atom. The C_{21} position shows the same tendency. Here the log P value changes by 0.42 ± 0.22 ($n = 6$) per carbon atom with increasing chain length. The introduction of a chlorine atom in place of OH causes only a slight increase in the log P value.

The two HPLC methods described for the determination of the lipophilicity of glucocorticosteroids are more rapid than the shake-flask method, and are more convenient than the TLC procedure.

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Stability-Indicating Assay for Phenylbutazone: High-Performance Liquid Chromatographic Determination of Hydrazobenzene and Azobenzene in Degraded Aqueous Phenylbutazone Solutions

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Received December 30, 1982, from the *Laboratoire de Chimie Analytique, Faculté de Pharmacie, 34060 Montpellier Cedex, France.* Accepted for publication February 2, 1984.

Abstract ◻ A high-performance liquid chromatographic method was developed for the simultaneous determination of azobenzene, hydrazobenzene, and four other decomposition products in phenylbutazone injectable formulations. Separation was achieved on a C_{18} column, with 0.1 M Tris-citrate buffer (pH 5.25) and acetonitrile (52:48), at a flow rate of 2 mL/min and a detection wavelength of 237 nm. Diphenylamine was used as an internal standard. The limit of quantitation is 0.5% (with respect to phenylbutazone) of each degraded product. The detectability is 2.4×10^{-3} μg for azobenzene and 1.5×10^{-3} μg for hydrazobenzene. The limit of quantitation may be lowered to 0.1% (with respect to phenylbutazone) for azobenzene and hydrazobenzene in the presence of the two major decomposition products, which have been determined in commercially available injectable formulations. A higher sensitivity was obtained for azobenzene using the mobile phase 0.1 M Tris-citrate buffer (pH = 5.25) and acetonitrile (40:60) with detection at 314 nm. Under these conditions, 0.025% (with respect to phenylbutazone) of azobenzene is quantitated.

Keyphrases ◻ Phenylbutazone—HPLC, stability-indicating assay, degradation products ◻ Azobenzene—HPLC determination ◻ Hydrazobenzene—HPLC determination

The sodium salt of phenylbutazone (I) in aqueous solution undergoes hydrolysis and, to a small extent, oxidation and decarboxylation according to degradation Scheme I (1). Among these degradation products, some are of particular interest because of their deleterious effects: 4-butyl-4-hydroxy-1,2-diphenyl-3,5-pyrazolidinedione (II) may be involved in allergic reactions (2); hydrazobenzene (VIII) and azobenzene (IX) are suspected carcinogens (3). Despite their toxicity, no analytical method has been proposed for the identification and quantification of VIII and IX in phenylbutazone formulations. Only separation on chromatographic columns and identification by TLC have been reported as evidence for the presence of IX in commercial injections after prolonged storage (4). The present study was undertaken to complete preliminary work (5, 6); the conditions used previously in the high-performance liquid chromatographic (HPLC) procedure (6) did not allow the determination of VIII and IX within acceptable time. In this report, an improved, rapid, and sensitive HPLC procedure is presented that allows simultaneous determination of trace levels of II, III, IV, VI, VIII, and IX and a monitoring of the stability of I in injections.

EXPERIMENTAL SECTION

Materials and Reagents—Compounds I, II, III, IV, and VI were used as received[1]. Compounds VIII and IX, diphenylamine (DPA), Tris, and citric acid were analytical reagent grade. HPLC-grade acetonitrile, distilled-in-glass grade methanol, and water were also used. Injectable formulations were commercial formulations[2] (600 mg of the sodium salt of phenylbutazone, 6 mg of dibucaine, propylene glycol, and water per 3 mL of solution).

The HPLC[3] was equipped with a variable-wavelength UV detector[4]. The separation was carried out on a laboratory-made column (15 cm × 4.0 mm) containing microsilica particulate-bonded (5-μm) octadecylsilane[5]. The mobile phase A was 0.1 M Tris-citrate buffer (pH 5.25) and acetonitrile (52:48). The citrate buffer was filtered through a 0.45-μm filter[6], and the mixture was deaerated before use.

