Streptonigrin and Lavendamycin Partial Structures. Preparation of 7-Amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylic Acid: A Probe for the Minimum, Potent Pharmacophore of the Naturally Occurring Antitumor-Antibiotics

Masami Yasuda [*] and Dale L. Boger [1]

Deparments of Chemistry and Medicinal Chemistry, Purdue University,
West Lafayette, Indiana 47907

Received February 26, 1987

The preparation of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylic acid (**4**) constituting a potential minimum, potent pharmacophore of streptonigrin (**1**) and lavendamycin (**2**), two structurally-related naturally-occurring antitumor-antibiotic, is detailed. In contrast to observations associated with streptonigrin and lavendamycin in which the C-6′ acid *potentiates* the antitumor, antimicrobial, and cytotoxic activity of the naturally-occurring, substituted 7-aminoquinoline-5,8-quinone AB ring systems, the C-6′ carboxylic acid of **4** *diminishes* the observed antimicrobial and cytotoxic properties of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone.

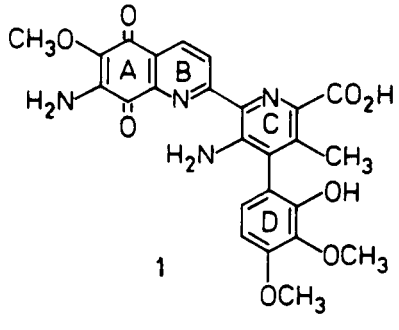
J. Heterocyclic Chem., **24**, 1253 (1987).

Streptonigrin (**1**), a highly substituted and highly functionalized quinoline-5,8-quinone first isolated from *Streptomyces flocculus* [2,3], has been shown to possess potent cytotoxic properties, confirmed broad spectrum antitumor activity, *in vitro* and *in vivo* antiviral properties, and displays potent, broad spectrum antimicrobial properties [3]. Its potential, widespread clinical use has been precluded only by its potent toxicity which is derived from sever bone marrow suppression [4]. Continued and recent efforts have explored the clinical use of streptonigrin in combination chemotherapy with agents including vincristine, prednisone, and bleomycin [5].

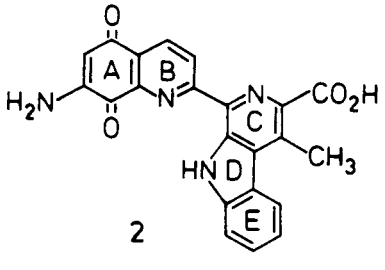
The antimicrobial and antitumor properties of lavendamycin (**2**), an antitumor-antibiotic recently isolated from *Streptomyces lavendulae* and shown to be structurally and biosynthetically related to streptonigrin, have been examined and with notable exceptions it was found to be comparable albeit less potent than streptonigrin in its observed spectrum of activity [6].

Present efforts have shown that streptonigrin cellular toxicity may be attributed to the depletion of NADPH/NADH [3], the uncoupling of oxidative phosphorylation, and/or the single-strand cleavage of DNA [3,7]. This latter effect, which disrupts DNA synthesis and which has been studied in cell free systems, has been actively pursued as the potential mechanism of streptonigrin antitumor activity [3,7-17].

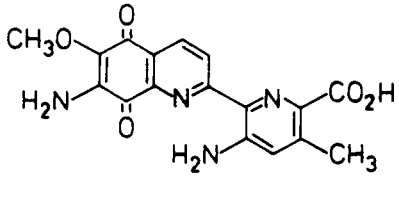
The streptonigrin induced cell-free, single-strand cleavage of covalently-closed circular-DNA (*ccc*-DNA) [8-10] requires: (1) an apparent, *in situ* reduction (NADH activa-



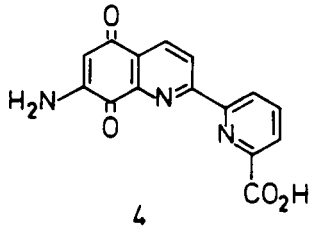
1



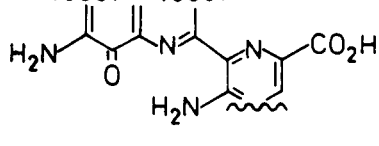
2



3



4



I

tion [7-14], AB quinoline-5,8-quinone → AB hydroquinone/semiquinone radical), (2) is facilitated by the presence of metal cations including copper(II) and iron(II) [8-12,15], (3) is inhibited completely by the addition of ethylenediaminetetraacetic acid [8-11,15], (4) requires the presence and assumed activation of molecular oxygen [8-15], and (5) is inhibited by superoxide oxidoreductase (EC 1.15.1.1) *and* hydrogen peroxide oxidoreductase (EC 1.11.1.6) [8-11]. Conflicting reports of direct and indirect experimental evidence which suggest the (lack of) association or intercalation of streptonigrin with double-stranded DNA in the (absence) presence of divalent metal cations continues to cloud the potential mechanism for streptonigrin induced DNA cleavage [7,8,12,16-18].

Consequently, two distinct mechanisms have been advanced to accomodate the streptonigrin-induced single-strand cleavage of DNA, streptonigrin cellular toxicity, and presumed mechanism of antitumor activity: (1) the direct participation of streptonigrin as its hydroquinone in the reductive generation of free, diffusable hydroxyl radical (·OH) from molecular oxygen proximal [12] or distal [8-10] to DNA or; (2) the direct, covalent interaction of the intermediate streptonigrin semiquinone radical with double-stranded DNA [7].

Early, limited studies employing derivatives of streptonigrin [19,20] defined the structural components required (7-amino-6-methoxyquinoline-5,8-quinone) for *in vitro* and *in vivo* cytotoxic, antitumor, or antimicrobial activity as well as those which appear to potentiate (C-6′ carboxylic acid, C-3′ amine) the activity of the naturally occurring agent and led Rao to propose I as the potent, active pharmacophore of the naturally occurring material [20]. Extensive investigations focusing on streptonigrin partial structures [21a] including Rao's preparation of **3**, lavendamycin partial structures [21b], as well as simple, substituted quinoline-5,8-quinones [11,15,20-23], or heterocyclic-fused *p*-benzoquinones [15,22] have confirmed and defined the cytotoxic, antimicrobial, and potential antitumor properties of the simplified quinone systems. In selected instances, an excellent correlation of the reduction potential of the quinone system and the extent of cell-free single-strand DNA cleavage has been observed [11,15]. None, however, have been described to possess the comparable cytotoxic, antimicrobial, or antitumor potency of streptonigrin despite the enhanced or comparable redox properties [3,20].

