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The Invention of Radical Reactions. Part XXVIII A New Very Photolabile *O*-Acyl Thiohydroxamic Acid Derivative as Precursor of Carbon Radicals

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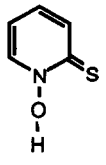
Abstract: A new thiohydroxamic acid was synthesized and found to be an excellent generator of carbon radicals *via* its *O*-acyl derivatives.

Carbon and other radicals play an increasingly important role in organic synthesis[1]. However, the synthetic usefulness of these radicals depends on the disciplinary groups present and on the reagents used for generating them. This is one of the reasons that *O*-acyl derivatives of thiohydroxamic acids (like those of **1**[2] and **3**[3]) (Barton esters, **2**)[2] have become popular for synthetic purposes as generators of radicals. The radicals can be formed by simple photolysis with visible or U.V. light[4] and the thiocarbonyl acts as a disciplinary group for the original radical or for other radicals produced indirectly. We have shown recently[5], that *O*-acyl quinazolinethione derivatives **4** are even more photolabile and useful generators of carbon radicals than similar derivatives of **1** or **3**.



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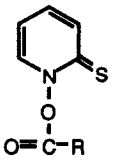

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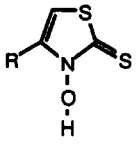

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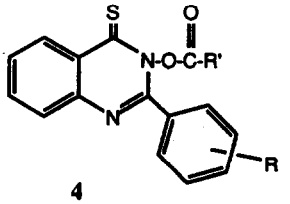

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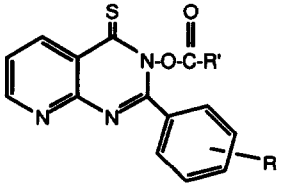

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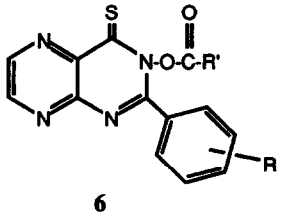

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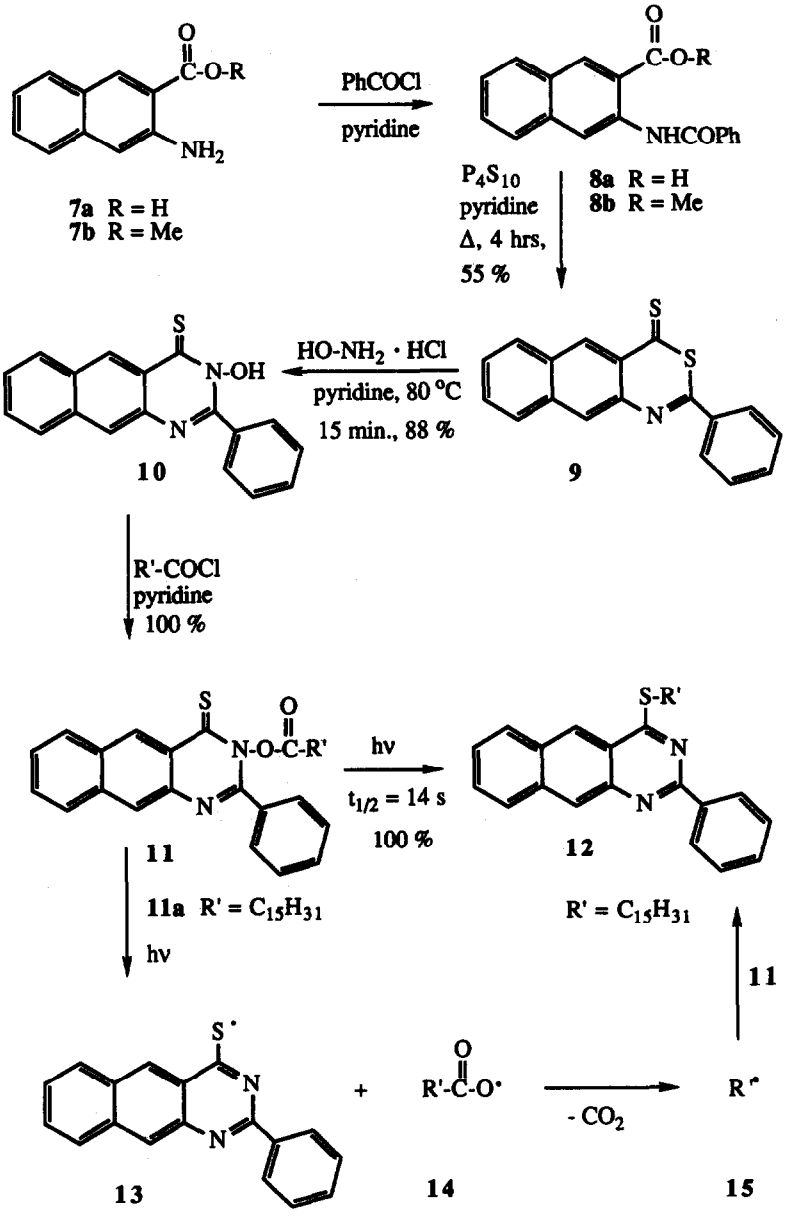
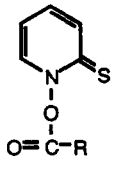