Standard Solutions—An initial mixed stock solution was prepared in the mobile phase using I (200 μg/mL) and II, III, IV, VI, VIII, and IX (100 μg of each/mL). This solution was suitably diluted in the mobile phase to give standard solutions. An internal standard solution (diphenylamine, 500 μg/mL in the mobile phase) was added to each diluted standard solution to give a 100-μg/mL concentration of diphenylamine. The final concentration range was from 5 to 160 μg/mL for I and from 2.5 to 80 μg/mL for II-IV, VI, VIII, and IX.

Test Solutions—Recovery studies were carried out on laboratory-prepared injections similar to commercial formulations with the following amounts

[1] Gifts from Geigy Laboratories, Basel, Switzerland.
[2] Butazolidine; Geigy.
[3] SP 8000; Spectra Physics.
[4] SF 770; Schoeffel.
[5] Lichrosorb RP-18; Merck, Darmstadt, W. Germany.
[6] Sartorius.

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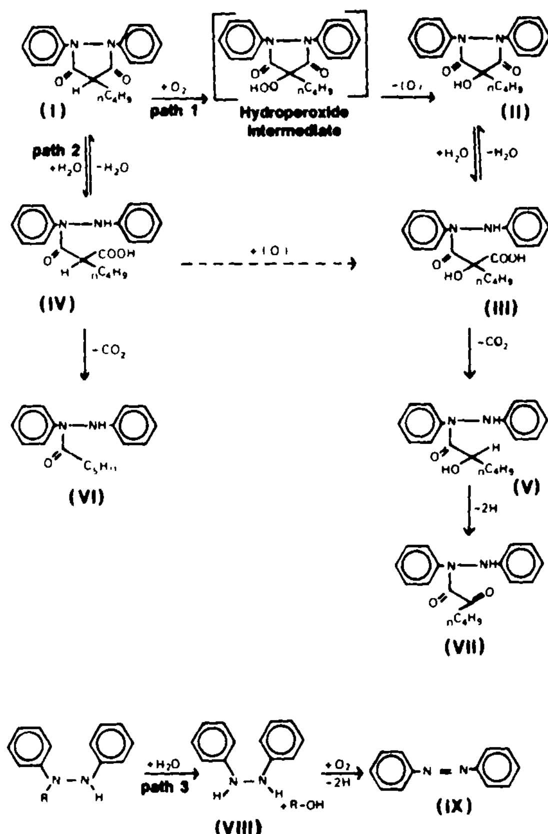

Scheme I—Degradation pathways of phenylbutazone according to Ref. 1. Key: (I) phenylbutazone; (II) 4-butyl-4-hydroxy-1,2-diphenyl-3,5-pyrazolidinedione; (III) 3-hydroxy-2-oxohexanoic acid 1,2-diphenylhydrazide; (IV) 3-carboxy-2-oxohexanoic acid 1,2-diphenylhydrazide; (V) 2-hydroxyhexanoic acid 1,2-diphenylhydrazide; (VI) hexanoic acid 1,2-diphenylhydrazide; (VII) 2-oxohexanoic acid 1,2-diphenyl hydrazide; (VIII) hydrazobenzene; (IX) azobenzene.

added: 1% (with respect to I) of II-IV, VI, VIII, and IX; 0.5% (with respect to I) of II-IV, VI, VIII, and IX; 0.2% (with respect to I) of VIII and IX in the presence of 3% (with respect to I) of III and IV; 0.1% (with respect to I) of VIII and IX in the presence of 3% (with respect to I) of III and IV. These prepared solutions and the commercial injections were diluted in the mobile phase and internal standard solution was added to match the calibration graph.

A 10-μL aliquot of each standard solution and 10 μL of test solution were injected in duplicate onto the chromatograph. The apparatus was operated at ambient temperature. The flow rate was 2 mL/min, the pressure was 140 ± 2 bars, and the detector was set at 237 nm or 314 nm, with a sensitivity of 0.1 AUFS.

RESULTS AND DISCUSSION

Specimen chromatograms of a standard solution recorded at 237 nm (suitable wavelength for simultaneous determination of I-IV, VI, VIII, and IX) and 314 nm (maximum absorbance wavelength for IX in the mobile phase) are shown in Figs. 1 and 2, respectively. A better sensitivity for IX and a negligible absorbance of I-IV, VI, and VIII is observed at 314 nm. Diphenylamine may be used as an internal standard at 237 and 314 nm. An excipient blank was injected. No interference was observed at these wavelengths.

