Xanthenes: Fluorone Derivatives. 1[1]

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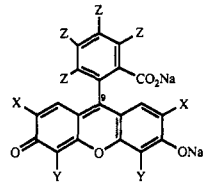
Several new fluorone derivatives including 2,4,5,7-tetraiodo-6-hydroxy-3-fluorone, 2,4,5,7-tetrabromo-6-hydroxy-3-fluorone, and 2,4-diiodo-6-methoxy-3-fluorone were synthesized and their spectral and photophysical properties investigated.

Background

The xanthenes 1 are among the oldest synthetic dyes. Fluorescein was prepared originally in 1871 by Baeyer[2] by the condensation of resorcinol with phthalic anhydride catalyzed by zinc chloride. Eosin, tetrabromofluorescein, was synthesized by Fischer and was the subject of subsequent controversy between Baeyer and Hoffmann.[3]



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generic xanthene skeleton: X = H, halogen; Y = H, halogen; Z = halogen, H

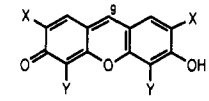
The xanthenes have many applications and the spectroscopic properties of each of them has been studied in great detail and the subject of many reports.[4] Eosin has been used as a marker for components of the white cells (eosinophils) since the 19th century. Fluorescein is used as a fluorescent tracer for everything from antifreeze to HIV virus. Rose Bengal, which has been the subject of our attention for many years,[5] is among the most important laboratory dyes for the generation of singlet oxygen. The xanthenes can both be oxidized and reduced photochemically, and this is also a useful property.[6]

The xanthenes, because they are so samiliar and so old, have not been the subject of much recent attention. Basic derivatives in the series are unknown and the fundamental characteristics which derive as a result are not yet outlined. We have undertaken recently new synthetic studies aimed at expanding the fundamental xanthene skeleton.

The literature provides many examples of compounds with various substituted aromatic nuclei at C-9 and other examples with different substituents on the xanthene ring. The basic skeleton, however, has not been tampered with (Table I).[7] It is apparent that the crowded aromatic subunit will slow reactions involving the formation of intermediates at C-9 and retard their subsequent reactivity as well. This observation predicts slower rates of electron transfer, for example, and subsequent photoreduction than would be expected for unsubstituted xanthenes. Our interest was to synthesize a new series of dyes (2) without substituents at that position and to investigate the effect of C-9 substitution on photochemical and photophysical properties.

Table I. Some Common Xanthene Derivatives

xanthenes (1)	X	Y	Z
Rose Bengal	I	I	Cl
phloxin	Br	Br	Cl
erythrosin	I	I	H
eosin	Br	Br	H
	Cl	Cl	H
	I	H	H
	Br	H	H
	H	Cl	H
	Cl	H	H
fluorescein	H	H	H



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The synthesis involves three steps, cyclized condensation, reduction and oxidation (Scheme I).

2,2′,4,4′-Tetrahydroxybenzophenone was heated in water at 200–220 °C, and 3,6-dihydroxyxanthone was obtained on cooling. The reduction of 3,6-dihydroxyxanthone with activated zinc either in the presence of alcohol with aqueous hydrochloric acid or in sodium hydroxide solution gave complex mixtures under acidic conditions and returned the starting material under basic conditions. However, when xanthone 4 was treated with borane–tetrahydrofuran complex in THF, the reduction product 3,6-dihydroxyxanthane (5) was separated in very high yield. 3,6-Dihydroxyxanthane treated with DDQ in ethanol to give the fluorescein analog 6-hydroxy-3-fluorone (6) (HF).[8,9] 3,6-Dihydroxyxanthane treated with bromine in basic solution gave the unsubstituted analog of eosin, 2,4,5,7-tetrabromo-6-hydroxy-3-fluorone (7) (TBHF). 2,4,5,7-Tetraiodo-6-hydroxy-3-fluorone (8) (TIHF), the analog of erythrosin, was obtained by iodination of 3,6-dihydroxyxanthane with iodine and iodic acid in ethanol.

