dd, 1H, $J=1.5$, 5 Hz, C6-H), 8.55 (dd, 1H, $J=2$, 8 Hz, C4′-H), 8.78 (dt, $J=2$, 5 Hz, C6′-H), 9.25 (t, 1H, $J=2$ Hz, C2′-H). The sample contains a minor amount of another isomeric compound, as shown by minor signals in the NMR spectrum. *Anal.* Calcd for C$_{14}$H$_{14}$N$_2$O: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.2; H, 6.4; N, 12.1.

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