Chromatographic Parameters—Table I lists the chromatographic data for phenylbutazone and its main decomposition products, expressed as the capacity factor k', the theoretical plate height H, the asymmetry factor A_s (7) under the conditions used in the present study (mobile phase A). To check the efficiency of acetonitrile on the selectivity, a modified mobile phase 0.1 M Tris-citrate buffer (pH 5.25)-acetonitrile-methanol (52:30:18) was used. No separation efficiency was obtained and a dramatic increase in the capacity factors and increased pressure (p = 218 bars) were observed.

Comparative data using mobile phase B, 0.1 M Tris-citrate buffer (pH 5.25) and acetonitrile (60:40) and the conditions used in a previous paper (flow rate,

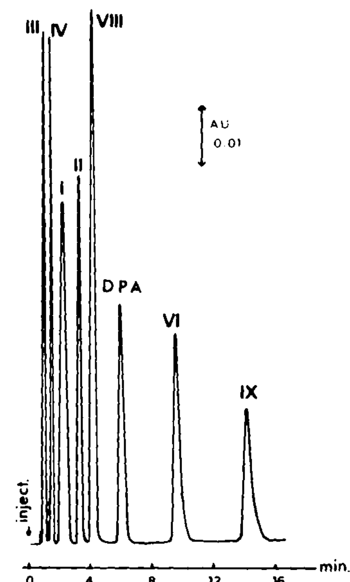

Figure 1—*Chromatogram of a standard solution of I (97.0 µg/mL), II (44.0 µg/mL), III (36.0 µg/mL), IV (40.0 µg/mL), VI (54.4 µg/mL), VIII (56.0 µg/mL), IX (48.0 µg/mL), and DPA (82.5 µg/mL). The mobile phase was 0.1 M Tris-citrate buffer (pH 5.25)-acetonitrile (52:48); flow rate was 2 mL/min, and pressure was 140 bars. Detector sensitivity was 0.1 AUFS, chart recorder speed was 0.5 cm/min, and λ was 237 nm.*

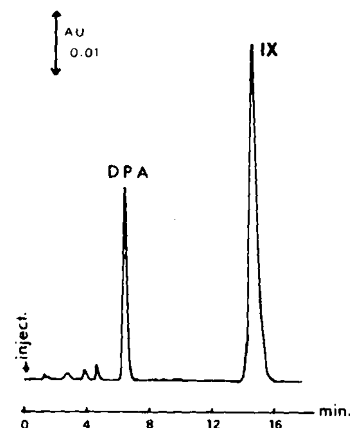

Figure 2—*Chromatogram of a standard solution recorded at 314 nm. Standard solution and conditions were the same as in Fig. 1.*

2.0 mL/min) (6), are given in Table I. Mobile phase B could not achieve the separation within an acceptable time. Accordingly, mobile phase A was chosen for the simultaneous determination of the degradation compounds.

Stability Studies—Hydrazobenzene (VIII) has been reported (1) to undergo easy oxidation into azobenzene and *trans*-azobenzene (IX) is susceptible to isomerization into *cis*-azobenzene under photolytic conditions (8). The stability of I-IV, VI, VIII, and IX was tested by separately injecting onto the chromatograph, at different time intervals, a solution of each compound (0.12

Table I—Chromatographic Data of Phenylbutazone and Its Main Decomposition Products

Compound	Mobile Phase A			Mobile Phase B
	k'	H, mm	A_s	k'
I	1.914	0.616	1.10	4.700
II	3.276	0.042	1.40	9.000
III	0.086	0.216	1.40	0.560
IV	0.569	0.118	1.43	1.740
VI	11.948	0.028	1.21	38.820
VIII	4.603	0.032	1.33	12.380
IX	19.983	0.024	1.37	55.040
DPA	7.138	0.027	1.37	—

Table II—Minimum Detectable Amount and Sensitivity for Phenylbutazone and Its Main Decomposition Products

Compound	Minimum Detectable Amount, μg[a] λ = 237 nm	λ = 314 nm	Sensitivity λ = 237 nm	λ = 314 nm
I	4.8×10^{-3}	—	11.377	—
II	1.8×10^{-3}	—	14.740	—
III	1.1×10^{-3}	—	14.296	—
IV	1.2×10^{-3}	—	14.385	—
VI	4.5×10^{-3}	—	16.387	—
VIII	1.5×10^{-3}	—	19.214	—
IX	6.0×10^{-3}	2.40×10^{-3}	14.739	37.305

[a] Determined in the presence of I (20 μg).

mg·mL^{-1}) in the mobile phase. After 3 h at ambient temperature, under diffused light, no decomposition was observed for I–IV and VI. Only 1.37% of VIII was oxidized and no isomerization of IX was observed. Under chromatographic conditions used in this study, the retention time of *cis*-azobenzene relative to *trans*-azobenzene was 0.25 min.