One other simple modification in the skeleton also seemed to be significant. The ortho halogens retard substitution at C-6 in the classical xanthenes. Thus, though it is relatively easy to convert fluorescein to its ethers, Rose Bengal is converted to its methyl ether or related analogs only with great difficulty.[10] Nevertheless it is known that nonionizable functions at C-6 confer completely different absorption and emission properties on the dyes, as well as

(1) Contribution no. 143 from the Center for Photochemical Sciences.
(2) von Baeyer, A. *Chem. Ber.* **1871**, *5*, 255.
(3) von Hoffmann, A. W. *Ber.* **1875**, *8*, 55.
(4) See, for example: Lion, Y.; Gandin, E.; Van de Vorst, A. *Photochem. Photobiol.* **1980**, *31*, 305.
(5) Neckers, D. C. *J. Photochem. Photobiol.* **1989**, *47*, 1.
(6) See, for example, the oxidation of Rose Bengal: Linden, S. M.; Neckers, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 1257. Reduction of Rose Bengal: Zakzrewski, A.; Neckers, D. C. *Tetrahedron* **1987**, *43*, 4507.
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(9) Confolone, P. N. *J. Heterocycl. Chem.* **1990**, *27*, 31.
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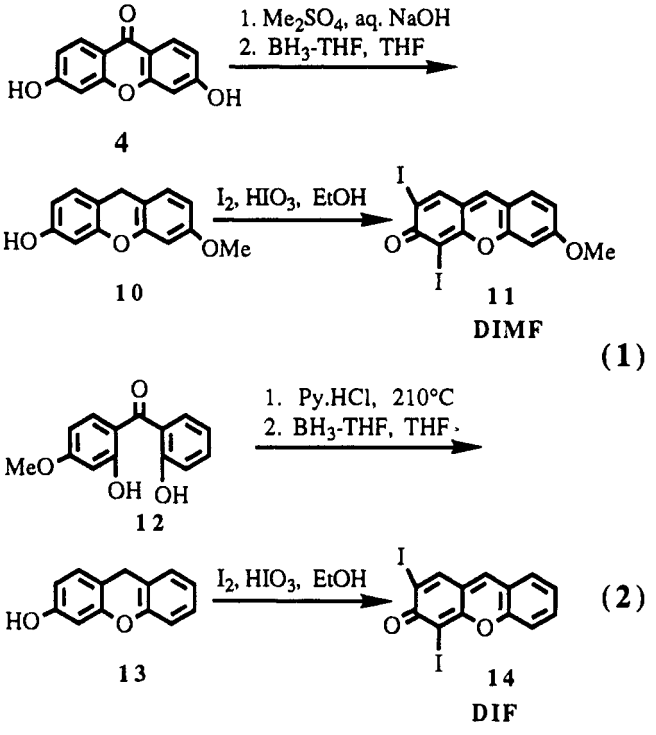
Table II. General Properties of Unsubstituted Xanthenes

	HF	TBHF	TIHF	DIMF
λ_{max}	see Table III			
λ_{fl}	see Table IV			
ϕ_{fl}	0.95	0.52	0.13	0.03
$\lambda_{ph}{}^{77K}{}_{EtOH}$			690	676
$\tau_{ph}{}^{77K}$			1.7 ms	
pK_a	5.97	3.29	4.08	
E_{ox}	1.04	1.09	1.34	
E_{red}	−0.95	−0.95	−0.99	

Table III. Absorption Spectra in Different Solvents

	HF	TBHF	TIHF	DIMF
MeOH–10% H_2O	490	516	526	
MeOH	500	526	532	470
EtOH	504 (24 000)	530 (39 300)	536 (91 200)	470 (23 500)
i-PrOH	510	532	538	472
t-BuOH	514	534	538	
BzOH	508	536	542	
CH_3CN	518	534	538	466
acetone	520	536	542	466
THF	520	536	540	468
DMF	524	536	542	468
toluene				474

solubilities.[11] Therefore we also synthesized simple ether quinones. The synthesis and spectroscopic properties of 2,4-diiodo-6-methoxy-3-fluorone (11) (DIMF) from 3-hydroxy-6-methoxy xanthane 10 is reported (eq 1). We have also synthesized the parent diiodofluorone 14 (DIF), which has similar properties in every respect with DIMF, from 3-hydroxyxanthane (13) (eq 2).



Photophysical Properties

The photophysical properties of the new fluorone derivatives are summarized in Tables II–IV. Essentially the compounds are like their ancient analogs. The color, fluorescence quantum yield, appearance of fluorescence, lack of phosphorescence, and electrochemical potentials of HF are virtually identical to those of fluorescein. TBHF resembles eosin in virtually every regard; similarly TIHF resembles erythrosin.

