Novel Oxidation Products from a 9(10*H*)-Acridinone

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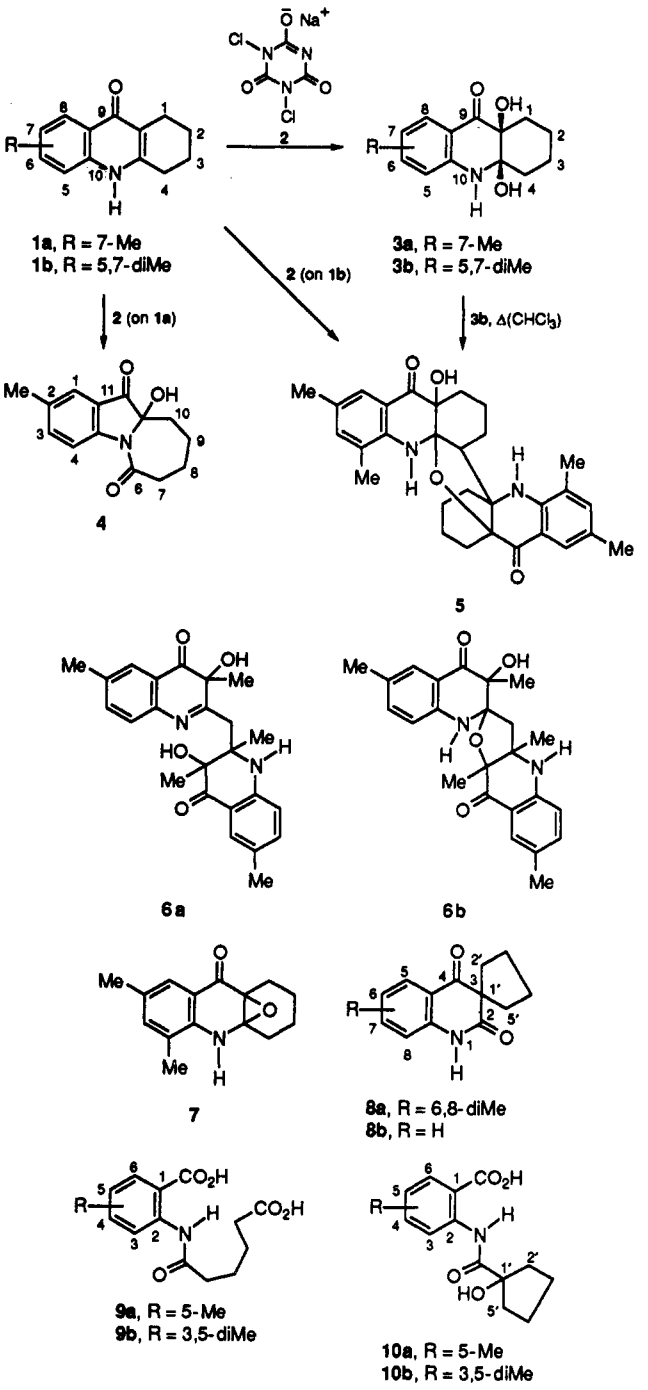
We recently[1] described the reaction between tetrahydro-9(10*H*)-acridinone **1a** and sodium dichloroisocyanurate (**2**) to give initially, *cis*-4a,9a-dihydroxyhexahydroacridinone **3a**, and eventually, hexahydro-6*H*-azepino[1,2-*a*]-indoledione **4** (Scheme I). The analogous 5,7-dimethylacridinone **1b** yielded the corresponding diol **3b** and several minor uncharacterized byproducts labeled P1, P2, and P3 in order of decreasing R_f values.[2] Because of the possibility that one or more of the latter substances were intermediate in the reaction events leading from **1** and **2** to **3** and/or **4**, their respective structures were investigated with the following outcomes.