Linearity of response was demonstrated for each solute by plotting the peak area ratio of solute to the internal standard against the solute concentration, from mixed standard solutions with equivalent concentration of degradation compound. The calibration graphs were linear for each compound with a correlation coefficient >0.998 in all instances. Each calibration graph intersected the origin. A similar correlation was obtained using the peak heights instead of the peak area.

Repeatability was assessed by five replicate determinations of a standard solution (80 μg/mL for I and 40 μg/mL for each degradation product) and a laboratory prepared injection with 3% of each degradation compound (with respect to I). For the standard solutions the data, expressed as the *CV*, were 1.57% (I), 2.86% (II), 1.88% (III), 3.85% (IV), 5.54% (VI), 2.22% (VIII), and 2.86% (IX). For the laboratory-prepared injection, the data were 0.59% (I), 1.66% (II), 1.00% (III), 0.67% (IV), 0.67% (VI), 1.75% (VIII), and 1.35% (IX).

The detectability [amount (μg) that gives a peak height equal to twice the background for the maximum on-column level tolerable for I] and the sensitivity (change in the area value, measured at the maximum detector sensitivity, resulting from a concentration change of one unit in μg/mL) were evaluated at 237 and 314 nm (Table II). The best wavelength for the detection of azobenzene is 314 nm.

The recovery studies on laboratory prepared injectable formulations with and without added amounts of degradation products are given in Table III. To determine trace amounts of decomposition products, a high concentration of phenylbutazone (2 mg/mL) had to be injected and a blank determination corresponding to an equal concentration of phenylbutazone had to be carried out. Recovery data presented in Table III are corrected from the blank determination. It must be noted that 0.5% (with respect to I) is the limit of quantitation for II because of the resolution between I and II in the presence of a large amount of I. The recovery studies for the two carcinogenic compounds (VIII and IX) were carried out at lower limits in the presence of the main degradation products (III and IV) determined in commercially available injectable formulations (5, 6) within the limit of validity. From Table III, 0.1% (with respect to I) may be estimated as the lowest limit of quantitation for VIII at 237 nm with acceptable accuracy. At 314 nm, where I, III, and IV are not interfering, the limit of quantitation of IX could be lowered to 0.05% (with respect to I).

Table III—Recovery Data from Laboratory Prepared Injectable Formulation

		Amount Added, mg	Amount Found, mg	Relative Error, %
Placebo +	I	600.00	588.06	−1.99
	I	600.00	591.14	−1.48
	II	6.00	5.85	−2.5
	III	6.00	5.76	−4.06
Placebo +	IV	6.00	5.74	−4.30
	VI	6.00	6.26	+4.37
	VIII	6.00	5.85	−2.47
	IX	6.00	6.05	+0.79
	I	600.00	603.60	+0.60
	II	3.00	2.85	−4.89
	III	3.00	3.08	+2.86
Placebo +	IV	3.00	2.99	−0.37
	VI	3.00	3.15	+4.95
	VIII	3.00	3.16	+5.31
	IX	3.00	3.21	+6.95
	I	600.00	584.58	−2.57
	III	18.00	16.89	−6.16
Placebo +	IV	18.00	17.78	−1.20
	VIII	1.2	1.27	+5.83
	IX	1.2[a]	1.16	−3.33
	I	600.00	592.80	−1.20
	III	18.00	19.36	+7.57
Placebo +	IV	18.00	17.68	−1.75
	VIII	0.6	0.656	+9.33
	IX	0.6[a]	0.588	−2.00

[a] Determined at 314 nm.