The effective ability for 8-hydroxyquinolines (*cf.* streptonigrin → streptonigrin semiquinone radical or hydroquinone) to complex divalent metal cations [24], and the feasible potentiation of the streptonigrin hydroquinone (8-hydroxyquinoline) metal chelation, oxygen activation process by the streptonigrin pyridyl N-1′/C-6′ carboxylate *or* the acidic C-3′ pyridyl amine have provided an attractive rationale for the observed cytotoxic, antimicrobial, and antitumor potency as well as cell-free single-strand DNA cleavage efficacy of streptonigrin [3,12]. Moreover, the well-established potentiation of the cytotoxic, antimicrobial, and antitumor properties which may be attributed to the streptonigrin C-6′ carboxylic acid ($CO_2H \gg CO_2CH_3 \sim CONHNH_2$) [3,19], the recognized metal chelation properties of related 2,2′-bipyridyl systems [25,26], as well as the recent demonstration of the affinity [27,28], specificity [27,28], and nuclease oxidative cleavage of native and synthetic polynucleotides promoted by 1,10-phenanthroline metal complexes [27] have suggested indirectly that it is the streptonigrin/lavendamycin pyridyl N-1′/C-6′ carboxylate which may be responsible for the enhanced efficacy of the naturally occurring materials [36].

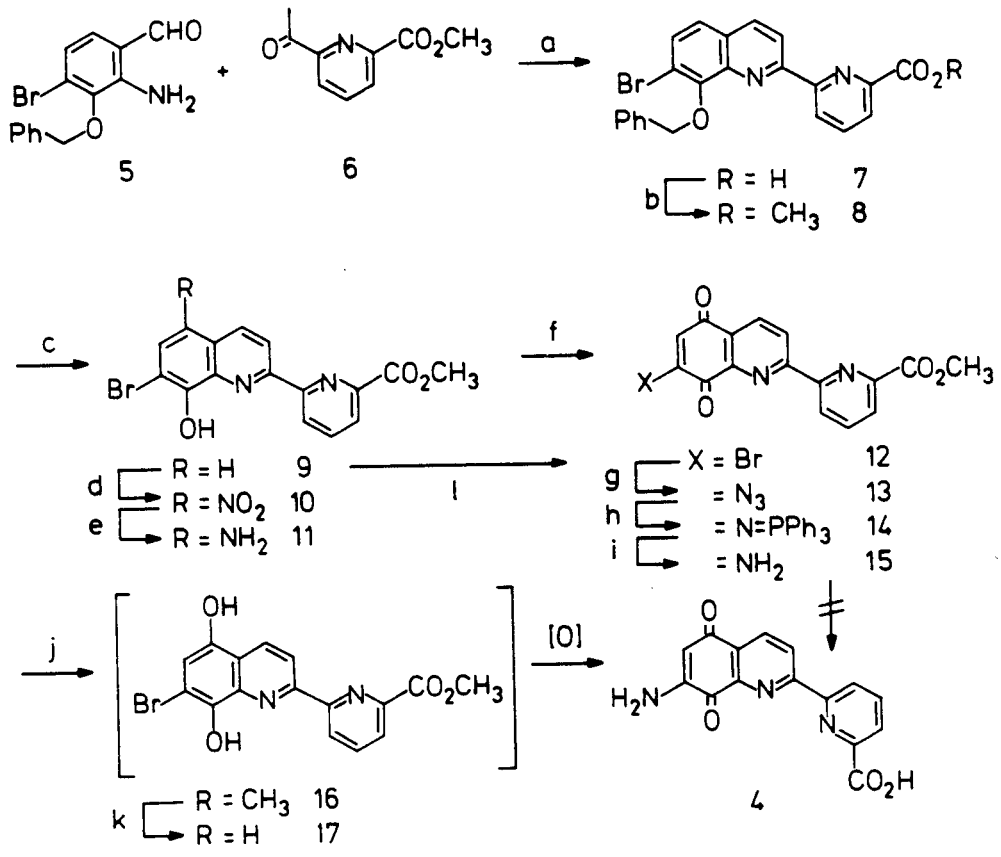
Herein we detail the preparation of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylic acid (**4**) constituting this potential minimum, potent pharmacophore of streptonigrin (**1**) and lavendamycin (**2**).

Preparation of 7-Amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylic Acid (**4**).

The preparation of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylic acid (**4**) is based on the application of the Friedlander condensation [29] of 2-amino-3-(benzyloxy)-4-bromobenzaldehdye (**5**) [21b] with methyl 2-acetylpyridine-6-carboxylate (**6**) [30] for quinoline introduction and assemblage of the carbon framework of **4**. The selection of **5** for use in the Friedlander condensation represents one in which the 2-aminobenzaldehyde possesses suitable functionality for pentultimate 7-aminoquinoline-5,8-quinone introduction [21b] and one in which the Friedlander condensation [29] could be anticipated to proceed uneventfully.

Consistent with expectations, condensation of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**5**) [21b] with methyl 2-acetylpyridine-6-carboxylate [30] [**6**, 4.0 equivalents of Triton B (*N*-benzyltrimethylammonium hydroxide) [31], tetrahydrofuran, 0° (1 hour), 25° (3 hours), 94-98%] provided 8-(benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline-6′-carboxylic acid (**7**) directly as the free carboxylic acid, Scheme I. *In situ*, methyl ester hydrolysis promoted by *N*-benzyltrimethylammonium hydroxide (Triton B) proved competitive with the base-promoted Friedlander condensation. Efforts to effect the condensation of **5** with **6** employing limiting quantities of base (Triton-B, 1.0 equivalents) or alternative conditions customarily employed to promote a Friedlander condensation failed to provide the methyl ester **8** in competitive conversions [32]. Optimization of the Friedlander condensation and concurrent, *in situ* methyl ester hydrolysis employing excess Triton-B (4.0 equivalents) provided the carboxylic acid **7** directly in excellent yield (94-98%). Fischer esterification of **7** (10% hydrochloric acid, methanol, 25°, 18 hours,

Scheme I [a]



[a] (a) 4.0 Equivalents of Triton B [*N*-benzyltrimethylammonium hydroxide, tetrahydrofuran, 0-25°, 4 hours, 98%. (b) 10% Hydrochloric acid, methanol, 25°, 18 hours, 85%. (c) Hydrogen bromide (g), methylene chloride, 60°, 10 hours, 97%. (c) 5.0 Equivalents of nitric acid, nitromethane, 0°, 1 hour. (e) Aluminum amalgam, tetrahydrofuran-water (10:1), 0°, 6 minutes. (f) 5.0 Equivalents of manganese dioxide, 35% sulfuric acid, 0°, 10 minutes, 33% from **9**. (g) 1.1 Equivalents of sodium azide, tetrahydrofuran-water, 25°, 21 hours, 89%. (h) 1.0 Equivalent of triphenylphosphine, methylene chloride, 25°, 10 minutes. (i) Acetic acid, water, tetrahydrofuran (3:2:3), 25°, 12 minutes, 56% from **13**. (j) 1.05 Equivalents of sodium dithionite, tetrahydrofuran-water (1:1), 25°, 0.5 hour. (k) 7.0 Equivalents of potassium hydroxide, 25°, 1 hour, 90% from **15**. (l) 20 Equivalents Fremy's salt, acetone-methanol:0.5*M* potassium dihydrogenphosphate, 25°, 5 hours, 32%.