Compound P1, an alkali-insoluble solid, had a molecular formula of $C_{30}H_{34}N_2O_4$ from elemental analysis and MS implicating it as a dimeric diol derivative. Its IR absorptions were indicative of OH and/or NH and carbonyl functions. The ^1H NMR spectrum exhibited signals for four methyl groups, an isolated one-proton multiplet, multiplets for disparate methylene protons, three D_2O-exchangeable protons, and four aromatic protons. From the ^{13}C NMR and DEPT spectra we concluded that molecular P1 possesses twelve quaternary, two carbonyl, five methine, and seven methylene carbons in addition to the four methyl carbons shown in the ^1H NMR spectrum. The aforementioned data, supplemented with that from an NOE experiment which established the two amino protons as each proximate to an aromatic methyl group, is accommodated in the structural framework **5** and of a geometry[3] depicted in Figure 1. Structure **5** formally results from the condensation of two diol **3b** molecules with concomitant loss of two water molecules. Direct evidence of the condensation process was obtained by heating **3b** in concentrated $CHCl_3$ solution and by evaporative distillation of its $CHCl_3$ extract at an elevated temperature, when it was partially converted into dimer P1 (**5**) (and compound P2, *vide infra*). The formation of **5** may be rationalized (Scheme II) by invoking mechanistic events similar to those previously envisaged for the production of a related dimer[1] of assigned structure **6a** and supplemented here with a recently[4] reported imine addition reaction. The mass spectrum of P1 (**5**) displayed a weak molecular ion (*m/z*) 486 and included two major signals at *m/z* 243 and 244, respectively (*m/z* 242 was absent) and a moderately intense peak at *m/z* 187, tentatively attributable to the fragmentation species depicted in Scheme III. In the light of the above, formulation **6a** has been reassessed by means of a comprehensive NOE experiment, resulting in its modification to molecular framework **6b**, analogous to that of **5** and of geometry pictured in Figure 2.

Scheme I



Compound P2, also a yellow solid, proved to be isomeric ($C_{30}H_{34}N_2O_4$, MS *m/z* 486) with compound P1. IR absorptions were indicative of OH and/or NH, and C=O functionalities. The ^1H NMR spectrum showed a one-proton multiplet, a six-proton multiplet overlapping a methyl group singlet, a six-proton methylene multiplet, three additional methyl singlets, two other one-proton multiplets, four aromatic protons, and three D_2O-exchangeable protons; two of the latter, the amino protons, exchanged significantly less rapidly than did the hydroxyl proton. The ^{13}C NMR and DEPT experiments revealed all 30 carbon atoms consisting of four methyl, seven methylene, five methine, and fourteen quaternary carbons (including two carbonyl functions). NOE experiments established that the amino protons each were proximate

(1) Staskun, B. *J. Org. Chem.* **1988**, *53*, 5287.
(2) Marais, J. L. C.; Pickl, W.; Staskun, B. *J. Org. Chem.* **1990**, *55*, 1969.
(3) This is one possible diastereomer.
(4) Staskun, B.; van Es, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 511.