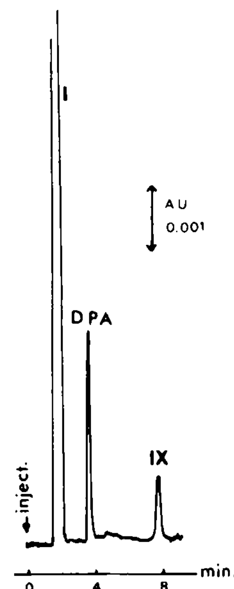

Figure 3—*Chromatogram of a laboratory-prepared injectable formulation of I (2.180 mg/mL), IX (0.525 μg/mL), and spiked with DPA (4.975 μg/mL). The mobile phase was 0.1 M Tris-citrate buffer (pH 5.25) and acetonitrile (40:60). Flow rate was 2.0 mL/min and pressure was 127 bars. Detector sensitivity was 0.01 AUFS, chart recorder speed was 0.5 cm/min, and λ was 314 nm.*

To increase the detectability and the sensitivity for azobenzene, a more eluting mobile phase C [0.1 M Tris-citrate buffer–acetonitrile (40:60)] was used. Standard solutions of IX were prepared using mobile phase C as follows: 100 μg/mL of DPA was added to make an internal standard of 5 μg/mL. The concentration of IX ranged from 0.3 to 2.0 μg/mL. Good linearity was observed for the calibration graph ($r > 0.999$). The chromatogram of a laboratory-prepared injection with added amount 0.025% (with respect to I) of IX is given in Fig. 3. The recovery was 107.04% by peak area and 94.53% by peak height measurements. The detectability was 1.3×10^{-3} μg.

Commercial Injectable Formulation Analysis—Commercial injection samples issued from two different batches, within the limit of validity, were analyzed with the mobile phases A and C. For one sample, I was 99.73% of the declared value, III was 0.92% (with respect to I), and IV was 5.32% (with respect to I). For the second sample, I was 100.00%, III was 0.8% (with respect to I), and IV was 3.77%. Neither hydrazobenzene nor azobenzene were detected in these two batches.

CONCLUSIONS

The proposed method allows the detection of hydrazobenzene and azobenzene at trace levels: 1.5×10^{-3} μg for VIII, 2.4×10^{-3} μg for IX with mobile phase A, and 1.3×10^{-3} μg for IX with mobile phase C. The resolution obtained for these two carcinogenic substances from phenylbutazone and its two major decomposition products usually found in injections, allows the simultaneous determination of 0.1% of each with satisfactory accuracy. Due to the high toxicity of hydrazobenzene and azobenzene, such an assay should be carried out as a stability-indicating assay for the phenylbutazone injectable formulations susceptible to hydrolysis.

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Autoxidation and Hydrolysis Kinetics of the Sodium Salt of Phenylbutazone in Aqueous Solution

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Abstract □ The present investigation offers experimental results concerning the degradation kinetics of the sodium salt of phenylbutazone based on a reliable HPLC procedure. The method allows the simultaneous determination of the parent compound and its main decomposition products. The degradation kinetics at 37°C were compared at pH 7.9 and 10.0 and under oxygen and nitrogen atmospheres. Parallel tests were carried out in the dark and under photolytic conditions for the aforementioned conditions. The influence of traces of iron and a chelating agent of iron on the degradation was studied. At pH 7.9 and pH 10.0 the main degradation products are 3-hydroxy-2-oxohexanoic acid 1,2-diphenylhydrazide and 3-carboxy-2-oxohexanoic acid 1,2-diphenylhydrazide. Azobenzene is formed only at pH 10.0. At pH 7.9, in the dark, the degradation proceeds with a lag phase. In contrast, no lag phase is observed under photolytic conditions. The process of autoxidation and hydrolysis is catalyzed by traces of iron both in the dark and under irradiation conditions. An unexpected increase in the degradation is observed in the presence of iron(III) and EDTA in aerobic conditions and under irradiation.

Keyphrases □ Phenylbutazone—autoxidation, hydrolysis, degradation, degradation products, effects of light and pH

Numerous accounts on the stability of phenylbutazone (I) in drugs have been reported (1–7). A degradation pathway has been suggested which involves oxidation and hydrolysis (4). Furthermore, Schmid (8) has shown that the hydrolysis of I to IV is reversible.

Kinetics of the degradation of the sodium salt of phenylbutazone in aqueous solution have been previously investigated (9, 10) using UV spectrophotometry. The procedure was only valid for the determination of the parent compound; the kinetics of formation of the degradation products were not evaluated.