Table IV. Emission Spectra in Different Solvents

	HF	TBHF	TIHF	DIMF
MeOH	506	537	544	542
EtOH	513	539	548	544, 468
i-PrOH	516	543	550	
DMF		543	552	
THF		544	553	543, 573
toluene				546, 584

The absorption and emission spectra also demonstrate the familiar red shifts in polar solvents. As in the case of the parent xanthenes, they are also subject to the effects of hydrogen bonding. Thus the absorption and emission maxima are shifted farthest to the red in polar, aprotic solvents like DMF, less so by less polar protic solvents like *i*-PrOH, and the least by MeOH and water. Using these new fluorone derivatives as visible photoinitiators was studied.[12] Their application in organic synthesis was in progress. We have not studied aggregation phenomena in the series.[13]

Experimental Section

General. The dyes studied were purified by TLC. HPLC-grade solvents from Aldrich were used as received. Absorption spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer. The same solvents used to solubilize the samples were used as the references. Emission spectra were measured on a SPEX 212 Fluorolog spectrofluorometer. Beer's law was followed in the molar range of 10^{-6} to 10^{-8} M for the dyes studied. Quantum yields of fluorescence were measured relative to rhodamine 6G in ethanol or crystal violet in methanol. Triplet lifetimes were obtained with a SPEX 1934 C phosphorometer. pK_as were determined in a series of citric acid and sodium dibasic phosphate buffers. The total concentration of citric acid and sodium dibasic phosphate is 0.01 M. The solvent was 10% MeOH–H_2O. pH was measured by a Orion Research 501 digital ionalyzer accurate to +0.03 pH unit. Redox potentials of the dyes were measured on EG and PAR Model 175 universal programmers with a Houston Omnigraphic 2000 XY recorder. Tetra-*n*-butylammonium perchlorate was used as the electrolyte. Infrared spectra were recorded on a Galaxy Series Model GL-6020 FT-IR infrared spectrometer, the NMR spectra were taken with a Varian XL-200 nuclear magnetic resonance spectrometer, and the mass spectra were obtained from a Hewlett-Packard 5987A GC-mass system either by utilizing a direct insertion probe method or after passing the sample through the HP 5800 gas chromatograph. High resolution mass spectra were recorded on a Kratos Model MS-50 spectrometer. The purity of all products was assessed as >95% via ^1H NMR analysis. Full NMR spectra are available as supplementary material.

Synthetic Procedures. 3,6-Dihydroxyxanthone (4). 2,2',4,4'-Tetrahydroxybenzophenone (2.5 g, 10.15 mmol) was heated in 20 mL of water at 195–200 °C for 4 h (Aldrich pressure tube). After cooling, the crude product was filtered and mixed with 25 mL of water. The resulting suspension was refluxed for 15 min and filtered at about 60 °C. Pure 3,6-dihydroxyxanthone (2.15 g) was obtained in 90.4% yield. It did not melt below 330 °C. ^1H NMR (DMSO): δ 10.780 (s, 2 H), 7.983 (d, 2 H, J = 8.6 Hz), 6.822 (m, 4 H). IR (KBr): 3384, 3148, 1612, 1454, 1250, 1176, 1115, 845 cm^{-1}. HRMS m/e for $C_{13}H_8O_4$: calcd 228.04226, measured 228.04225.

3,6-Dihydroxyxanthane (5). To a suspension of 3,6-dihydroxyxanthone (0.57 g, 2.5 mmol) in 60 mL of THF was added 10 mL of borane–tetrahydrofuran complex (1.0 M in THF) at room temperature under nitrogen. After stirring for 2.5 h at rt, the reaction mixture became a clear solution. Solvent was removed and 10 mL of 0.5 N HCl was added. The yellow solid product