PhCOCl
pyridine
7a R = H
7b R = Me
8a R = H
8b R = Me
P4S10
pyridine
Δ, 4 hrs,
55 %
HO-NH2 · HCl
pyridine, 80 °C
15 min., 88 %
10
9
R'-COCl
pyridine
100 %
hν
t1/2 = 14 s
100 %
11
11a R' = C15H31
12
R' = C15H31
hν
11
13
14
15
- CO2

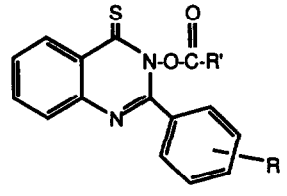
Varying the substituents R of **4**, however, changed only ε, but did not shift λ_{max} (Table 1). As a continuation of this work we have attempted to obtain other thiohydroxamic acids with different absorption maxima in the UV-visible region. Synthesis of two thiohydroxamic acids **5** and **6** was not promising due to low yields in the synthetic sequence.

The commercially available 3-amino-2-naphthoic acid **7a** (Aldrich), however, was successfully transformed to the thiohydroxamic acid **10**. Thus, **7a** was esterified with diazomethane and *N*-benzoylated to furnish **8b** in nearly quantitative yield. The alternative sequence (**7a** ⟶ **8a** ⟶ **8b**) gave less satisfactory yields. The amide **8b** was then cyclized in boiling pyridine to **9** in 55% yield (not optimized). Upon treatment with hydroxylamine hydrochloride in pyridine at 80 °C, **9** was transformed to the thiohydroxamic acid **10** (88%). This compound is the precursor of highly photolabile *O*-acyl-thiohydroxamic acid derivatives **11** (e.g. **11a**, R' = $C_{15}H_{31}$). When photolyzed with visible (tungsten) light, **11a** easily furnished the rearranged product **12** *via* the acyloxy radical **14** and the carbon radical **15** in quantitative yield. Because of the relatively long chains (with quantum yields up to 60) observed also in the case of the quinazolinethione analogue **4**[5], the thiyl radical is formed presumably in very small concentrations, the chain being carried by the **11** + **15** ⟶ **12** + **14** process.



2a R = 1-pentadecyl

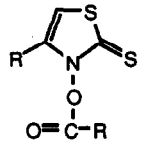
2b R = CH_3



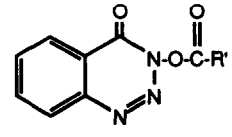
4a R = Ph, R' = 1-pentadecyl

4b R = 1-naphthyl, R' = 1-pentadecyl

4c R = 4-MeO-Ph, R' = 1-pentadecyl



16 R = Ph, R' = 1-pentadecyl



17[6] R' = 1-pentadecyl

Table 1 UV-visible data of *O*-acyl hydroxamic- and thiohydroxamic acid derivatives

Compound	**2a**	**2b**	**4a**	**4b**	**4c**	**11a**	**16**	**17**
λ_{max} (nm)	367	366	356	355	358	325	324	283
ε	7000	6000	14290	15000	12540	21810	10900	7019

It was part of the aim of this study to determine the effects of the various substituents in **4** on the UV-visible absorption. It was also of interest to discover the effect of extending the conjugation of the quinazoline aromatic ring, which is present in compound **4**, on the thiocarbonyl λ_{max}. Thus it is clear from Table 1 that differing substituents at position C-2 have no effect on the λ_{max}(C=S) which is equal to approximately 356 nm for **4a-c**.