Since II, VIII, and IX (see *Scheme I* of the immediately preceding paper for the structures of the degradation products) have been suspected to have noxious properties (11, 12) it is useful to investigate, under different conditions, the degradation kinetics of I together with the formation of all its decomposition products. In the present work, a reliable HPLC procedure (13) has been used to follow simultaneously the kinetics of the breakdown of the parent compound and the formation of six main degradation compounds, using experimental conditions which complement previous work (9, 10).

EXPERIMENTAL SECTION

Materials, Reagents, and Solutions—Phenylbutazone and its decomposition products (II[1], III[1], IV[1], VI[1], VIII, and IX) were used as received (see *Scheme I* of the immediately preceding paper for the structures of the degradation products). All chemicals were analytical reagent grade and water was glass distilled.

The study was conducted at pH 7.9 or 10.0 using a 3.24×10^{-3} M concentration of I and an ionic strength of $\mu = 0.5$. The solutions were prepared in 0.2 M ammonium acetate buffer (when a buffer effect was studied at pH 7.9 the buffer concentrations were 0.1, 0.2, and 0.3 M). The experiments were carried out at pH 7.9 and 10.0 without additives, and at pH 7.9 in the presence of iron and iron and EDTA.

For each set of experiments, the sodium salt of phenylbutazone solution (solution A) was prepared in a volumetric flask (100 mL) by dissolving phenylbutazone (100 mg) in a minimum amount of concentrated NaOH (~4 M). Solution A was then added to a volume of 100 mL as described below.

For experiments at pH 7.9 and 10.0, without additives, an acetic acid solution was added to solution A to get a 0.2 M (or 0.1 M, or 0.3 M) final acetate concentration. The pH was adjusted[2] to 7.9 or 10.0 with ammonium hydroxide. Potassium chloride and water were added to a volume of 100 mL to have an ionic strength of $\mu = 0.5$.

For experiments in the presence of iron, a saturated solution of iron(III) chloride in the buffer was prepared by shaking (in a water bath at 40°C) iron(III) chloride in the buffer for 48 h. The filtered solution was added to solution A to make 100 mL. The iron concentration was determined in the filtrate by atomic absorption spectrophotometry[3] using a graphite furnace. The concentrations of the solution was 0.008×10^{-3} M iron(III).

For experiments in the presence of iron and EDTA, an appropriate amount of EDTA was added to an aliquot of the solution described above. The concentrations of the solutions were 0.008×10^{-3} M and 10.52×10^{-3} M with respect to iron(III) and EDTA.

Sample Processing—For each experiment, 3-mL aliquots of the solution were transferred to 10-mL standard antibiotic vials. The vials were closed with a rubber seal. The solutions were bubbled for 3 min with either oxygen or nitrogen through the rubber cap using inlet and outlet syringe needles.

Sets of vials corresponding to the different experiments were placed in the same incubator at 37 ± 1°C. The ceiling of the incubator was fitted with a distributed light source delivering a radiative power ~1% of that emitted by the sun on a bright day. The amount of near UV and visible radiation received by the solutions was estimated using actinometry[4] and was found to be 800 $\mu W/cm^2$. The set of vials to be studied in the dark was enclosed in a light-tight

[1] Gifts from Geigy Laboratories, Basel, Switzerland. These compounds were described in G. Pawelczyk and R. Wachowiak, *Diss. Pharm. Pharmacol.*, **20**, 653 (1968).
[2] Potentiograph Metrohm E 436.
[3] Model 420 equipped with an H.G.A. graphite furnace; Perkin-Elmer.
[4] In a first step, the spectral power distribution of a lamp was measured by means of a calibrated spectroradiometer. Then, a graph of the yield in Fe^{2+} ions *versus* lamp power was obtained using potassium ferrioxalate actinometry. Actinometer preparation and final titration followed the Parker and Hatchard procedure (C. A. Parker and C. G. Hatchard, *J. Phys. Chem.*, **63**, 22 (1959); see also C. A. Parker in "Photoluminescence of Solutions," American Elsevier, New York, N.Y. 1968, p. 210). The irradiation step only was different, since we used the full spectrum of the lamp. The last step was the measurement of the actual sample in the incubator. Once the absorbed power was measured, yield was obtained following standard procedures using the power distribution of the lamp, the yield *versus* wavelength quantum yield change of the actinometer, and the absorption curve of the sample.

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