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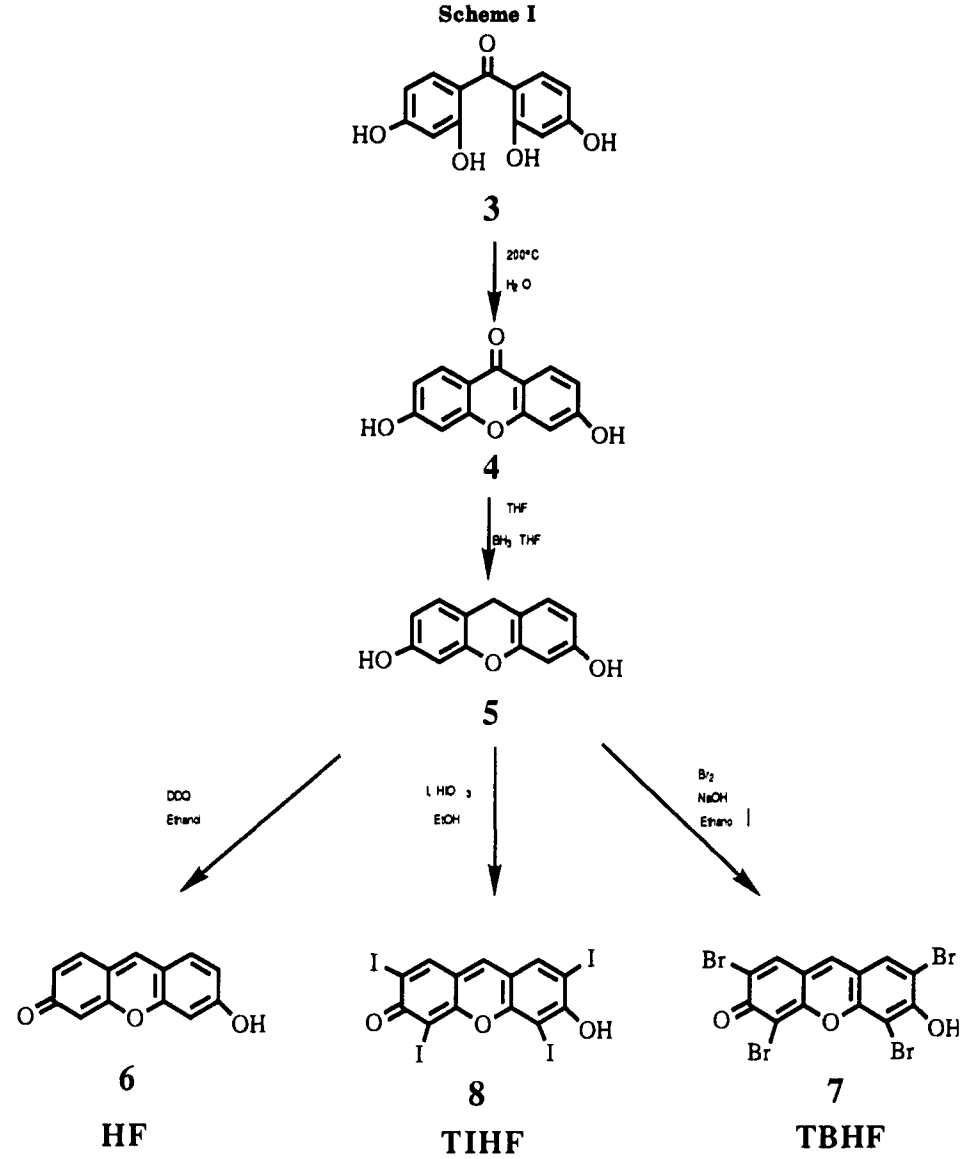
Scheme I



was filtered and 0.5 g of 3,6-dihydroxyxanthane (94.0%) obtained. ^{1}H NMR (DMSO): δ 9.406 (s, 2 H), 6.970 (d, 2 H, J = 8.4 Hz), 6.455 (dd, 2 H, J = 8.4, 2.4 Hz), 6.391 (d, 2 H, J = 2.4 Hz), 3.758 (s, 2 H). IR (KBr): 3345, 1612, 1504, 1458, 1300, 1161, 1103, 991, 856 cm^{-1}. HRMS m/e for $C_{13}H_{10}O_3$: calcd 214.06240, measured 214.06205.

