2-(2-Butylamino)ethanol (7). Ethanolamine (1.06 g, 0.017 mol) was reacted for 30 min with 1.5 equiv of methyl ethyl ketone. The resulting oxazolidine[10] was reduced and worked up as described above to give 1.5 g (75%) of **7**: bp 70–71 °C at 5.5 mmHg (lit.[7a] bp 88–88.5 °C at 17 mmHg).

1-(Isopropylamino)-2-propanol (8). A 1 M solution of 534 mg (7.12 mmol) of 1-amino-2-propanol in absolute ethanol was stirred with 1.5 equiv of acetone. Condensation to the oxazolidine[10] took place within 45 min at 25 °C. The solution was cooled to 0 °C and reduced with 407 mg (10.7 mmol) of sodium borohydride within 5 min as described above to give 580 mg (70%) of **8**: bp 46 °C at 4 mmHg (lit.[7b] bp 75.5–76 °C at 22 mmHg).

1-(Isoamylamino)-2-propanol (9). A 1 M solution of 554 mg (7.4 mmol) of 1-amino-2-propanol (**2**) in absolute ethanol was consensed with isovaleraldehyde to form the corresponding oxazolidine[11] in 10 min. Reduction and workup were carried out as described above. Distillation of the crude product gave 862 mg (81%) of **9**: bp 70–71 °C at 2.3 mmHg (lit.[7b] bp 105.5–106 °C at 19 mmHg); the amine crystallized out on standing: mp 157–185 °C.

1-(Cyclohexylamino)-2-propanol (10). The amine **2** (531 mg, 7.08 mmol) was condensed with cyclohexanone, as described above. Oxazolidine[10] formation took place within 15 min. The solution was treated with sodium borohydride at 0 °C for 5 min and worked up as described above. The residue was dissolved in HCl and washed with methylene chloride. The aqueous portion was made basic with 5% sodium hydroxide, extracted with methylene chloride, dried, and evaporated. The crude amine was vacuum distilled to give 1.10 g (99%) of **10**: bp 77–87 °C at 2.2 mmHg (lit.[7b] 126–126.5 °C at 20 mmHg).

1-Phenyl-2-(isobutylamino)-1-propanol (11). A solution of 515 mg (3.4 mmol) of norephedrine was stirred with 1.5 equiv of isobutyraldehyde in absolute ethanol at 25 °C. The corresponding oxazolidine formed in 15 min. To the solution was added 190 mg (5 mmol) of sodium borohydride at 25 °C, and the progress of the reduction was followed by gas chromatography. The oxazolidine[10] was totally reduced in 15 min. The mixture was cooled, 10% HCl was added dropwise to adjust the solution to pH 1, and the solvent evaporated to near dryness under vacuum. The residue was taken up in 10 mL of water, filtered, made basic with sodium hydroxide, and extracted with methylene chloride. The solution was dried over sodium sulfate, the solvent removed on a rotary evaporator, and the crude product recrystallized from hexane to give 535 mg (76%) of **11**: mp 67–68 °C; mp (hydrochloride) 210–211 °C (lit.[8] mp 210–211 °C).

1-Phenyl-2-(isopropylamino)-1-propanol (12). A solution of 730 mg (4.8 mmol) of norephedrine in 5 mL of absolute ethanol was stirred with 1.5 equiv of acetone for 15 min. To the resulting oxazolidine was added 342 mg (9 mmol) of sodium borohydride, and the mixture was then stirred for 20 min. The reaction was worked up as described above and the crude product recrystallized from petroleum ether to give 816 mg (88%) of **12**, mp 89–90 °C (lit.[8] mp 91–92 °C).

1-Phenyl-2-(*n*-heptylamino)-1-propanol (13). A solution of 592 mg (3.9 mmol) of **3** in 4 mL of absolute ethanol was stirred with 1.5 equiv of *n*-heptanal for 15 min. The resulting oxazolidine was reduced with 209 mg (5.5 mmol) of sodium borohydride for 15 min at 25 °C and worked up as described above. After recrystallization from petroleum ether it gave 819 mg (84%) of **13**: mp 62–63 °C, mp (hydrochloride) 230–223 °C (lit.[8] mp 66–76 °C, mp (amine·HCl) 228–229 °C).