0022-3263/93/1958-7594$04.00/0

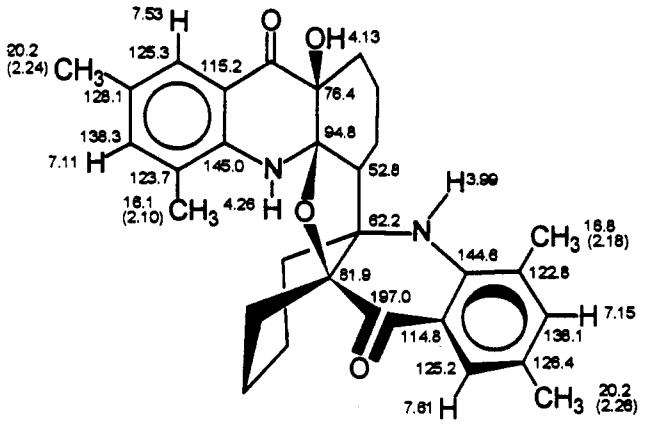
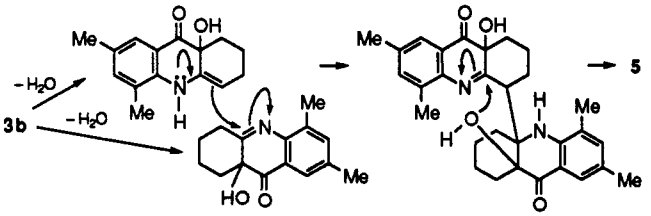
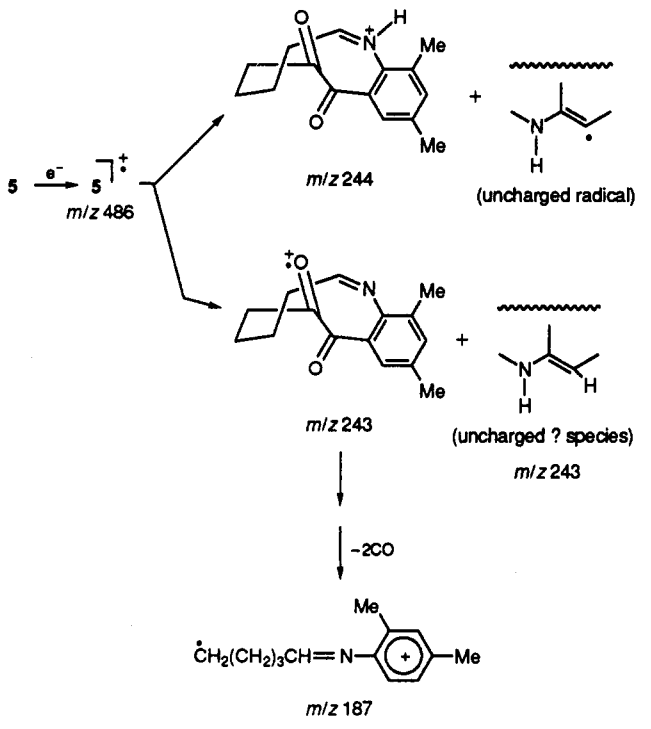


Figure 1.

Scheme II



Scheme III



to an aromatic methyl group and to each other. The MS of P2 was virtually identical with that of P1. These data allow for the conclusion that compounds P1 and P2 have the same molecular framework **5** and differ mainly in their spatial geometries. Figure 3 depicts a geometry[3] for P2 consistent with the spectral data and which makes explicable the shielding of a methyl group (δ 1.60) and the deshielding of an amino proton (δ 6.62) in terms of the anisotropic effects of a proximate benzene ring.

Compound P3 was obtained as a colorless solid of molecular formula $C_{15}H_{17}NO_2$ from elemental analysis and MS (m/z = 243) and with IR absorptions suggesting the presence of amino, ketone, and amide functions. The ^{1}H

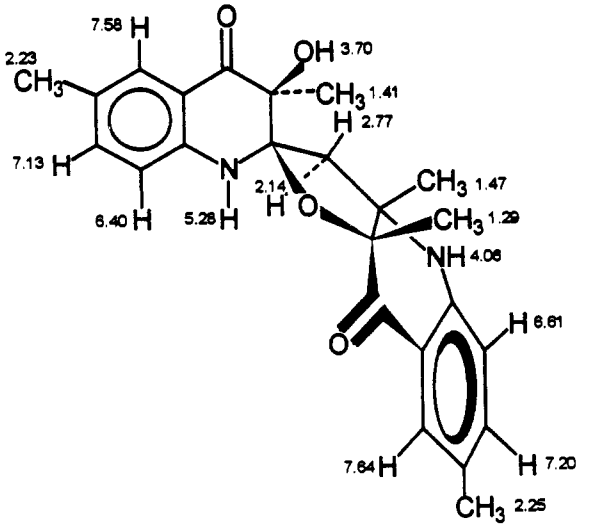


Figure 2.