6-Hydroxy-3-fluorone (HF) (6). To a solution of 3,6-dihydroxyxanthane (2.14 g, 10 mmol) in 60 mL of ethanol at 25 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.78 g, 12 mmol). The reaction mixture was stirred for 8 h at room temperature. The yellow precipitate was filtered and washed with ethanol. 3-Hydroxy-6-fluorone (1.9 g) was obtained in 90% yield. ^{1}H NMR (DMSO): δ 8.203 (s, 1 H), 7.589 (d, 2 H, J = 8.8 Hz), 6.659 (d, 2 H, J = 9.2 Hz), 6.478 (s, 2 H). HRMS m/e for $C_{13}H_8O_3$: calcd 212.04734, measured 212.04768. IR (KBr): 3420, 3065, 1647, 1593, 1465, 1275, 1194, 1153, 848 cm^{-1}.

2,4,5,7-Tetrabromo-6-hydroxy-3-fluorone (TBHF) (7). To a solution of 3,6-dihydroxyxanthane (4.28 g, 20 mmol) in 150 mL of ethanol was added sodium hydroxide solution (4.8 g, 120 mmol in 10 mL of H_2O). The solution was cooled to 0 °C and then Br_2 (22.4 g, 140 mmol) was slowly added. After addition, the reaction mixture was stirred for 8 h at room temperature. The precipitate was filtered off and washed with ethanol. 2,4,5,7-Tetrabromo-3-hydroxy-6-fluorone (9.6 g, 90.8%) was obtained. ^{1}H NMR (DMSO): δ 8.309 (s, 1 H), 8.244 (s, 2 H). HRMS m/e for $C_{13}H_4O_3Br_2{}^{79}Br_2{}^{81}$: calcd 527.68556, measured 527.68672. IR (KBr): 3441, 3038, 1612, 1574, 1464, 1219, 941 cm^{-1}.

2,4,5,7-Tetraiodo-6-hydroxy-3-fluorone (TIHF) (8). Iodic acid (16.4 g, 93 mmol) dissolved in a minimum amount of water (approximately 1 mL per g) was added dropwise over 20 min to a solution of 10 g (46.7 mmol) of 3,6-dihydroxyxanthane and 29.8 g (118 mmol) of iodine in 1 L of absolute ethanol. This mixture was stirred over 2 h during which the dark brown solution slowly turned a red orange as the solid TIHF precipitated. The mixture was then warmed for an hour at 60 °C. After cooling, the mixture was filtered and washed with water and ethanol, and the crude solid was triturated with absolute ethanol and refiltered to give, after drying under vacuum, 29 g (87%) of a red solid. ^{1}H NMR (DMSO): δ 8.31 (s, 2 H), 8.07 (s, 1 H). HRMS m/e for $C_{13}H_4O_3I_4$: calcd 715.6347, measured 715.6348. IR (KBr): 3414, 3024, 1601, 1562, 1518, 1448, 1211, 920 cm^{-1}.

3-Hydroxy-6-methoxyxanthane (10). To a solution of 4.0 g (16.5 mmol) of 6-hydroxy-3-methoxyxanthone[14] in 150 mL of anhydrous THF under nitrogen was added 41 mL (41 mmol) of 1 M BH_3 in THF with stirring. Stirring was continued overnight at room temperature. The solvent was stripped and the residue washed with aqueous NaOH, dissolving the product completely. After filtration to remove the impurities, the solution was acidified, filtered, and washed with water to yield 3.73 g (99%) of **10**. ^{1}H NMR (DMSO): δ 3.72 (3 H, s), 3.32 (2 H, s), 6.46 (2 H, m), 6.63 (2 H, m), 7.00 (1 H, d, J = 8.12 Hz), 7.10 (1 H, d, J = 9.46 Hz). IR (KBr): 3416, 1612, 1502, 1462, 1200, 1165, 1103, 837 cm^{-1}. MS m/e: 228, 227, 212, 197, 184, 128.

2,4-Diiodo-6-methoxy-3-fluorone (DIMF) (11). To a solution of 0.228 g (1 mmol) of **10** and 0.508 g (4 mmol) of iodine in 20

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mL of EtOH was added 0.211 g (1.2 mmol) of iodic acid in a minimum of water dropwise with stirring. A precipitate formed immediately and the reaction was stirred 1 h additional at room temperature. Then it was warmed to 50 °C for 15 min. Filtration and washing with ethanol and water yielded 0.44 g (92%) of orange solid. ^{1}H NMR (DMSO): δ = 3.95 (3 H, s), 7.10 (1 H, dd, J = 8.72, 2.38 Hz), 7.10 (1 H, d, J = 2.38 Hz), 7.86 (1 H, d, J = 6.74 Hz), 8.35 (1 H, s), 8.46 1 H, s). IR (KBr): 3021, 1720, 1574, 1531, 1462, 1277, 1223, 1014, 910, 837 cm^{-1}. MS m/e: 478, 450, 351, 323, 196, 181, 125.