85%) followed by *O*-debenzylation of **8** (hydrogen bromide (gas), methylene chloride, 60°, 7 hours, 94-97%) [33] provided methyl 7-bromo-8-hydroxy-2-(2'-pyridyl)quinoline-6'-carboxylate (**9**).

Extensive efforts to effect the direct oxidation of phenol **9** to the 7-bromoquinoline-5,8-quinone **12** employing conventional [34-36] and recent variants [37] of a Fremy's salt oxidation (potassium nitrosodisulfonate) [34] proved modestly successful. As a result of the modest conversion and the erratic nature (0-30%) of the direct oxidation of **9** [38-40] under even the best conditions devised, a dependable, three-step alternative for 7-bromoquinoline-5,8-quinone introduction was investigated. Nitration of the free phenol **9** provided the exceptionally insoluble nitrophenol **10** and subsequent, sequential aluminum amalgam reduction [41] and manganese dioxide oxidation [42] provided the reactive 7-bromoquinoline-5,8-quinone **12** as a yellow, crystalline solid. The combination of aluminum amalgam-manganese dioxide in the reduction (**10** → **11**) - oxidation (**11** → **12**) sequence detailed in scheme I proved more satisfactory and more convenient than efforts employing a sodium dithionite reduction [43] and those using a potassium nitrosodisulfonate [34] or chromic acid oxidation [37].

Conversion of 7-bromoquinoline-5,8-quinone **12** to the corresponding 7-aminoquinoline-5,8-quinone followed the approach developed in conjunction with efforts on the total synthesis of lavendamycin [21b]. Direct C-7 sodium azide displacement of the 7-bromoquinoline-5,8-quinone under carefully controlled experimental conditions in a reaction which is sensitive to the presence of excess sodium azide provided the 7-azidoquinoline-5,8-quinone **13**. Azide reduction, which was most effectively accomplished employing triphenylphosphine [44], provided methyl 7-amino-2-(2'-pyridyl)quinoline-5,8-quinone-6'-carboxylate (**15**) in a reduction which proceeds without competitive

quinone reduction and with the intermediacy of the stable, characterizable triphenylphosphine imine **14**. Efforts to promote the hydrolysis of **15** to provide **4** directly were unsuccessful due to predominant and competitive nucleophile addition to the AB quinoline-5,8-quinone system. *In situ* reduction of the quinone to the corresponding hydroquinone (**16**) followed by base-promoted methyl ester hydrolysis provided the desired carboxylic acid **4**. Oxidation of hydroquinone **17** to quinone **4** occurs upon workup and exposure to air [48].

In Vitro Cytotoxic and Antimicrobial Activity.

The *in vitro* antimicrobial assays were performed using an agar-dilution/streak assay against seven microorganisms: *Staphylococcus aureus* ATCC 13709, *Escherichia coli* ATCC 9637, *Salmonella gallinarum* ATCC 9184, *Klemsiella pneumoniae* ATCC 10031, *Mycobacterium smegmatis* ATCC 607, *Pseudomonas aeruginosa* ATCC 27853, and *Candida albicans* ATCC 10231 [45]. The results (MIC, μg/ml) are detailed in Table I. *In vitro* inhibitory concentration for 50% cell growth relative to untreated controls (IC_{50}, μg/ml) for B16 mouse melanoma, L1210 mouse leukemia, P388 mouse leukemia (9PS), and human epidermoid carcinoma of the nasopharynx (9KB) were performed following established protocols and the results are detailed in Table I. A comparison of the results obtained with streptonigrin and streptonigrin methyl ester (Table I, entry 1-2) reaffirm the potency conveyed by the streptonigrin free C-6′ carboxylic acid. The 7-aminoquinoline-5,8-quinone AB ring system is sufficient for observable activity (Table I, entry 3) and the potency is enhanced by its substitution with a 2-(2′-pyridyl) group (Table I, entry 4). In the *in vitro* cytotoxic cell culture assays, 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone proved equipotent with streptonigrin. Introduction of the C-6′ methoxycarbonyl group diminishes the antimicrobial and cytotoxic properties (Table I, entry 5). A loss of antimicrobial and cytotoxic activity was observed with **4** which accompanied the introduction of the C-6′ carboxylic acid (Table I, entry 6), onto 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone.

The observed *in vitro* testing results detailed in Table I and the lack of activity observed with **4**; a potential minimum, potent pharmacophore of the naturally-occurring antitumor-antibiotics streptonigrin and lavendamycin; indirectly substantiate the apparent importance of the streptonigrin C-ring N-1′ nitrogen *and/or* C-3′ amino substituent for observable activity. Thus, in contrast to observations associated with streptonigrin and lavendamycin in which the C-6′ carboxylic acid potentiates the antitumor, antimicrobial, and cytotoxic activity of the naturally-occurring antitumor-antibiotics, the C-6′ carboxylic acid of **4** diminishes the observed antimicrobial and cytotoxic properties of 7-amino-2-(2′-pyridyl)quinoline-5,8-quinone.