Registry No. **1**, 141-43-5; **2**, 78-96-6; **3**, 700-65-2; **4**, 110-73-6; **5**, 109-56-8; **6**, 2842-38-8; **7**, 35265-04-4; **8**, 41063-31-4; **9**, 96307-00-5; **10**, 103-00-4; **11**, 15145-92-3; **11**·HCl, 15263-01-1; **12**·HCl, 53457-43-5; **13**, 96307-01-6; **13**·HCl, 96307-02-7; CH_3CHO, 75-07-0; Me_2CO, 67-64-1; MeCOEt, 78-93-3; $CH_3CH(CH_3)CH_2CHO$, 590-86-3; $(CH_3)_2CHCHO$, 78-84-2; $CH_3(CH_2)_5CHO$, 111-71-7; cyclohexanone, 108-94-1; 2-methyl-2,3,4,5-tetrahydroisoxazole, 16250-70-7; 2,2-dimethyl-2,3,4,5-tetrahydroisoxazole, 20515-62-2; 2-cyclohexyl-2,3,4,5-tetrahydoisoxazole, 177-04-8; 2-methyl-2-ethyl-2,3,4,5-tetrahydroisoxazole, 17026-89-0; 2,2,5-trimethyl-2,3,4,5-tetrahydroisoxazole, 52837-54-4; 2-(2-methyl-*n*-propyl)-5-methyl-2,3,4,5-tetrahydroisoxazole, 96307-03-8; 2-cyclohexyl-5-methyl-2,3,4,5-tetrahydroisoxazole, 90267-83-7; 2-isopropyl-4-methyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 96307-04-9; 2,2,4-trimethyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 60980-85-0; 2-*n*-hexyl-4-methyl-5-phenyl-2,3,4,5-tetrahydroisoxazole, 96307-05-0.

Supplementary Material Available: Full NMR data for compounds **4** thru **13** (2 pages). Ordering information is given on any current masthead page.

(11) Fore a review on the formation and chemistry of oxazolidines see: Bergman, E. D. *Chem. Rev.* **1953**, *53*, 309.

Synthesis of Antibiotic SS-228R. Strong Base Induced Cycloaddition of Homophthalic Anhydrides

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Two types of naphthacenediones, 1,6,7-trihydroxy-9-methyl- (**2**) and 1,6,10-trihydroxy-8-methylnaphthacene-5,12-diones (**4**), were prepared by the cycloaddition of 8-methoxy-6-methyl- (**9**) and 5-methoxy-7-methylhomophthalic anhydrides (**10**) with 2-bromojuglone methyl ether (**11**), thus establishing the structure of the antibiotic SS-228R as **4**.

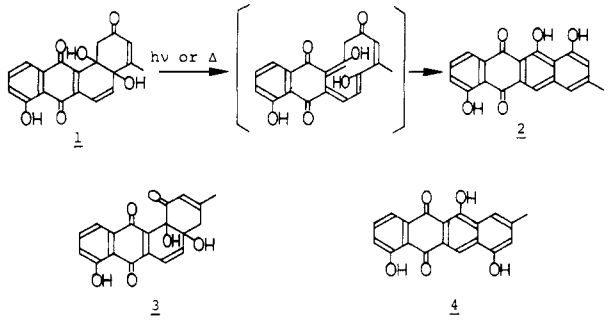
The antibiotic SS-228Y (**1**), obtained from a species of Chainia isolated from shallow sea mud, is known to inhibit the growth of Gram-positive bacteria and dopamine-β-hydroxylase and is very labile to light and heat, being converted into SS-228R (**2**) (Scheme I).[1] Their structures had been deduced by spectroscopic data, especially by extensive ^1H-{^1H} NOE experiments. In 1982, Ikekawa and Omura et al. reconsidered these structures based on biosynthetic studies of the antibacterial and antitumor antibiotics, the vineomycins, and proposed other biosynthetically acceptable structures (**3** and **4**) for SS-228Y and SS-228R without the synthesis of these compounds (Scheme I).[2] We have now synthesized both compounds (**2** and **4**) assigned to SS-228R by the strong base induced

(1) (a) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176. (b) Kitahara, T.; Naganawa, H.; Okazaki, T.; Okami, Y. Umezawa; H. *Ibid.* **1975**, *28*, 280. (c) Faulkner, D. J. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Halsted Press; New York, 1978; Vol. 2, p 19.

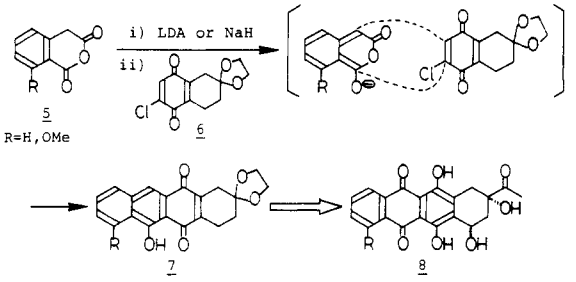
(2) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *J. Antibiot.* **1982**, *35*, 602.