The molar extinction coefficient is double that of the N-hydroxy-2-thiopridone derivative **2a**, ε = 12,500-15,000 for **4a-c** as opposed to that of ε = 7,000 for **2a**. It is also of interest to note that the benzotriazine-4(3H)-one derivative **17** has a molar extinction coefficient of only ε = 7,019, similar to that of **4a**. Thus, it could be assumed that C2-aryl substituents increase the molar extinction coefficient of the quinazoline system without shifting the absorption maxima.

When conjugation on the parent aromatic ring in the quinazoline-4-thione system is increased as it is in **11a** the λ_{max} for the thiocarbonyl absorption shifts towards the ultraviolet (λ_{max} = 325nm). This is also accompanied by an increase in the molar extinction coefficient (ε = 21,810). The compound **11a** is strongly yellow due to a tail at λ_{max} = 400nm (ε = 7,000) but this tail remains when the compound undergoes decarboxylative rearrangement to sulphide **12**.

The absorption at 325nm disappears however as can be seen from Fig. 1. which shows the UV-visible absorption of **11a** and **12** overlaid.

We found that the half-life of the photolytic rearrangement of **11** to **12** (*via* **15**) was 14 s, the shortest we have ever observed. This half-life still allows careful synthetic manipulations with **11** in darkness or in darkroom conditions. Thus, the use of **10** to synthesize acyl derivatives **11** provides a new source of carbon radicals that can be generated very effectively by simple visible (tungsten) light photolysis. For comparison we have already

recorded for **2a** a half-life of 200 s and for **17** a half-life of 19 s under the same conditions as cited above for **11a**.[5] The thiazole **16**[7] can be photolysed with a tungsten light (300W) for two hours and only 50% of the rearranged sulphide is formed.

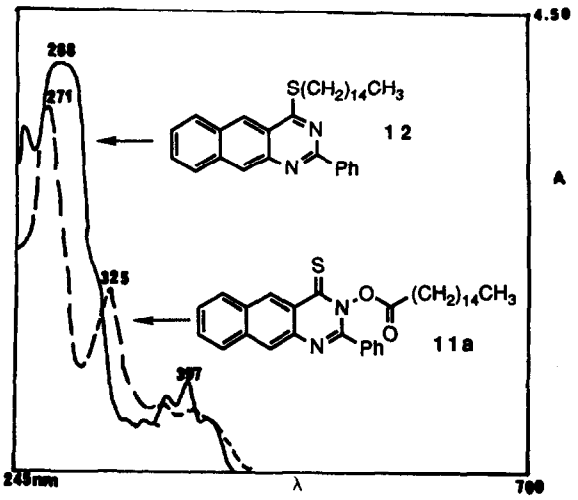


Fig. 1. UV-Visible absorption spectra for 2-phenyl-3-palmitoyloxybenzoquinazoline-4(3H)-thione **11a** and its rearranged derivative **12**.

Experimental

General Procedures and Starting Materials.