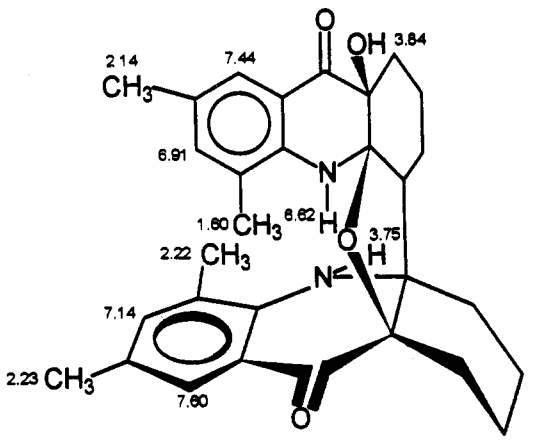


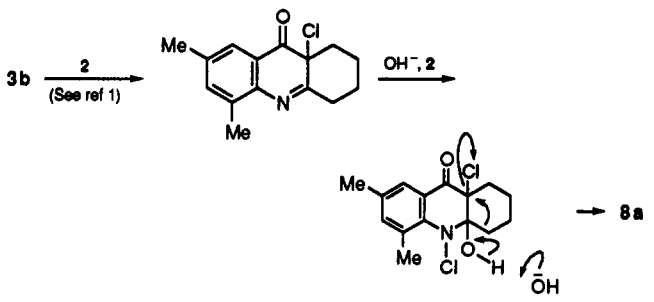
Figure 3.

NMR spectrum exhibited signals for two methyl groups, two disparate multiplets (4H each) for eight methylene protons, one D_2O-exchangeable proton (near δ 7.8), and two aromatic protons. Structural formulations such as **7** were eliminated, leaving only spiroquinolinedione **8a** as also compatible with the data from a ^{13}C NMR spectrum coupled with a DEPT analysis and with a NOE experiment. Thus, the two former spectra established the presence of seven quaternary carbons, including two carbonyl functions, two tertiary methine carbons, two sets of two equivalent methylene carbons (i.e. four carbons), and two methyl carbons for a total of 15 carbons, while the NOE experiment revealed the D_2O-reactive proton to be proximate to a methyl group and distant from the methylene protons. Assignment **8a** moreover accommodates the relatively low-field (^{1}H NMR) absorption of the amide proton (near δ 7.8), as found in the related carbostyril.[5] The demethylated "parent" compound **8b** has been obtained by Kaneko[6] from photolysis of 9-chlorotetrahydroacridine 10-oxide in alcohol, and Scheme IV outlines how spiroquinolinedione **8a** might have arisen from diol **3b** and **2** *via* a modification of the Kaneko[6] ring-contraction process.

(5) *The Sadtler Guide to NMR Spectra*; Sadtler Research Laboratories, Inc.: Philadelphia, 1972; p 484.

(6) Kaneko, C.; Yokoe, I.; Yamada, S.; Ishikawa M. *Chem. Pharm. Bull.* **1969**, *17*, 1290.

Scheme IV



Earlier,[1] diol **3a** had been reacted with H_2O_2 in neutral CH_3OH solution to obtain a product soluble in aqueous 1 M NH_3 which from its IR spectrum appeared to be acid **9a**. This finding contrasts with the observation[7] that H_2O_2 is inactive toward 1,2-glycols. Reinvestigation of our product (~60%) has now shown it to have molecular formula $C_{14}H_{17}NO_4$ and to be the unexpected anthranilic acid derivative **10a**. IR absorptions indicated the presence of OH and/or NH and C=O functions, while the ^1H NMR ($CDCl_3$) spectrum contained signals for a methyl group, eight methylene protons as a complex multiplet, three aromatic protons (including one anisotropically deshielded at δ 8.66), a broad D_2O-exchangeable absorption due to an hydroxyl (*vide infra*), and a carboxylic acid proton. In CD_3SOCD_3, the methylene absorptions were more clearly disparate, appearing as a multiplet (6H) centered at δ 1.7 and a multiplet (2H) centered at δ 2.0 and with the aforementioned OH proton now exhibited as a sharp signal (1H). The ^1H NMR signal for the amide proton in **10a** was not detected but is also not observed in related 2-acetamidobenzoic acids.[8] Recourse to ^{13}C NMR and DEPT spectra established that the new acid possesses two carbonyl functions, three aromatic and one nonaromatic, i.e. four, quaternary carbons, three methine carbons, two sets of two (i.e. four) equivalent methylene carbons, and one methyl carbon, as in formulation **10a**. A similar oxidation of 5,7-dimethylacridinediol **3b** with neutral H_2O_2 afforded the corresponding 3,5-dimethylbenzoic acid **10b** (~50%) as evidenced from an equally comprehensive spectral examination. Moreover, in an NOE experiment, irradiation of the C-3 methyl substituent (δ 2.14) in **10b** produced an observable enhancement only at H-4 (δ 7.25), consistent with the geometry indicated for **10b**. The requisite 2-(ω-carboxypentanamido)benzoic acid **9b**, for spectral (IR, ^1H NMR) comparison with **10b**, was obtained from acridinone **1b** and singlet oxygen.[9] Azepinoindoledione **4**, by contrast, was unaffected by 30% H_2O_2 in neutral CH_3OH solution, which suggested that in diols **3a** and **3b** the amino function was the site initially susceptible to oxidation, but details of the reaction pathway remain to be clarified.