0022-3263/85/1950-2273$01.50/0

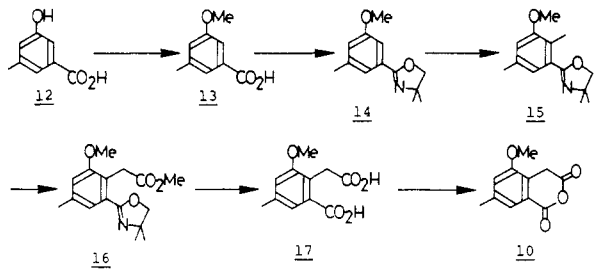
Scheme I



Scheme II



Scheme III



cycloaddition of homophthalic anhydrides and have established the structure of SS-228R as **4**, proposed by the latter investigators, which strongly supports that SS-228Y should have the structure **3**. Recently we reported[3] that condensation of homophthalic anhydrides (**5**) with halonaphthoquinone derivatives (**6**) produced high yields of the corresponding tetracyclic compounds (**7**) leading to anthracyclinones (**8**), in which the nucleophilic end (C-4 position) of **5** regioselectively attacked the unsubstituted olefinic site of **6** (Scheme II). We have now applied this cycloaddition utilizing 8-methoxy-6-methyl- (**9**) and 5-methoxy-7-methylhomophthalic anhydrides (**10**) with 2-bromojuglone methyl ether (**11**)[4] to the synthesis of **2** and **4**.

The starting anhydride (**9**) was prepared by the Diels–Alder reaction of 6-methoxy-4-methyl-2-pyrone with 1,3-dicarbethoxyallene followed by alkaline hydrolysis and dehydrative cyclization.[5] The unknown 5-methoxy-7-methylhomophthalic anhydride (**10**) was synthesized from 5-hydroxy-3-methylbenzoic acid (**12**)[6] via five intermediates

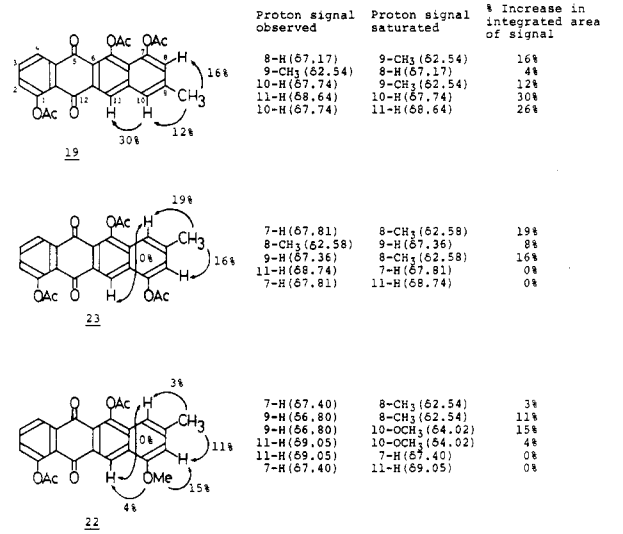
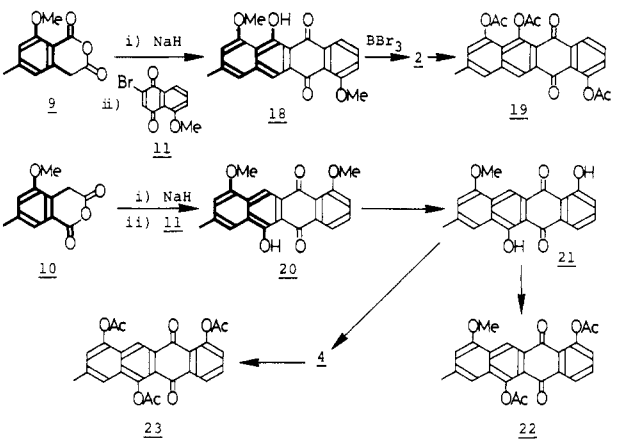


Figure 1.

Scheme IV



(**13**–**17**) in 10% overall yield by an efficient synthetic route shown in Scheme III. It has as its key features an oxazole-directed ortho lithiation,[7] methylation, deprotonation sequence,[8] acylation of the resulting benzyl anion with dimethyl carbonate, acid hydrolysis of the ester and oxazoline units to the diacid, and dehydrative cyclization of the diacid to form the required anhydride (**10**).

The synthesis of **2** and **4** and their derivatives (**18**–**23**) began from the anhydrides **9** and **10**, respectively, as outlined in Scheme IV. Treatment of the sodio anion of **9** with **11** gave a 73% yield of the naphthacenedione (**18**) as the sole product. Demethylation of **18** with boron tribromide in methylene chloride gave **2**, which was converted into 1,6,7-triacetoxy-9-methylnaphthacene-5,12-dione (**19**) by treatment with acetic anhydride in pyridine. The isomeric naphthacenedione (**20**) was obtained by the reaction of the sodio anion of **10** with **11** in 87% yield. Mild demethylation of **20** with boron tribromide in methylene chloride gave the monodemethylated naphthacenedione (**21**), which was further demethylated with boron tribromide to give **4**. Acetylation of these naphthacenediones (**21** and **4**) with acetic anhydride in pyridine gave the corresponding diacetoxy- (**22**) and triacetoxynaphthacenediones (**23**), respectively. The physical

(3) (a) Tamura, Y.; Wada, A.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1981**, *22*, 4283. (b) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H.; Kita, Y. *J. Org. Chem.* **1982**, *47*, 4376. (c) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *Ibid.* **1984**, *49*, 473. (d) Tamura, Y.; Akai, S.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1984**, *25*, 1167. (e) Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, *40*, 4539.