Melting points were determined with a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. UV spectra were recorded on a Beckman DU-7 spectrometer. ^{1}H and ^{13}C NMR spectra were determined for solutions in deuteriochloroform (unless specified otherwise) with TMS internal reference on Varian Gemini 200, Varian XL 200E or Varian XL 400 instruments. Gas chromatography (glc) measurements were performed on a Chrompack Packard Model 439 gas chromatograph on 30 m capillary columns. GC-MS data were obtained on a Hewlett-Packard 5890 GC-MS system. Mass spectra were obtained on a VG Analytical 70S high resolution double focusing magnetic sector

mass spectrometer with attached VG 11/250J data system in the EI or FAB mode. FAB spectra were obtained neat or in glycerol matrix. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia. Solvents were used either as purchased or dried and purified by standard methodology. N-Hydroxy-2-thiopyridone was isolated from its sodium salt (Omadine^{R}). A 40% solution of the sodium salt of N-hydroxy-2-thiopyridone was a kind gift of the Olin Corporation, Cheshire, CT. Other reference compounds and starting materials were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

Methyl 3-Benzoylamino-2-naphthoate **8b.**

3-Amino-2-naphthoic acid **7a** (4.2 g, 80% tech., 17.9 mmol) was suspended in methanol (400 ml) at 0°C and treated with a diazomethane solution in ether (~80 mmol) prepared earlier. Once the yellow color of diazomethane persisted and there was no precipitate present the ice bath was removed and the solution was allowed to attain room temperature. The methanol and ether were evaporated under reduced pressure and a ^{1}H NMR spectrum was recorded which showed complete esterification. The resulting solid was dissolved in dry pyridine and the flask was sealed and cooled to 0°C with an ice bath. Benzoyl chloride (2.6 ml, 22 mmol) was then added to the sealed solution by syringe over a period of ten minutes. The resulting mixture was stirred overnight after which the contents of the flask were poured onto crushed ice. Once the ice had melted the precipitate was filtered and then dried (CH_2Cl_2/anhydrous $MgSO_4$). Filtration and evaporation yielded the crude solid which was crystallized from CH_2Cl_2/hexanes to give 4.33 g (1st crop) and 1.133 g (2nd crop) 99% yield of the title compound; mp 150-151°C; IR ($CHCl_3$, cm^{-1}) 3312, 3006, 1685, 1539, 1294; UV-vis ($CHCl_3$) λ_{max1} = 364 nm, ε = 3 025, λ_{max2} = 269 (310) nm, ε = 24 610(9 224); ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H), 7.40-7.62 (m, 5H), 7.80-7.96 (t, 2H), 8.02-8.20 (m, 2H), 8.65 (s, 1H), 9.40 (s, 1H), 12.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 52.7 (CH_3), 115.7 (C_q), 117.5, 125.5 (2 x CH), 127.2 (2 x CH), 127.8 (CH), 128.4 (C_q), 128.8 (2 x CH), 128.9 (C_q), 129.3, 131.8, 133.4 (3 x CH), 134.9, 136.4, 136.6 (3 x CH), 165 6, 169.0 (2 x C=O); MS m/e 305 (M^+), 273 (M^+–OCH_3+H), 246 (M^+–CO_2CH_3).

2-Phenyl-[g]-naphthothiazine-4-thione **9.**

Methyl 3-benzoylamino-2-naphthoate **8b** (4.07 g, 13.3 mmol), phosphorus pentasulfide (12 g, 2 equivalents) and freshly distilled dry pyridine (150 ml) were placed in a round bottom flask equipped with a condenser and drying tube. The stirred solution was then immersed into an oil bath preheated to 140°C and boiled. The reaction was followed by tlc and after four hours the reaction was deemed complete. The heating

was stopped and the hot reaction mixture was poured on crushed ice. Once the ice melted, the precipitate formed was filtered, redissolved in methylene dichloride and dried with anhydrous magnesium sulfate. After removal of the solvent in vacuum the resulting solid was crystallized from methylene dichloride and ethanol. The first two crops gave the title compound 2.2456 g, 55.3%; mp 180-181°C; IR ($CHCl_3$, cm^{-1}) 3033, 1599, 1550, 1201, 1013; UV-vis ($CHCl_3$) λ_{max1} = 460 nm, ε = 3 800, λ_{max2} = 354 nm, ε = 15 780, λ_{max3} = 305 (273) nm, ε = 37 740 (23 380); ^1H NMR ($CDCl_3$) δ 7.50-7.60 (m, 5H), 7.98-8.60 (d, 1H), 8.10-8.20 (m, 3H), 8.40 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 125.5 (C_q), 126.8 (2 x CH), 127.7, 128.0, 128.1 (3 x CH), 129.1 (2 x CH), 129.7, 130.5, 130.6, 132.0 (4 x CH), 133.1, 135.9, 137.2, 138.1 (4 x C_q), 158.6 (N=C–), 212.6 (C=S); MS m/e 305 (M^+), 273 (M^+–S); Anal. Calcd. for $C_{18}H_{11}NS_2$: C, 70.79; H, 3.63; N, 4.59; S, 21.00. Found: C, 70.72; H, 3.60; N, 4.60; S, 20.88.