Experimental Section

General.[1] Melting points are uncorrected. IR spectra were measured as thin films on KBr plates. NMR spectra were measured in $CDCl_3$ unless otherwise stated. ^{13}C resonances were assigned by DEPT, XHCORR, and COLOC experiments, and coupling connectivities were determined by selective ^1H decoupling and COSY experiments. Chromatographic separations and TLC details are as described in ref 1.

Isolation of Products P1, P2, and P3. The components P1, P2, and P3 in the product mixture (orange gum, ~400 mg) obtained[2] from the reaction between acridinone **1b** and **2** were first separated using flash chromatography on Merck Kieselgel 60 (230–400 mesh) eluting with 15:1 benzene–acetone. Approximate yields: P1, 130 mg; P2, 70 mg; P3, 100 mg. Compound P2 could not be isolated entirely free of P1 contaminant; a sample showing ca. <10% P1 impurity (TLC) and suitable for spectral analysis was obtained using preparative TLC. R_f values (fluorescence of spot on TLC plate at 366 nm): P1, 0.92 (yellow); P2, 0.85 (yellow); P3, 0.76 (blue).

Compound P1 (5) (major dimer): yellow crystals (from methanol), mp > 240 °C; IR 3440, 3408, 1668, 1655 cm^{-1}; ^1H NMR δ 1.3–1.7 (m, ~10H), 1.8–2.0 (m, 4 H), 2.10 (s, 3H), 2.18 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 2.9 (br t, 1 H), 3.99 (s, 1H, slow exchange with D_2O), 4.13 (s, 1H, fast exchange with D_2O), 4.26 (s, 1H, slow exchange with D_2O), 7.11 (d, 1H, J = 1 Hz), 7.15 (d, 1H, J = 1 Hz), 7.53 (d, 1H, J = 1 Hz), 7.61 (d, 1H, J = 1 Hz); ^{13}C NMR δ 16.1, 16.85, 18.5, 19.3, 19.35, 20.2, 20.25, 21.6, 29.25, 29.6, 32.6, 52.8, 62.2, 76.4, 81.9, 94.8, 114.8, 115.2, 122.8, 123.7, 125.2, 125.3, 126.4, 128.1, 138.1, 138.3, 144.6, 145.0, 197.0, 197.8; MS m/z 486 (M^+), 244, 243, 187; HRMS calcd for $C_{30}H_{34}N_2O_4$ 486.2520, found 486.2474. Anal. Calcd for $C_{30}H_{34}N_2O_4$ (486.61): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.52, H, 6.79; N, 5.27.