(4) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.

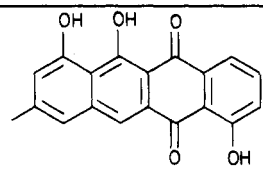
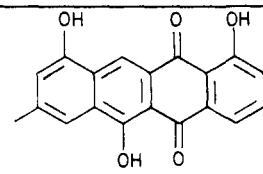
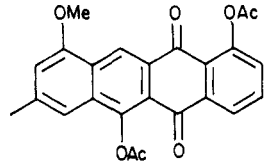
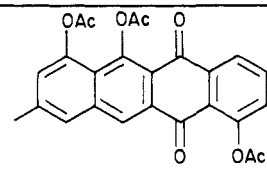
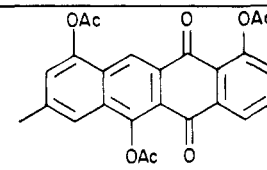
(5) Tamura, Y.; Fukata, F.; Tsugoshi, T.; Sasho, M.; Nakajima, Y.; Kita, Y. *Chem. Pharm. Bull.* **1984**, *32*, 3259.

(6) Turner, F. A.; Gearien J. E. *J. Org. Chem.* **1959**, *24*, 1952.

(7) (a) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. (b) Gschwend, H. W.; Hamdan, A. *Ibid.* **1975**, *40*, 2008. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1. (d) Watanabe, M. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 728.

(8) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1982**, *47*, 3652.

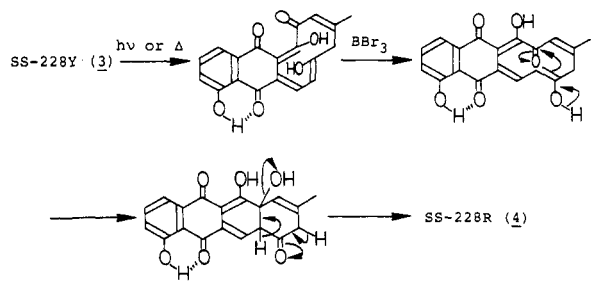
Table I. Physical and Spectral Data for SS-228R, the Monomethyl Diacetate of SS-228R, and the Triacetate of SS-228R

	SS-228R	 2	 4
mp	255–266 °C dec ($MeOH–CH_3COCH_3$)	244–250 °C dec	258–267 °C dec ($MeOH–CH_3COCH_3$)
m/e	320 (M^+, base peak)	320 (M^+, base peak)	320 (M^+, base peak)
IR (tablet)	1635sh, 1605 cm^{-1}	1620, 1610, 1580 cm^{-1}	1635sh, 1605 cm^{-1}
λ_{max}[a]	264, 295sh, 306sh, 495		262, 293sh, 305sh
λ_{max}[b]	267, 560		267, 575
^1H NMR[c]	9.22 (s, 1 H), 7.95 (d, *J* = 1.0 Hz, 1 H), 7.94 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.63 (t, *J* = 8.5 Hz, 1 H), 7.58 (d, *J* = 1.0 Hz, 1 H), 7.34 (dd, *J* = 8.5, 1.5 Hz, 1 H), 2.35 (s, 3 H)	insoluble in C_5D_5N	9.15 (s, 1 H), 7.88 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.87 (d, *J* = 1.0 Hz, 1 H), 7.55 (t, *J* = 8.5 Hz, 1 H), 7.28 (dd, *J* = 8.5, 1.5 Hz, 1 H), 2.34 (s, 3 H)
	monomethyl diacetate of SS-228R		 22
mp	214–216 °C dec ($CHCl_3$)	214–223 °C dec ($CHCl_3–C_6H_6$)	
m/e	418, 376, 334 (base peak), 319	418, 376, 334 (base peak), 319	
IR	1760, 1665, 1618, 1590	1765sh, 1670, 1620, 1590	
λ_{max}[d]	262, 280sh, 293, 305, 370, 438	261, 280sh, 293, 304	
^1H NMR[e]	9.04 (d, *J* = 1.0 Hz, 1 H), 8.23 (dd, *J* = 7.0, 1.0 Hz, 1 H), 7.74 (t, *J* = 7.0 Hz, 1 H), 7.41 (m, 1 H), 7.37 (dd, *J* = 7.0, 1.0 Hz, 1 H), 6.80 (m, 1 H), 4.02 (s, 3 H), 2.61 (s, 3 H), 2.51 (s, 3 H), 2.49 (s, 3 H)	9.05 (d, *J* = 1.0 Hz, 1 H), 8.22 (dd, *J* = 7.0, 1.0 Hz), 7.73 (t, *J* = 7.0 Hz, 1 H), 7.40 (m, 1 H), 7.35 (dd, *J* = 7.0, 1.0 Hz, 1 H), 6.80 (m, 1 H), 4.02 (s, 3 H), 2.62 (s, 3 H), 2.54 (s, 3 H), 2.50 (s, 3 H)	
	triacetate of SS-228R	 19	 23
mp	235–238 °C dec ($CHCl_3$–MeOH)	238–242 °C dec ($CHCl_3$–MeOH)	234–240 °C dec ($CHCl_3$–MeOH)
m/e	446 (M^+), 404, 362, 320 (base peak)	446 (M^+), 404, 362, 320 (base peak)	446 (M^+), 404, 362, 320 (base peak)
IR	1775, 1675	1775, 1680, 1630, 1595	1770, 1675, 1625, 1590
λ_{max}[d]	252, 280sh, 291, 302, 410, 425sh	251, 279sh, 289, 301, 407	252, 278sh, 290, 302, 407
^1H NMR[e]	8.74 (d, *J* = 1.0 Hz, 1 H), 8.26 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.80 (m, 1 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.42 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.37 (m, 1 H), 2.65 (s, 3 H), 2.58 (s, 3 H), 2.54 (s, 3 H), 2.52 (s, 3 H)	8.64 (bs, 1 H), 8.24 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.78 (t, *J* = 8.0 Hz, 1 H), 7.74 (m, 1 H), 7.40 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.17 (m, 1 H), 2.60 (s, 3 H), 2.54 (s, 3 H), 2.51 (s, 3 H), 2.44 (s, 3 H)	8.74 (d, *J* = 1.0 Hz, 1 H), 8.26 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.81 (m, 1 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.42 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.36 (m, 1 H), 2.66 (s, 3 H), 2.58 (s, 3 H), 2.55 (s, 3 H), 2.52 (s, 3 H)