2-Phenyl-3-hydroxy-3,4-dihydro-[g]-benzoquinazoline-4-thione **10**.

2-Phenyl-[g]-naphthothiazine-4-thione **9** (258 mg, 0.84 mmol) was dissolved in the minimum amount of boiling ethanol (2 ml) to which was added hydroxylamine hydrochloride (64 mg, 1.1 equivalents) and sodium acetate (96 mg). Following the immediate color change the solution was allowed to cool and the resulting crystals were filtered. Recrystallization from ethanol gives the title compound as bright yellow needles 225 mg, 88%; mp 183-184°C; IR ($CHCl_3$, cm^{-1}) 3062, 1588, 1563, 1506, 1478, 1333, 1260; UV-vis ($CHCl_3$) λ_{max1} = 430 nm, ε = 3 740, λ_{max2} = 408 nm, ε = 6 275, λ_{max3} = 389 nm, ε = 6 150, λ_{max4} = 335 nm, ε = 12 560, λ_{max5} = 280 nm, ε = 35 100; ^1H NMR ($CDCl_3$) δ 7.50-7.70 (m, 5H), 7.99-8.19 (m, 4H), 8.42 (s, 1H), 9.14 (s, 1H), 11.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 124.6 (C_q), 127.2 (2 x CH), 128.1 (CH), 128.3 (2 x CH), 128.8, 129.3 (2 x CH), 129.8 (2 x CH), 130.9, 131.1 (2 x CH), 131.9, 132.5, 136.4, 137.8 (4 x C_q), 145.8 (C=N), 177.7 (C=S); Anal. Calcd. for $C_{18}H_{12}N_2OS$: C, 71.03; H, 3.97; N, 9.20; S, 10.53. Found: C, 70.97; H, 3.98; N, 9.13; S, 10.43.

Methyl 2-(N-Benzoylamino)-nicotinate.

Prepared as for **8b**, 74% yield; mp 155-156°C; IR (CH_2Cl_2, cm^{-1}) 3287, 3037, 2956, 1700, 1600, 1485, 1238, 1137, 902; UV-vis ($CHCl_3$) λ_{max1} = 273 nm, ε = 8 016; ^1H NMR ($CDCl_3$) d 3.98 (s, 3H), 7.08-7.15 (m, 1H), 7.48-7.64 (m, 3H), 8.06-8.14 (m, 2H), 8.33-8.39 (m, 1H), 8.71-8.75 (m, 1H), 11.80 (s, 1H); ^{13}C NMR ($CDCl_3$) d 52.7 (CH_3), 111.2 (C_q), 118.2 (CH), 127.4 (2 x CH), 128.6 (2 x CH), 132.0 (CH),

134.6 (C_q), 139.7 (CH), 152.8 (C_q), 153.4 (CH), 164.1 (O–C=O), 167.4 (N–C=O); Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.56; H, 4.73; N, 10.90.

2-Phenyl-3-hydroxy-2'3'-pyridoquinazoline-4-thione .

Prepared as for **10**, 11% yield, too unstable to characterize fully. ^1H NMR ($CDCl_3$) δ 7.52-7.70 (m, 4H), 8.18-8.26 (m, 2H), 8.87-8.95 (m, 1H), 9.14-9.17 (m, 1H), 11.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 122.3 (C_q), 123.6 (CH), 128.3 (2 x CH), 130.3 (2 x CH), 130.9 (C_q), 132.0, 139.1 (2 x CH), 151.6 (C_q), 157.1 (CH), 177.8 (C_q), 222.6 (C=S).