Compound P2 (minor dimer): yellow solid, mp > 200 °C; IR 3445, 3350, 3325, 1668, 1650 cm^{-1}; ^1H NMR δ 0.92 (m, 1 H), 1.5–1.75 (m, ~6H), 1.60 (s, 3H), 1.86–2.1 (m, ~6H), 2.14 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.80 (d, 1H, J = 15 Hz), 3.0 (dd, 1H, J = 3, 12 Hz), 3.75 (br s, 1 H, slow exchange with D_2O), 3.84 (s, 1H, fast exchange with D_2O), 6.62 (s, 1H, slow exchange with D_2O), 6.91 (s, 1H), 7.14 (s, 1H), 7.44 (s, 1H), 7.60 (s, 1H); ^{13}C NMR δ 15.8, 16.7, 20.1, 20.3, 20.7, 21.1, 22.15, 22.35, 30.6, 33.4, 35.5, 44.1, 64.05, 76.3, 83.0, 98.4, 115.25, 116.5, 122.8, 123.2, 124.7, 126.7, 127.1, 128.4, 137.75, 137.9, 143.0, 144.1, 189.0, 195.45; MS m/z 486 (M^+), 244, 243, 187; HRMS calcd for $C_{30}H_{34}N_2O_4$ 486.2520, found 486.2479.

Compound P3. 6,8-Dimethyl-1*H*-quinoline-3-spiro-1′-cyclopentane-2,4-dione (8a): colorless crystals (from MeOH), mp 222–223 °C; insol 2 M NaOH; IR 3210, 2950, 1690, 1650, 1610, 1600, 1490 cm^{-1}; ^1H NMR δ 1.85–1.91 (m, 4H), 2.17–2.19 (m, 4H), 2.30 (s, 3H), 2.32 (s, 3H), 7.22 (s, 1H), 7.61 (s, 1H), 7.84 (br s, 1H, exchanged with D_2O); ^{13}C NMR δ 16.7, 20.45, 27.1, 36.6, 63.1, 118.9, 123.5, 125.5, 132.3, 137.0, 138.0, 176.0, 197 .55; MS m/z 243 (M^+), 214, 202, 187, 149. Anal. Calcd for $C_{15}H_{17}NO_2$ (243.31): C, 74.05, H, 7.04; N, 5.76. Found: C, 74.10; H, 7.22, N, 5.73.

2-(1′-Hydroxycyclopentanecarboxamido)-5-methylbenzoic Acid (10a). To diol **3a** (300 mg) dissolved in MeOH (30 mL) was added 30% H_2O_2 (15 mL), and the solution was kept at rt for ~5 h (until TLC 3:1 C_6H_6–acetone showed negligible remaining **3a**). The reaction was allowed to evaporate in the hood overnight to afford a residue of crude acid **10a**: colorless, woolly needles (from aqueous acetone; 185 mg); mp 176–177 °C; soluble in aqueous 2 M NH_3 from which solution **10a** was precipitated unchanged upon acidification with 2 M HCl; IR 3380, 3240, 2950, 1680, 1655, 1585, 1520 cm^{-1}; ^1H NMR δ 1.8–2.0 (m, ~6H), 2.2–2.4 (m ~ 5H), 3–5 (variable) (br 1H, exchanged with D_2O), 7.40 (dd , 1H, J = 2.2, 8.7 Hz), 7.89 (d, 1H, J = 2 Hz), 8.66 (d, 1H, J = 8.6 Hz), 11.8 (br s, 1H, exchanged with D_2O); ^1H NMR (CD_3SOCD_3) δ 1.6–1.8 (m, 6H), 1.9–2.1 (m, 2H), 2.30 (s, 3H), 5.72 (s, 1H, exchanged with D_2O), 7.41 (dd, 1H, J = 2.0, 8.5 Hz), 7.80 (d, 1H, J = 2.0 Hz), 8.63 (d, 1H, J = 8.5 Hz), 12.1 (s, 1H, exchanged with D_2O); ^{13}C NMR (CD_3OD) δ 20.7, 25.7, 40.4, 84.8, 117.8, 121.0, 132.6, 133.7, 135.5, 139.35, 170.5, 178.2. Anal. Calcd for $C_{14}H_{17}NO_4$ (263.30): C, 63.86; H, 6.51; N, 5.32. Found: C, 63.41; H, 6.70; N, 5.20.