Table I

In Vitro Antimicrobial and Cytotoxic Activity of Natural and Synthetic Quinoline-5,8-quinones [45]

	Antimicrobial (MIC, μg/ml)						Cytotoxic (IC_{50}, μg/ml)		
	S. aureus ATCC 13709	*E. Coli* ATCC 9637	*S. gallinarum* ATCC 9184	*K. Pneumoniae* ATCC 10031	*M. smegmatis* ATCC 607	*C. Albicans* ATCC 10231	*P. aeruginosa* ATCC 27853	L-1210	B-16	9PS(P388)	9KB
Streptonigrin	< 0.1	6.25	1.56	0.1	1.56	12.5	6.25	0.61	0.48	0.045	0.0025
Streptonigrin methyl ester	> 100	> 100	> 100	> 100	> 100	> 100	> 100	3.1	1.5	0.22	0.53
7-Aminoquinoline-5,8-quinone	12.5	50	25	50	12.5	50	> 100	0.34	0.14	0.19	0.74
7-Amino-2-(2′-pyridyl)-quinoline-5,8-quinone	3.12	> 100	100	100	0.78	50	> 100	0.42	0.26	0.0023	0.10
15	6.25	> 50	> 50	50	6.25	> 50	> 50	0.40	0.90	3.9	0.17
4	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 10	> 10	> 10	> 10

Further studies on the identification of the structural features of streptonigrin and lavendamycin which are responsible for potentiation of the observed cytotoxic activity and their relationship to a chemical mechanism of action of streptonigrin are in progress.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra (pmr) were recorded on a Varian FT-80A, Varian XL-200, Nicolet NT-200, or Nicolet NT-470 and chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane (0.00 ppm). Infrared spectra (ir) were recorded on a Perkin Elmer 1420 or a Perkin Elmer 1710 Fourier transform spectrometer as potassium bromide pellets. Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Electron impact mass (eims) and chemical ionization mass spectra (cims) were recorded on a Varian CH-5 or a Finnegan 4000 spectrometer. High-resolution mass spectra (hrms) were recorded on a Kratos MS-50 spectrometer. Chromatography was performed on a 60-200 mesh silica gel. Tetrahydrofuran and ether were distilled from benzophenone ketyl. Methanol was distilled from magnesium methoxide. *N,N*-Dimethylformamide was distilled from calcium hydride. Methylene chloride was distilled from phosphorus pentoxide. All extraction and chromatographic solvents; ethyl acetate, hexane, and methylene chloride; were distilled prior to use. Activated manganese dioxide was obtained from Alfa Products and was dried (150°, 6-12 hours) prior to use. All reactions requiring anhydrous conditions and/or an inert atmosphere were performed under a positive pressure of nitrogen or argon.

Methyl 8-(Benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline-6′-carboxylate (**8**).

A solution of methyl 2-acetylpyridine-6-carboxylate (**6** [30], 123 mg, 0.69 mmole, 1.0 equivalent) in tetrahydrofuran (7 ml) was treated with a 40% methanolic solution of *N*-benzyltrimethylammonium hydroxide (Triton-B [31], 1.15 g, 2.75 mmoles, 4.0 equivalents) at 0° under nitrogen. A solution of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde (**5** [21b], 231 mg, 0.76 mmole, 1.1 equivalents) in tetrahydrofuran (1.0 ml) was added to the reaction mixture. The reaction mixture was stirred at 0° (1 hour) and at 25° (3 hours), diluted with saturated ammonium chloride (5 ml), and further diluted with water (20 ml). The precipitated white solid was collected by filtration, washed with water, *n*-hexane, and the solvent was removed *in vacuo* to afford the carboxylic acid **7** (280 mg, 299 mg theoretical, 94%, 94-98%) as a white solid, mp 215-216°; pmr (80 MHz, deuteriochloroform): δ 8.78 (1H, dd, J = 7.6, 1.4 Hz, C-5′H), 8.55 (1H, d, J = 8.7 Hz, C-4H), 8.33 (1H, d, J = 8.7 Hz, C-3H), 8.32 (1H, dd, J = 7.6, 1.4 Hz, C-3′H), 8.05 (1H, t, J = 7.6, 7.6 Hz, C-4′H), 7.77 (1H, d, J = 8.9 Hz, C-6H), 7.53 (1H, d, J = 8.9 Hz, C-5H), 7.30-7.75 (5H, m, aromatic H), 5.57 (2H, s, CH_2Ph); ir (potassium bromide): ν 3400, 3026, 1600, 1578, 1566, 1494, 1431, 1406, 1385, 1371, 1325, 1256, 1215, 1089, 964, 845, 783 cm^{-1}; eims m/e (relative intensity) 434/436 (M^+, 1/1, 3), 357/359 (1/1, 6); cims: (ammonia) m/e (relative intensity) 435/437 (M + 1, 1/1 base); hrms: m/e for $C_{22}H_{15}BrN_2O_3$, calculated 434.0266, found 434.0271.

The carboxylic acid **7** (208 mg, 0.48 mmole) was added to a stirred solution of 10% hydrochloric acid methanol (15 ml) at 0°. The reaction was stirred at 25° (18 hours) before the solvent was removed *in vacuo*. The crude reaction product was dissolved in methylene chloride (30 ml), washed with water (20 ml) and saturated aqueous sodium chloride (20 ml), dried (sodium sulfate), and concentrated *in vacuo*. Chromatography (silica gel, 1 × 20 cm 10% ethyl acetate-hexane eluant) afforded pure **8** (183 mg, 215 mg theoretical, 85%) as a white solid, mp 130.5-131.5°; pmr (80 MHz, deuteriochloroform): δ 8.77 (1H, d, J = 8.7 Hz, C-4H), 8.72 (1H, dd, J = 7.6, 1.3 Hz, C-5′H), 8.28 (1H, d, J = 8.7 Hz, C-3H), 8.18 (1H, dd, J = 7.6, 1.3 Hz, C-3′H), 7.93 (1H, t, J = 7.6, 7.6 Hz, C-4′H), 7.70 (1H, d, J = 8.8 Hz, C-6H), 7.48 (1H, d, J = 8.8 Hz, C-5H), 7.35-7.76 (5H, m, aromatic H), 5.58 (2H, s, CH_2Ph), 4.05 (3H, s, CO_2CH_3); ir (potassium bromide): ν 1733, 1604, 1588, 1496, 1455, 1374, 1323, 1252, 1143, 1091, 836, 727 cm^{-1}; eims: m/e (relative intensity) 448/450 (M^+, 1/1, 5), 371/373 (1/1, 13); cims: (ammonia) m/e (relative intensity) 449/451 (M + 1, 1/1, base); hrms m/e for $C_{23}H_{17}BrN_2O_3$, calculated 448.0422, found 448.0427.

Anal. Calcd. for $C_{23}H_{17}BrN_2O_3$: C, 61.48; H, 3.81; N, 6.24. Found: C, 61.21; H, 3.77; N, 6.01.

7-Bromo-8-hydroxy-2-(2′-pyridyl)quinoline-6′-carboxylate (**9**).