[a] In 80% MeOH. [b] In 80% MeOH, 0.2 N NaOH. [c] In C_5D_5N. [d] In $CHCl_3$. [e] In $CDCl_3$.

and spectral data of **2**, **4**, **19**, **22**, and **23** were compared with those reported[1] for SS-228R and its triacetate. The data, which are summarized in Table I, show that SS-228R has the structure **4**. A series of the nuclear Overhauser effect (NOE) experiments on **19**, **22**, and **23** were also performed by using 200-MHz NMR, since a different structure (**2**) was proposed for SS-228R by NOE experiments on the triacetate of SS-228R by using 100-MHz NMR.[1] Our results of NOE experiments on **19**, **22**, and **23** are in good accord with their structures shown in Figure 1 and show that the structure of SS-228R should be revised from **2** to **4**. The present study strongly suggests that SS-228Y has the structure **3** instead of **1** and the conversion of **3** to SS-228R (**4**) may be rationalized by Scheme V.

Scheme V



Experimental Section

General Methods. All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ (Me_4Si). Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (IR) spectra were determined with either sodium chloride blanks for tablet or 0.1-mm sodium chloride cells and chloroform as solvent. The progress of all reactions was monitored by thin-layer chromatography (TLC) which was performed on aluminum sheets coated

with silica gel-60 (F-254). For column chromatography, E. Merck silica gel (0.063–0.200 mm, 70–230 mesh ASTM) was used. Anhydrous tetrahydrofuran (THF) was obtained by distillation from the sodium benzophenone dianion under nitrogen. The starting 5-hydroxy-3-methylbenzoic acid (**12**) was prepared by the reported method.[6]

5-Methoxy-3-methylbenzoic Acid (13). Dimethyl sulfate (10 mL) was added dropwise to a stirred suspension of **12** (5 g, 32.9 mmol) in aqueous 30% NaOH (20 mL) over 5 min at room temperature. Additional aqueous 30% NaOH (20 mL) was added, and then the mixture was heated at 100 °C for 24 h and concentrated in vacuo. The residue was washed with ether (10 mL), dissolved in water, acidified with 35% HCl to pH 1, extracted with ether (3 × 100 mL), dried over magnesium sulfate, and evaporated to give a 78% yield (4.56 g) of **13** as a white solid. Recrystallization from methanol gave pure **13**: mp 133–137 °C; NMR ($CDCl_3$) δ 7.48 (m, 1 H), 7.38 (m, 1 H), 6.92 (m, 1 H), 3.81 (s, 3 H), 2.36 (s, 3 H); IR ($CHCl_3$) 1690, 1595 cm^{-1}. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.92; H, 6.08.