2-(1′-Hydroxycyclopentanecarboxamido)-3,5-dimethylbenzoic acid 10b was obtained (~50%) from diol **3b** (300 mg) in MeOH (30 mL) and 30% H_2O_2 (12 mL) following the above procedure: colorless, woolly needles (from aqueous acetone); mp 176-177 °C, soluble in aqueous 2 M NH_3; IR 3375, 3200 (br), 2950, 1720, 1655 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 1.6–1.8 (m, 6H), 1.9–2.1 (m, 2H), 2.14 (s, 3H), 2.29 (s, 3H), 5.6 (s, 1H, exchanged with D_2O), 7.25 (d, 1H, J = 1.5 Hz), 7.46 (d, 1H, J = 1.6 Hz), 9.8 (br s, 1H, exchanged with D_2O); ^{13}C NMR (CD_3COCD_3) δ 19.1, 20.7, 25.4, 40.05, 84.3, 125.95, 129.4, 135.5, 136.2, 136.5, 168.6, 175.5; MS m/z 277 (M^+), 174, 165, 147, 119; HRMS calcd for

(7) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061.
(8) Staskun, B. Unpublished work.
(9) Staskun, B.; Foote, C. S. *S. Afr. J. Chem.* **1984**, *37*, 182.

$C_{15}H_{19}NO_4$ 277.1315, found 277.1307. Anal. Calcd for $C_{15}H_{19}NO_4$ (277.32): C, 64.97; H, 6.91; N, 5.05. Found: C, 65.47; H, 6.85; N, 4.96.

2-(ω-Carboxypentanamido)-3,5-dimethylbenzoic Acid (9b). Rose Bengal sensitized photooxidation of acridinone **1b** (500 mg) was conducted as described[9] with **1a** for 20 min and gave the title compound (226 mg, 35%): colorless, woolly needles (from aqueous acetone), mp 174–176 °C,[10] soluble in aqueous 2 M NH_3: IR 3300, 2900, 1690, 1635 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 1.55–1.58 (m, 4H), 2.14 (s, 3H), 2.21–2.28 (m, ~7H), 7.23 (d, 1H, J = 1.4 Hz), 7.39 (d, 1H, J = 1.8 Hz), 9.3 (br s, 1H, exchanged with D_2O), 12.3 (br s, 1H, exchanged with D_2O); ^1H NMR (C_5D_5N) δ 1.95–2.06 (m, 4H), 2.21 (s, 3H), 2.46 (s, 3H), 2.54 (t, 2H, J = 7 Hz), 2.70 (t, 2H, J = 7 Hz), 7.15 (s, 1H), 8.10 (s, 1H), 10.4 (s, 1H, exchanged with D_2O); MS m/z 293 (M^+), 275 (M − 18), 257, 216, 202, 189, 174, 165, 147, 119. Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.42; H, 6.53, N, 4.78. Found: C, 61.50; H, 6.50; N, 4.76.

(10) Acids **9b**, **10a**, and **10b** all fortuitously had virtually the same mp (176 °C), which was depressed in mixed mp determinations.

Thermal Dimerization of diol 3b. (i) A concentrated solution of diol **3b** (180 mg) in $CHCl_3$ (1 mL) was refluxed for 1.5 h after which TLC (3:1 $PhCH_3$–acetone) indicated the presence of P1, P2, and unchanged **3b**. Preparative TLC of the product mixture with the same solvent system furnished samples of pure dimer P1 (~40 mg) and slightly contaminated P2 (5 mg), as verified from TLC, IR, and ^1H NMR. Spiroquinolinedione **8a** (P3) was not obtained.

(ii) A dilute solution of diol **3b** (20 mg) in $CHCl_3$ (5 mL) was refluxed for 1.5 h (TLC showed little if any change) and was then evaporatively concentrated (Rotavap, 60–70 °C water temperature) over several minutes. The residue was dissolved in $CHCl_3$ and the evaporative removal of solvent was repeated twice to afford a mixture containing P1, P2, and unchanged diol 3b (TLC, IR, ^1H NMR).

Acknowledgment. We thank Mrs. S. Heiss for recording several of the NMR spectra.