3-Hydroxyxanthane (13). To a suspension of 3-hydroxyxanthone[12] (2.41 g, 11.4 mmol) in 100 mL of THF was added 30 mL of borane/THF complex (1.0 M in THF) at room temperature under nitrogen. After stirring overnight, the reaction was quenched by adding water dropwise at 0 °C. The solvents were removed and 30 mL of 0.5 N HCl was added. The precipitate was collected and dissolved in NaOH. The solution obtained was filtered and acidified with 2 N HCl. 3-Hydroxyxanthane (2.2 g) was collected in 97% yield. ^{1}H NMR (d-DMSO; 200 MHz): δ 9.46 (2, 1 H), 7.18 (m, 2 H), 7.81 (m, 3 H), 6.47 (m, 2 H), 3.89 (s, 2 H). IR (KBr): 3276, 3067, 1609, 1462, 1234, 1149, 972, 843, 756 cm^{-1}. MS m/e: 198, 197.

2,4-Diiodo-3-fluorone (DIF) (14). Iodic acid (0.704 g, 4.0 mmol) was dissolved in a minimum of water and added dropwise to a solution of 3-hydroxyxanthane (0.40 g, 2 mmol) and iodine (1.02 g, 8.0 mmol) in 10 mL of EtOH. The mixture was stirred for 2 h at room temperature and the temperature then slowly raised to 60–70 °C for another 2 h. After cooling, the precipitate was filtered and washed with water and ethanol. 2,4-Diiodo-3-fluorone (0.81 g) was obtained in 90.8% yield. ^{1}H NMR (DMSO): δ 8.54 (s, 1 H), 8.38 (s, 1 H), 7.92 (d, 1 H, J = 7.6 Hz), 7.81 (m, 1 H), 7.67 (d, 1 H, J = 8.5 Hz), 7.48 (m, 1 H). IR (KBr): 3033, 1589, 1543, 1211, 914, 756 cm^{-1}. MS m/e: 448, 420, 321, 293, 254, 166, 148.

Conclusion

A new series of dyes based on the unsubstituted xanthene skeleton has been synthesized and their spectral properties have been reported.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **5**, **6**, **7**, **8**, **10**, **11**, **13**, and **14** (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of the Sterically Hindered Bis(pentachlorophenyl)acetic Acid and Derived Stable Free Radicals

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Bis(pentachlorophenyl)acetic acid esters were synthesized from the α-hydroxydiaryl acetate esters **13** via the free radicals **15** formed on homolytic cleavage of the α-chloro compounds **14**. The acid **8** underwent rapid decarboxylation in basic solution (e.g., Et_3N in THF) but could be dehydrated to the corresponding ketene **17**. Nucleophilic addition to the ketene provided a route to the corresponding amides (**21** and **19**) and nitrile **20**, the enolates of which underwent ready oxidation to the corresponding stable free radicals **15**, **22**, and **23**. Evidence for the structure and unusual stability of these free radicals is presented. Attempts to observe enols of acids or esters on the addition of water or alcohols to the sterically hindered ketene **17** were unsuccessful.

The stabilization of otherwise transient species by the introduction of bulky substituents is well-known.[1] Diverse examples include carbocations,[2] free radicals,[1,3] enols,[4] antiaromatic compounds[5] and compounds with carbon to second-row element pπ–pπ bonds.[6]

We have for some time been interested in the use of steric hindrance to stabilize ene-1,1-diols **2** which are the enol tautomers of carboxylic acids **1**. The ene-1,1-diol

1 **2**

isomers of substituted acetic acids can be stabilized by substitution with bulky aryl groups, such as 2,4,6-trimethyl- and pentamethylphenyl.[7,8] Nevertheless, their reactivity is still high, since they decay to the keto forms (the acids) in a matter of minutes, and they also react readily with molecular oxygen. Therefore, we have attempted to stabilize the ene-1,1-diol form by introducing two geminal C_6Cl_5 groups since (a) they would confer a moderate thermodynamic stabilization by π–π interaction

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