A solution of methyl 8-(benzyloxy)-7-bromo-2-(2′-pyridyl)quinoline-6′-carboxylate (**8**, 273 mg, 0.61 mmole) in methylene chloride (7 ml) saturated with hydrogen bromide gas was warmed at 60° for 10 hours in a sealed tube [33]. The reaction mixture was cooled and saturated sodium bicarbonate (5 ml) was added with stirring until the yellow suspension dissolved completely. The mixture was diluted with water (20 ml) and extracted with methylene chloride (3 × 15 ml). The combined organic extracts were dried (sodium sulfate), and the solvent was removed *in vacuo*. Trituration of the residue (hexane) afforded pure **9** (206 mg, 218 mg theoretical, 94%, 94-97%) as an off-white solid, mp 197-198°; pmr (470 MHz, deuteriochloroform): δ 8.77 (1H, d, J = 8.6 Hz, C-4H), 8.75 (1H, d, J = 8.0 Hz, C-5′H), 8.31 (1H, d, J = 8.6 Hz, C-3H), 8.22 (1H, d, J = 8.0 Hz, C-3′H), 8.06 (1H, t, J = 7.8, 7.8 Hz, C-4′H), 7.65 (1H, d, J = 8.8 Hz, C-6H), 7.30 (1H, d, J = 8.8 Hz, C-5H), 4.07 (3H, s, CO_2CH_3); ir (potassium bromide): ν 3380, 3076, 1732, 1584, 1494, 1460, 1440, 1308, 1247, 1166, 1115, 984, 835, 770 cm^{-1}; eims: m/e (relative intensity) 358/360 (M^+, 1/1, 90), 298/300 (1/1, base); cims: (ammonia) m/e (relative intensity) 359/361 (M + 1, 1/1 base); hrms m/e for $C_{16}H_{11}BrN_2O_3$, calculated 357.9953, found 357.9964.

Anal. Calcd for $C_{16}H_{11}BrN_2O_3$: C, 53.50; H, 3.09; N, 7.80. Found: C, 53.10; H, 3.07; N, 7.51.

Methyl 7-Bromo-2-(2′-pyridyl)quinoline-5,8-quinone-6′-carboxylate (**12**).

A stirred suspension of methyl 7-bromo-8-hydroxy-2-(2′-pyridyl)quinoline-6′-carboxylate (**9**, 205 mg, 0.57 mmole) in nitromethane (10 ml) was treated with a 1.0 *M* solution of nitric acid in nitromethane (2.90 ml, 2.90 mmole, 5 equivalents) at 0° under a nitrogen atmosphere and the mixture was stirred at 0° for 1 hour. The reaction mixture was diluted with water (100 ml) and extracted with methylene chloride (4 × 80 ml). The combined organic extracts were dried (sodium sulfate) and the solvent was removed *in vacuo*. Trituration of the crude product with *n*-hexane afforded methyl 7-bromo-8-hydroxy-5-nitro-2-(2′-pyridyl)quinoline-6′-carboxylate (**10**, 226 mg, 231 mg theoretical, 98%) as a yellow, insoluble solid, mp 217-218°; pmr (80 MHz, deuteriochloroform): δ 9.44 (1H, d, J = 9.2 Hz, C-4H), 9.02 (1H, d, J = 9.2 Hz, C-3H), 8.78 (1H, s, C-6H), 8.72 (1H, dd, J = 7.5, 1.3 Hz, C-5′H), 8.29 (1H, dd, J = 7.5, 1.3 Hz, C-3′H), 8.09 (1H, t, J = 7.5, 7.5 Hz, C-4′H), 4.08 (3H, s, CO_2CH_3); eims: m/e (relative intensity) 403/405 (M^+, 1/1, base); cims: (ammmonia) m/e (relative intensity) 404/406 (M + 1, 1/1, 72); hrms: m/e for $C_{16}H_{10}BrN_3O_5$, calculated 402.9804, found, 402.9812.

The nitrophenol **10** (20 mg, 0.050 mmole) was dissolved in tetrahydrofuran-water (3.3 ml, 10:1) and cooled to 0°. The mixture was treated with freshly prepared aluminum amalgam [41] (100 mg, 5 weight equivalents) for 6 minutes at 0°. The resulting reaction mixture was filtered through Celite. The Celite was washed with ethyl acetate (25 ml) and concentration of the filtrate afforded the crude aminophenol **11** (16.3 mg, 0.044 mole) as a brown solid.

Activated manganese dioxide (19 mg, 0.22 mmole, 5 equivalents) was added to a solution of crude **11** (16.3 mg, 0.044 mole) in aqueous sulphuric acid (35%, 1.5 ml) at 0°. The mixture was stirred at 0° for 10 minutes and filtered through Celite. The Celite was washed with water (20 ml) and methylene chloride (20 ml). The organic phase was separated and the aqueous layer was extracted with methylene chloride (2 × 10 ml). The combined organic layers were dried (sodium sulfate), and the solvent was removed *in vacuo*. Chromatography (siliga gel, 1 × 11.5 cm, 50% ethyl acetate-hexane eluant) afforded the pure 7-bromoquinoline-5,8-quinone **12** (6.0 mg, 0.016 mmole, 33% from **10**) as a yellow solid, mp 221-222°; pmr (80 MHz, deuteriochloroform): δ 9.02 (1H, d, J = 8.3 Hz, C-4H), 8.91 (1H, dd, J = 7.5, 1.5 Hz, C-5′H), 8.54 (1H, d, J = 8.3 Hz, C-3H), 8.25 (1H, dd, J = 7.5, 1.5 Hz, C-3′H), 8.05 (1H, t, J = 7.5, 7.5 Hz, C-4′H), 7.63 (1H, s, C-6H), 4.05 (3H, s, CO_2CH_3); ir (potassium bromide): ν

3057, 1720, 1696, 1664, 1580, 1458, 1434, 1316, 1302, 1294, 1247, 1136, 1119, 964, 842, 807, 745 cm^{-1}; cims: (ammonia) m/e (relative intensity) 357/377 (M + 2H + 1, base/80), 373/375 (M + 1, 20/base); hrms: m/e for $C_{16}H_9BrN_2O_4$, calculated 372.9824, found 372.9836.

Repetitive, comparable reactions (0.025-0.050 mmole) provided the 7-bromoquinoline-5,8-quinone **12** (24-33% overall from **9**).

Anal. Calcd. for $C_{16}H_9BrN_2O_4$: C, 51.49; H, 2.43; N, 7.51. Found: C, 51.24; H, 2.75; N, 7.15.

Methyl 7-Azido-2-(2'-pyridyl)quinoline-5,8-quinone-6'-carboxylate (**13**).