2-(3-Methoxy-5-methylphenyl)-4,4-dimethyl-2-oxazoline (14). A modification of the reported procedure[9] for the preparation of 2-(bromophenyl)-4,4-dimethyl-2-oxazolines was used. The acid **13** (4 g, 24 mmol) was added to thionyl chloride (8.4 g, 5.2 mL, 72 mmol). The mixture was stirred at 25 °C for 24 h and the excess thionyl chloride was distilled. The remaining dark oil was dissolved in methylene chloride (11 mL) and added dropwise to a stirred solution of 2-amino-2-methyl-1-propanol (4.28 g, 48 mmol) in methylene chloride (11 mL) at 0 °C. The mixture was stirred at 25 °C for 24 h and concentrated in vacuo to give a quantitative yield of the *N*-(2,2-dimethyl-3-hydroxypropyl)-benzamide as a white solid. Thionyl chloride (5.2 mL, 72 mmol) was added dropwise to the solid. The mixture was stirred at room temperature for 1 h, poured into 20% aqueous NaOH (100 mL), and extracted with ether (3 × 100 mL). The combined extract was washed with brine (20 mL), dried over potassium carbonate, and evaporated to yield an oily residue, which was purified by column chromatography (benzene–ether 10:1) to give an 86% yield (4.5 g) of **14** as a colorless oil: NMR ($CDCl_3$) δ 7.32 (br s, 1 H), 7.21 (br s, 1 H), 6.77 (br s, 1 H), 4.05 (s, 2 H), 3.77 (s, 3 H), 2.31 (s, 3 H), 1.35 (s, 6 H); IR ($CHCl_3$) 1640, 1590 cm^{-1}; exact mass calcd for $C_{13}H_{17}NO_2$ 219.1260, found 219.1282.

2-(3-Methoxy-2,5-dimethylphenyl)-4,4-dimethyl-2-oxazoline (15). A solution of **14** (1 g, 4.57 mmol) in THF (10 mL) was treated with a solution of *n*-BuLi (1.5 M, 4.3 mL, 6.9 mmol) in hexane at −45 °C (CH_3CN–dry ice bath) under nitrogen. The solution was allowed to warm to 0 °C, stirred for 30 min, and cooled to −45 °C, and methyl iodide (1.25 mL, 20 mmol) was added. The mixture was allowed to warm to room temperature, stirred for 1.5 h, poured into water (15 mL), and extracted with methylene chloride (3 × 50 mL). The combined extract was washed with brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo to give the crude **15**, which was purified by column chromatography (benzene–ether 10:1) to give a 57% yield (607 mg) of **15** as a colorless oil: NMR ($CDCl_3$) δ 7.06 (br s, 1 H), 6.68 (br s, 1 H), 4.03 (s, 2 H), 3.78 (s, 3 H), 2.31 (br s, 6 H), 1.36 (s, 6 H); IR ($CHCl_3$) 1640, 1605, 1580 cm^{-1}; exact mass calcd for $C_{14}H_{19}NO_2$ 233.1413, found 233.1386.

2-[2-(Carbomethoxymethyl)-3-methoxy-5-methylphenyl]-4,4-dimethyl-2-oxazoline (16). A solution of **15** (467 mg, 2 mmol) in THF (5 mL) was treated with a solution of *n*-BuLi (1.5 M, 2 mL, 3 mmol) in hexane at 0 °C under nitrogen. The solution was stirred for 1.5 h under the same conditions and dimethyl carbonate (1 mL, 11.8 mmol) was added dropwise at −45 °C. The mixture was allowed to warm to room temperature, stirred for 1.5 h, quenched with water (6 mL), and extracted with methylene chloride (3 × 50 mL). The combined extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give crude **16** as a yellow oil, which was purified by column chromatography (benzene–ether 15:1) to give a 45% yield (260 mg) of pure **16** as a colorless oil: NMR ($CDCl_3$) δ 7.18 (br s, 1 H), 6.72 (br s, 1 H), 4.08 (s, 2 H), 3.97 (s, 2 H), 3.78 (s, 3 H), 3.61 (s, 3 H), 2.32 (s, 3 H), 1.30 (s, 6 H); IR ($CHCl_3$) 1725, 1640, 1605, 1580 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.93; H, 7.27; N, 4.81. Found: C, 65.97; H, 7.42; N, 4.68.

(2-Carboxy-6-methoxy-4-methylphenyl)acetic Acid (17). A solution of **16** (390 mg, 1.34 mmol) in 4.5 N HCl (25 mL) was heated at reflux for 24 h. After cooling, the resulting crystals were collected. More crystals were obtained from the filtrate by the extraction with ether (3 × 100 mL). Totally, 71% yield (212 mg) of **17** was obtained. Recrystallization from ethyl acetate gave pure **17**: mp 183–185 °C; NMR ($CDCl_3$) δ 7.35 (br s, 1 H), 6.97 (br s, 1 H), 4.03 (s, 2 H), 3.82 (s, 3 H), 2.34 (s, 3 H); IR ($CHCl_3$) 1700, 1680, 1605 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.64; H, 5.37.

5-Methoxy-7-methylhomophthalic Anhydride (10). To a suspension of **17** (140 mg, 0.63 mmol) in dry acetone (2 mL) was added acetyl chloride (2 mL, 7 mmol) dropwise. The mixture was stirred at room temperature for 1.5 h and concentrated in vacuo to give a crude solid, which was washed with a small amount of acetone and *n*-hexane to give an 81% yield (105 mg) of crude **10**. Recrystallization from benzene–*n*-hexane gave pure **10**: mp 169.5–172 °C; NMR ($CDCl_3$) δ 7.69 (br s, 1 H), 6.97 (br s, 1 H), 3.95 (s, 2 H), 3.90 (s, 3 H), 2.45 (s, 3 H); IR (KCl) 1785, 1740, 1610 cm^{-1}; IR ($CHCl_3$) 1795, 1750, 1610, 1595 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.96; H, 4.77.