2-Phenyl-3-palmitoyloxy-3,4-dihydro-[g]-benzoquinazoline-4-thione **11a**.

Prepared as for **4a**, (94% yield); mp 63°C; IR ($CHCl_3$, cm^{-1}) 3062, 2927, 1803, 1588, 1492, 1449, 1351, 1322, 1244, 1188, 1042; UV-vis ($CHCl_3$) λ_{max1} = 400 nm, ε = 7 245, λ_{max2} = 369 nm, ε = 7 680, λ_{max3} = 325 nm, ε = 21 810, λ_{max3} = 271 nm, ε = 43 900; ^1H NMR ($CDCl_3$) δ 0.80-1.00 (m, 3 H), 1.05-1.60 (m, 26H), 2.24-2.60 (m, 2H), 7.40-7.70 (m, 5H), 7.72-7.80 (m, 2H), 7.94-7.99 (d, 1H), 8.07-8.11 (d, 1H), 8.30 (s, 1H), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7, 24.1, 28.6, 29.0, 29.2, 29.3, 29.5 (7 x CH_2), 29.6 (5 x CH_2), 31.4, 31.9 (2 x CH_2), 126.9, 127.1 (2 x CH), 127.5 (C_q), 127.9 (CH), 128.3 (2 x CH), 128.9 (CH), 129.0 (2 x CH), 129.6, 130.7 (2 x CH), 132.1 (C_q), 132.5 (CH), 132.6, 136.7, 137.5 (3 x C_q), 150.3 (–C=N), 168.8 (C=O), 183.9 (C=S); Anal. Calcd. for $C_{34}H_{42}N_2O_2S$: C, 75.24; H, 7.80; N, 5.16; S, 5.91. Found: C, 75.29; H, 7.84; N, 5.12; S, 6.00.

2-Phenyl-4-pentadecylthio-[g]-benzoquinazoline **12**.

Prepared by photolysis from **11a**, (98% yield); mp 89-90°C; IR ($CHCl_3$, cm^{-1}) 2927, 2854, 1597, 1509, 1460, 1319, 1125; UV-vis ($CHCl_3$) λ_{max} (ε): 418 nm (4 160), 397 nm (6 790), 378 nm (5 795), 288 nm (30 425), 252 nm (25 810); ^1H NMR ($CDCl_3$) d 0.80-1.00 (m, 3H), 1.1-1.7 (m, 24H), 1.8-2.0 (m, 2H), 3.52 (t, J = 7 Hz, 2H), 7.4-7.6 (m, 5H), 7.96-8.04 (m, 2H), 8.51 (s, 1H), 8.60-8.74 (m, 3H); ^{13}C NMR ($CDCl_3$) d 14.1 (CH_3), 22.7, 29.1, 29.2, 29.31, 29.35 (5 x CH_2), 29.6 (8 x CH_2), 29.9 (CH_2),121.0 (C_q), 123.8, 126.2, 126.6, 127.8, 128.1 (5 x CH), 128.4 (2 x CH), 128.6 (2 x CH), 128.9, 130.4 (2 x CH), 131.5, 136.3, 138.2, 143.9, 157.3, 172.7 (6 x C_q); Anal. Calcd. for $C_{33}H_{42}N_2S$: C, 79.48; H, 8.49; N, 5.62; S, 6.43. Found: C, 79.38; H, 8.51; N, 5.61; S, 6.35.

Half-life determination.

A standard 0.1 M solution of the acyl derivative in $CDCl_3$ (5 ml) with propyl acetate as the internal standard was made. Then seven 0.7 ml fractions were removed and injected into NMR tubes which had previously been sealed and flushed with argon. The NMR tubes were then placed in a 400 ml beaker covered three quarters of the way round with aluminium foil and containing 0°C water. The 250 W tungsten lamp was then placed next to the glass of the beaker and switched on at the same time as a stop clock. During the course of irradiation the samples were removed after set periods of time and the decomposition of the acyl derivative measured by ^1H NMR spectroscopy.

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