A stirred suspension of methyl 7-bromo-2-(2'-pyridyl)quinoline-5,8-quinone-6'-carboxylate (**12**, 24 mg, 0.064 mmole) in methylene chloride-water-methanol (0.65 ml, 9:2:2) was treated with sodium azide (4.6 mg, 0.071 mmole, 1.1 equivalents) at 25° under a nitrogen atmosphere and the mixture was stirred at 25° for 18 hours. The reaction mixture was diluted with water (20 ml), extracted with methylene chloride (3 × 10 ml), the combined organic extracts were dried (sodium sulfate), and the solvent was removed *in vacuo*. Rapid chromatography (silica gel, 1 × 11 cm, 30% ethyl acetate-hexane eluant) afforded pure **13** (18.0 mg, 21.6 mg theoretical, 84%) as a yellow-brown solid: mp 128-129°; pmr (80 MHz, deuteriochloroform): δ 9.00 (1H, d, J = 8.3 Hz, C-4H), 8.87 (1H, dd, J = 7.6, 1.5 Hz, C-5'H), 8.54 (1H, d, J = 8.3 Hz, C-3H), 8.24 (1H, dd, J = 7.6, 1.5 Hz, C-3'H), 8.04 (1H, t, J = 7.6, 7.6 Hz, C-4'H), 6.56 (1H, s, C-6H), 4.05 (3H, s, CO_2CH_3); ir (potassium bromide): ν 2120 (N_3), 1735, 1713, 1685, 1642, 1578, 1426, 1348, 1260, 985 cm^{-1}.

Similarly, a stirred suspension of **12** (5.0 mg, 0.013 mmole) in tetrahydrofuran-water (0.125 ml, 4:1) was treated with a solution of sodium azide (0.96 mg, 0.015 mmole, 1.1 equivalents) in 0.025 ml of water at 25° under a nitrogen atmosphere and was stirred at 25° for 21 hours. Chromatography (silica gel, 1 × 10.5 cm, 30% ethyl acetate-hexane eluant) afforded pure **13** (4.0 mg, 4.5 mg theoretical, 89%).

Methyl 7-Amino-2-(2'-pyridyl)quinoline-5,8-quinone-6'-carboxylate (**15**).

A stirred solution of **13** (18 mg, 0.054 mmole) in dry methylene chloride (1 ml) under a nitrogen atmosphere was treated with a solution of triphenylphosphine (14.1 mg, 0.054 mmole, 1.0 equivalents) in 0.5 ml of methylene chloride with stirring. Evolution of nitrogen was visible within 1 minute after addition of triphenylphosphine. After 10 minutes at 25° the solvent was removed *in vacuo*. Chromatography (silica gel, 1 × 9 cm, 40% ethyl acetate-hexane eluant) afforded the phosphine imine **14** (20 mg, 30.6 mg theoretical, 65%, 65-68%) as a red solid, mp 144-145°; pmr (80 MHz, deuteriochloroform): δ 8.81 (1H, d, J = 8.2 Hz, C-4H), 8.73 (1H, dd, J = 7.7, 1.5 Hz, C-5'H), 8.48 (1H, d, J = 8.2 Hz, C-3H), 8.16 (1H, dd, J = 7.7, 1.5 Hz, C-3'H), 8.01-7.25 (16H, m, C-4'H, aromatic H), 6.43 (1H, s, C-6H), 4.03 (3H, s, CO_2CH_3).

A suspensionof **14** (20 mg, 0.035 mmole) in 1.2 ml of tetrahydrofuran and 0.8 ml of water was treated with 1.2 ml of acetic acid and the solution was allowed to stir at 25° for 12 minutes. Chromatography (silica gel, 1 × 11 cm, 80-100% ethyl acetate-hexane gradient elution) and trituration of purified 7-aminoquinoline-5,8-quinone with ether to remove residual triphenylphosphine oxide afforded pure **15** (8.5 mg, 10.9 mg theoretical, 78%, 78-86%) as a red solid: mp > 250°; pmr (470 MHz, deuteriochloroform): δ 8.93 (1H, d, J = 8.3 Hz, C-4H), 8.85 (1H, d, J = 7.8 Hz, C-5'H), 8.55 (1H, d, J = 8.3 Hz, C-3H), 8.21 (1H, d, J = 7.8 Hz, C-3'H), 8.04 (1H, t, J = 7.8 Hz, C-4'H), 6.11 (1H, s, C-6H), 5.34 (2H, br s, NH), 4.05 (3H, s, CO_2CH_3); ir (potassium bromide): ν 3420, 3332, 1715, 1694, 1602, 1582, 1377, 1322, 1244, 1133, 830, 752 cm^{-1}; eims: m/e (relative intensity) 309 (M^+, 2), 251 (base); cims: (ammonia) m/e (relative intensity) 310 (M + 1, base); hrms: m/e for $C_{16}H_{11}N_3O_4$, calculated 309.0749, found 309.0746.

Anal. Calcd. for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.59; N, 13.59. Found: C, 62.40; H, 3.75; N, 13.26.

7-Amino-2-(2'-pyridyl)quinoline-5,8-quinone-6'-carboxylic Acid (**4**).

A stirred suspension of **15** (3.7 mg, 0.012 mmole) in 0.5 ml of tetrahydrofuran and 0.4 ml of water under a nitrogen atmosphere was treated with a solution of sodium dithionite (2.2 mg, 0.0126 mmole, 1.05 equivalents) in 0.1 ml of water at 25°. After 0.5 hour, 1 *N* aqueous potassium hydroxide (0.084 ml, 0.084 mmole, 7 equivalents) was added to the reaction mixture and stirring was continued at 25° for 1 hour. The reaction mixture was diluted with water (10 ml), acidified with the addition of 10% aqueous hydrochloric acid solution, and extracted with ethyl acetate (5 × 20 ml). The combined organic extracts were dried (sodium sulfate), and the solvent was removed *in vacuo*. The residue was washed with hexane to afford pure **4** (3.2 mg, 3.5 mg theoretical, 90%) as an orange solid, mp > 250°; pmr (470 MHz, deuteriodimethylsulfoxide): δ 8.88 (1H, d, J = 8.2 Hz, C-4H), 8.71 (1H, t, J = 8.1, 8.1 Hz, C-5'H), 8.48 (1H, t, J = 8.1, 8.1 Hz, C-3'H), 8.24 (1H, t, J = 8.1, 8.1 Hz, C-4'H), 8.19 (1H, d, J = 8.2 Hz, C-3H), 6.10 (2H, br s, NH_2), 5.91 (1H, s, C-6H); ir (potassium bromide): ν 3441, 3342, 1704, 1636, 1611, 1585, 1454, 1356, 1260, 1195, 1040, 996, 883, 782 cm^{-1}; cims: (ammonia) m/e (relative intensity) 298 (M + 2H + 1, base), 296 (M + 1, 42); hrms: m/e for $C_{15}H_9N_3O_4$, calculated 295.0593, found 295.0584.

Anal. Calcd. for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found: C, 61.22; H, 3.22; N, 14.02.