6-Hydroxy-1,7-dimethoxy-9-methylnaphthacene-5,12-dione (18). A mixture of **9** (50 mg, 0.24 mmol) and NaH (60% in mineral oil, 10.8 mg, 0.26 mmol) in THF (2 mL) was stirred at room temperature for 15 min. After cooling to 0 °C, a solution of **11** (65 mg, 0.24 mmol) in THF (2 mL) was added to the mixture. The whole was stirred at 0 °C for 5 min, allowed to warm to room temperature, and stirred for 1.5 h. The mixture was quenched with saturated aqueous ammonium chloride (1 mL), acidified with 10% HCl to pH 1, and extracted with methylene chloride (3 × 30 mL). The combined extract was dried over sodium sulfate and concentrated in vacuo to give a solid, which was purified by column chromatography (benzene–ether 7:1) to give a 73% yield (61 mg) of **18** as red crystals: mp over 300 °C; NMR ($CDCl_3$) δ 15.57 (s, 1 H), 8.07 (dd, 1 H), 8.03 (s, 1 H), 7.72 (t, 1 H), 7.34 (m, 1 H), 7.34 (dd, 1 H), 6.05 (d, 1 H), 4.06 (s, 6 H), 2.51 (s, 3 H); IR ($CHCl_3$) 1665, 1620, 1580 cm^{-1}; exact mass calcd for $C_{21}H_{16}O_5$ 348.0998, found 348.1028.

1,6,7-Trihydroxy-9-methylnaphthacene-5,12-dione (2). To a cooled solution of **18** (45 mg, 0.13 mmol) in methylene chloride (23 mL) at −78 °C was added a solution of boron tribromide (3.3 g, 13 mmol) in methylene chloride (2 mL) dropwise under nitrogen. The green colored mixture was stirred for 1 h under the same conditions, allowed to warm to room temperature, and stirred for 2 h. The mixture was poured into a mixture of saturated aqueous sodium bicarbonate and crushed ice, extracted with chloroform (3 × 30 mL), dried over sodium sulfate, and concentrated in vacuo to give a solid, which was purified by column chromatography (chloroform) to give a 59% yield (24.5 mg) of **2**; exact mass calcd for $C_{19}H_{12}O_5$ 320.0682, found 320.0669.

1,6,7-Triacetoxy-9-methylnaphthacene-5,12-dione (19). A solution of **2** (40 mg, 0.13 mmol) and acetic anhydride (3 mL) in pyridine (3 mL) was allowed to stand at room temperature overnight and concentrated in vacuo to give a solid, which was purified by column chromatography (benzene–ether 5:1) to give a 48% yield (27 mg) of **20** as yellow crystals. Recrystallization from chloroform–methanol gave pure **19**; exact mass calcd for $C_{25}H_{18}O_8$ 446.0999, found 446.0983.

6-Hydroxy-1,10-dimethoxy-8-methylnaphthacene-5,12-dione (20). This was prepared from **10** (96.3 mg, 0.47 mmol), sodium hydride (60% in mineral oil, 21 mg, 0.52 mmol), and **11** (125.5 mg, 0.47 mmol) by the same method as described for the preparation of **18**. The crude solid was purified by column chromatography (chloroform) to give an 87% yield (142 mg) of **20** as red crystals. Recrystallization from benzene gave pure **20**: mp 271–275 °C; NMR ($CDCl_3$) δ 14.27 (s, 1 H) 8.61 (s, 1 H), 8.05 (dd, 1 H), 7.81 (s, 1 H), 7.71 (t, 1 H), 7.34 (dd, 1 H), 6.86 (br s, 1 H), 4.05 (s, 3 H), 4.01 (s, 3 H), 2.54 (s, 3 H); IR (KCl) 1660, 1620, 1550 cm^{-1}; IR ($CHCl_3$) 1660, 1620, 1580 cm^{-1}. Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.40; H, 4.63. Found: C, 72.46; H, 4.54.

1,6-Dihydroxy-10-methoxy-8-methylnaphthacene-5,12-dione (21). To a cooled solution of **20** (27.5 mg, 0.079 mmol) in methylene chloride (5 mL) at −78 °C was added a solution of boron tribromide (2.1 g, 8 mmol) in methylene chloride (1 mL) dropwise under nitrogen. The green colored mixture was stirred for 1 h

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under the same conditions, allowed to warm to room temperature, and stirred for 2 h. Workup of the reaction mixture as described for the preparation of **2** from **18** gave a 95% yield (25 mg) of **21**. Recrystallization from chloroform gave pure **21**: mp 298–300 °C; NMR ($CDCl_3$) δ 14.38 (s, 1 H), 12.96 (s, 1 H), 8.64 (d, 1 H), 7.82 (dd, 1 H), 7.77 (m, 1 H), 7.60 (t, 1 H), 7.22 (dd, 1 H), 6.84 (d, 1 H), 4.00 (s, 3 H), 2.55 (s, 3 H); IR (KCl) 1610, 1570 cm^{-1}; exact mass calcd for $C_{20}H_{14}O_5$ 334.0839, found 334.0827.