Acknowledgements.

This work was assisted financially by the National Institutes of Health (CA 42056) and the Alfred P. Sloan Foundation. We would like to thank Steven D. Drake of the Department of Medicinal Chemistry, University of Kansas for antimicrobial testing, Professor Paul A. Kitos of the Department of Biochemistry, University of Kansas for B16 and L1210 cell culture cytotoxicity testing and Linda Jacobsen of the Purdue University Cancer Center-Cell Culture Lab for 9PS (P388) and 9KB cell culture cytotoxicity testing.

REFERENCES AND NOTES

[1] National Institutes of Health research career development award recipient, 1983-1988 (CA 01134). Alfred P. Sloan research fellow recipient, 1985-1989.

[2] Streptonigrin isolation: K. V. Rao, and W. P. Cullen, *Antibiot. Ann., 950* (1959), and later shown to be identical with bruneomycin (*Actinomyces albus var. bruneomycini*); E. S. Kudrina, O. L. Olkhovatova, L. I. Murav'eva, and G. F. Gauze, *Antibiotiki,* **11**, 400 (1966); M. G. Brazhnikova, V. I. Ponomarenko, I. N. Kovsharova, E. B. Kruglyak, and V. V. Proshlyakova, *Antibiotiki,* **13**, 99 (1968); and rufochromomycin (*S. rufochromogenes*) *Chem. Abstr.,* **55**, 25158 (1961); Streptonigrin structure identification: K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.,* **85**, 2532 (1963); Streptonigrin single-crystal X-ray structure determination: Y.-Y. H. Chiu, and W. N. Lipscomb, *J. Am. Chem. Soc.,* **97**, 2525 (1975); Total Syntheses: S. M. Weinreb, F. Z. Basha, S. Hibino, N. A. Khatri, D. Kim, W. E. Pye, and T.-T. Wu, *J. Am. Chem. Soc.,* **104**, 536 (1982); A. S. Kende, D. P. Lorah, and R. J. Boatman, *J. Am. Chem. Soc.,* **103**, 1271 (1981); D. L. Boger, and J. S. Panek, *J. Am. Chem. Soc.,* **107**, 5746 (1985).

[3] Review: [a] S. J. Gould, and S. M. Weinreb, *Forschr. Chem. Org. Naturst.,* **41**, 77 (1982); [b] J. Hajdu, "Metal Ions in Biological Systems", Vol **19**, 1985, chapter 3, p 53; [c] J. W. Lown, "Bioorganic Chemistry", E. E. Van Tamelen, ed, Academic Press, New York, NY, 1977, pp 95-121; [d] B. K. Bhuyan, "Antibiotics", I. D. Gottlieb and P. D. Shaw, eds, Springer-Verlag, New York, NY, 1967, p 175, [e] J. W. Lown, *Mol. Cell. Biochem.,* **55**, 17 (1983).

[4] Streptonigrin toxicity: W. L. Wilson, C. Labra, and E. Barrist, *Antibiot. Chemother.,* **11**, 147 (1961); C. A. Hackethal, R. B. Golbey, C. T. C. Tan, D. A. Karnofsky, and J. H. Burchenal, *Antibiot. Chemother.,* **11**, 178 (1961).

[5] D. T. Kuang, R. M. Whittington, H. H. Spenser, and M. E. Patno, *Cancer,* **23**, 597 (1969); N. I. Nissen, T. Pajak, O. Glidewell, H. Blom, M. Flaherty, D. Hayes, R. McIntyre, and J. F. Holland, *Cancer Treatment Rep.,* **61**, 1097 (1977); R. J. Forcier, O. R. McIntyre, N. I. Nissen, T. F. Pajak, O. Glidewell, and J. F. Holland, *Med. Pediatr. Oncol.,* **4**, 351 (1978); P. Banzet, C. Jacquillat, J. Civatte, A. Puissant, J. Maral, C. Chastang, L. Israel, S. Belaich, J. C. Jourdain, M. Weil, and G. Auclerc,

Cancer, **41**, 1240 (1978); M. GoutLemerle, C. Rodary, and D. Sarrazin, *Arch. Fr. Pediatr.*, **33**, 527 (1976).

[6] Lavendamycin structure determination: T. W. Doyle, D. M. Balitz, R. E. Grulich, D. E. Nettleton, S. J. Gould, C.-h. Tann, and A. E. Moews, *Tetrahedron Letters*, **22**, 4595 (1981); Isolation, antimicrobial, antitumor testing: D. M. Balitz, J. A. Bush, W. T. Bradner, T. W. Doyle, F. A. O'Herron, and D. E. Nettleton, *J. Antibiot.*, **35**, 259 (1982); Total Syntheses: A. S. Kende, and F. H. Ebetino, *Tetrahedron Letters*, **25**, 923 (1984); S. Hibino, M. Okazaki, M. Ichikawa, K. Sato, and T. Ishizu, *Heterocycles*, **23**, 261 (1985); D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **50**, 5790 (1985); A. V. R. Rao, S. P. Chavan, and L. Sivadasan, *Tetrahedron*, **42**, 5065 (1986); Biosynthesis: W. R. Erickson, and S. J. Gould, *J. Am. Chem. Soc.*, **107**, 5831 (1985).

[7] N. R. Bachur, S. L. Gordon, and M. V. Gee, *Cancer. Res.*, **38**, 1745 (1978); N. R. Bachur, S. L. Gordon, M. V. Gee, and H. Kon, *Proc. Natl. Acad. Sci. USA*, **76**, 954 (1979).

[8] R. Cone, S. K. Hasan, J. W. Lown, and A. R. Morgan, *Can. J. Biochem.*, **54**, 219 (1976); No evidence was found for streptonigrin:DNA interaction in the presence or absence of copper(II).

[9] J. W. Lown, and S.-K. Sim, *Can. J. Biochem.*, **54**, 446 (1976).

[10] J. W. Lown, S.-K. Sim, and H.-H. Chen, *Can. J. Biochem.*, **56**, 1042 (1978).

[11] J. W. Lown, and S.-K. Sim, *Can. J. Chem.*, **54**, 2563 (1976).

[12] Divalent metal cations including manganese(II), zinc(II), cadmium(II), and copper(II) promote the association of streptonigrin with calf thymus DNA and enhance *Escherichia coli* antimicrobial activity, see: J. R. White, *Biochem. Biophys. Res. Commun.*, **77**, 387 (1977).

[13] K. Ishizu, H. H. Dearman, M. T. Huang, and J. R. White, *Biochim. Biophys. Acta*, **165**, 283 (1968); J. R. White, and H. H. Dearman, *Proc. Natl. Acad. Sci. USA*, **54**, 887 (1965).