1,6,10-Trihydroxy-8-methylnaphthacene-5,12-dione (4). To a cooled solution of **20** (60 mg, 0.183 mmol) in methylene chloride (10 mL) at −78 °C was added a solution of boron tribromide (4.7 g, 18.3 mmol) in methylene chloride (1 mL) dropwise under nitrogen. The green colored mixture was stirred for 1 h under the same conditions, allowed to warm to room temperature, and stirred overnight. Workup of the reaction mixture as described for the preparation of **2** from **18** gave a 51% yield (30 mg) of **4**. Recrystallization from methanol–acetone gave pure **4**; exact mass calcd for $C_{19}H_{12}O_5$ 320.0685, found 320.0695.

1,6-Diacetoxy-10-methoxy-8-methylnaphthacene-5,12-dione (22). A solution of **21** (20 mg, 0.06 mmol) and acetic anhydride (1 mL) in pyridine (1 mL) was allowed to stand at room temperature for 12 h and concentrated in vacuo to give a solid, which was purified by column chromatography (benzene–ether 10:1) to give a 92% yield (23 mg) of **22** as yellow crystals. Recrystallization from chloroform–benzene gave pure **22**; exact mass calcd for $C_{24}H_{18}O_7$ 418.1050, found 418.1050.

1,6,10-Triacetoxy-8-methylnaphthacene-5,12-dione (23). A solution of **4** (14 mg, 0.044 mmol) and acetic anhydride (1 mL) in pyridine (1 mL) was allowed to stand at room temperature for 12 h. Workup as described above gave a 50% yield (10 mg) of **23** as yellow crystals. Recrystallization from chloroform–methanol gave pure **23**; exact mass calcd for $C_{25}H_{18}O_8$ 446.1008, found 446.1002.

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Temperature-Dependent Acid Dissociation Constants (K_a, ΔH_a, ΔS_a) for some *C*-Aryl Hydroxamic Acids: The Influence of C and N Substituents on Hydroxamate Anion Solvation in Aqueous Solution

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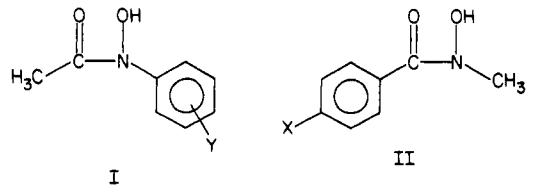
The acid dissociation constants (K_a) of a series of substituted *N*-methylbenzohydroxamic acids, 4-$XC_6H_4C(O)N(OH)CH_3$ (X = H, CH_3O, CH_3, NO_2) and 4-methoxybenzohydroxamic acid, 4-$CH_3OC_6H_4C(O)N(OH)H$, have been determined in aqueous solution (I = 2.0) over a range of temperatures. The pK_a values at 25 °C are as follows: 4-$XC_6H_4C(O)N(OH)CH_3$, X = H (8.28), X = CH_3O (8.67), X = CH_3 (8.50), X = NO_2 (7.94); 4-$CH_3OC_6H_4C(O)N(OH)H$, (8.76). The substituted *N*-methylbenzohydroxamic acids exhibit a trend in pK_a values that is consistent with the Hammett σ substituent parameters but with a ρ value of 0.6. ΔH_a and ΔS_a values fall in a narrow range (ΔH_a = 1.1–2.2 kcal/mol; ΔS_a = −31 to −36 cal/(K mol)) and represent minimum values for these parameters when compared with other C- and N-substituted hydroxamic acids. These results suggest that the C and N substituents influence the water solvation of the hydroxamate moiety −[C(=O)N(O⁻)−] and that the *N*-methylhydroxamate anions are the most highly solvated.

Hydroxamic acids are weak proton donors[1] which have numerous applications in such diverse fields as extractive metallurgy, corrosion inhibition, nuclear fuel processing, pharmaceuticals, fungicides, and analytical reagents. We are interested in structure–reactivity relationships as they apply to hydroxamic acid acidity[2,3] and iron(III) chelation[4–6] in aqueous solution. Of importance is the relative influence of the functional group on the carbon and nitrogen ends of the hydroxamic acid moiety, and the relative contributions of inductive and resonance effects.

In a previous report,[3] we investigated the temperature-dependent acidity of a series of substituted *N*-phenylacetohydroxamic acids (I). In this report, temperature-dependent acid dissociation constants have been determined in aqueous solution for a series of substituted



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