[14] H. L. White, and J. R. White, *Mol. Pharmacol.*, **4**, 549 (1968); H. L. White, and J. R. White, *Biochim. Biophys. Acta*, **123**, 648 (1966).

[15] I. A. Shaikh, F. Johnson, and A. P. Grollman, *J. Med. Chem.*, **29**, 1329 (1986).

[16] For early descriptions of the reversible and irreversible binding of streptonigrin to DNA, see: N. S. Mizuno, and D. P. Gilboe, *Biochim. Biophys. Acta.*, **224**, 319 (1970); Yu V. Dudnik, G. G. Gauze, V. L. Karpov, L. I. Kozmyan, and E. Padron, *Antibiotiki*, **18**, 968 (1973); *Chem. Abstr.*, **80**, 105000e (1974).

[17] Streptonigrin forms a streptonigrin:zinc(II):DNA ternary complex (1:7:25 nucleotides) stable to dialysis and gel filtration chromatography, see: K. V. Rao, *J. Pharm. Sci.*, **68**, 853 (1979).

[18] J. Hajdu, and E. C. Armstrong, *J. Am. Chem. Soc.*, **103**, 232 (1981).

[19] Derivatives of streptonigrin. Isopropylazastreptonigrin: W. B. Kremer, and J. Laszlo, *Cancer Chemother. Rep.*, **51**, 19 (1967); N. S. Mizuno, *Biochem. Pharmacol*, **16**, 933 (1967); Streptonigrin methyl ester: reference 3, 20 and W. B. Kremer, and J. Laszlo, *Biochem. Pharmacol*, **15**, 1111 (1966); 7-Hydroxy or 7-methoxy desaminostreptonigrin: see reference 20. 6-Demethylstreptonigrin: M. M. Cohen, M. W. Shaw, and A. P. Craig, *Proc. Nat. Acad. Sci. USA*, **50**, 16 (1963); 7-(*N*-2',4'-dihydroxy-6'-methylbenzoyl)aminostreptonigrin: J. Rosazza, unpublished work: see reference 3a; Streptonigrin methyl ester, hydrazide, and related streptonigrin C-6' carboxylate amides: Y. Inouye, H. Okada, S. K. Roy, T. Miyasaka, S. Hibino, N. Tanaka and S. Nakamura, *J. Antibiot.*, **38**, 1429 (1985). Streptonigrone: A. J. Herlt, R. W. Rickards, and J.-P. Wu, *J. Antibiot.*, **38**, 516 (1985).

[20] K. V. Rao, *Cancer Chemother. Rep. Part 2*, **4** (3), 11 (1974); J. S. Driscoll, G. F. Hazard, Jr., H. B. Wood, Jr. and A. Goldin, *Cancer Chemother. Rep. Part 2*, **4** (2), 1 (1974).

[21] Streptonigrin partial structures, preparation and biological evaluation: Streptonigrin AB ring system (7-Amino-6-methoxyquinoline-5,8-quinone) T. K. Liao, W. H. Nyberg, C. C. Cheng, *J. Heterocyclic Chem.*, **13**, 1063 (1976); *Angew. Chem. Int. Ed. Engl.*, **6**, 82 (1967); Streptonigrin CD ring system (inactive): T. K. Liao, P. J. Wittek, and C. C. Cheng, *J. Heterocyclic Chem.*, **13**, 1283 (1976); *J. Org. Chem.*, **44**, 870 (1979); Streptonigrin ABC ring system: K. V. Rao, *J. Heterocyclic Chem.*, **14**, 653 (1977); K. V. Rao, and H.-S. Kuo, *J. Heterocyclic Chem.*, **16**, 1241 (1979); K. V. Rao, and P. Venkateswarlu, *J. Heterocyclic Chem.*, **12**, 731 (1975); K. V. Rao, *J. Heterocyclic Chem.*, **12**, 725 (1975); Streptonigrin AB and ABC ring systems: D. L. Boger, and M. Yasuda, *Heterocycles*, **24**, 1067 (1986); Streptonigrin ABCD ring system: A. S. Kende, and P. C. Naegely, *Tetrahedron Letters*, 4775 (1978); [b] Lavendamycin partial structures: Lavendamycin AB, ABC, and CDE β-carboline ring systems, D. L. Boger, S. R. Duff, J. S. Panek, and M. Yasuda, *J. Org. Chem.*, **50**, 5782 (1985); D. L. Boger, and J. S. Panek, *Tetrahedron Letters*, **25**, 3175 (1984); D. L. Boger, and M. Yasuda, *Heterocycles*, **24**, 1067 (1986).

[22] J. Renault, S. Giorgi-Renault, M. Baron, P. Mailliet, C. Paoletti, S. Cros, and E. Voisin, *J. Med. Chem.*, **26**, 1715 (1983); J. Renault, S. Giorgi-Renault, P. Mailliet, M. Baron, C. Paoletti, and S. Cros, *Eur. J. Med. Chem.*, **16**, 24 (1981); *ibid.*, **16**, 545 (1981); *ibid.*, **18**, 134 (1983).

[23] E. M. Hodnett, C. Wongwiechintana, W. J. Dunn, III, and P. Marrs, *J. Med. Chem.*, **26**, 570 (1983) and references cited therein.

[24] For example, see: A. Albert, "Selective Toxicity", 4th Ed, Chapman and Hall, London, England, 1973.

[25] R. W. Hay, and C. R. Clark, *J. Chem. Soc., Dalton Trans.*, 1866 (1977); The log k formation (K_F) for copper(II) complexation with 2-methoxycarbonyl-8-hydroxyquinoline is $> 2 \times 10^8$ (K_F 8-hydroxyquinoline = 5×10^{12}) and metal-carbonyl binding was indirectly observed.

[26] D. J. Creighton, J. Hajdu, and D. S. Sigman, *J. Am. Chem. Soc.*, **98**, 4619 (1976).

[27] D. S. Sigman, *Acc. Chem. Res.*, **19**, 180 (1986).

[28] C. V. Kumar, J. K. Barton, and N. J. Turro, *J. Am. Chem. Soc.*, **107**, 5518 (1985); J. K. Barton, and A. L. Raphael, *Proc. Natl. Acad. Sci. USA*, **82**, 6460 (1985).

[29] C. C. Cheng, and S. J. Yan, *Org. React.*, **28**, 37 (1982).

[30] Methyl 6-acetylpyridine-2-carboxylate was prepared from pyridine-2,6-dicarboxylic acid.

[31] Available from Aldrich Chemical Co.

[32] Additional conditions investigated include: 2.0 equivalents of sodium methoxide, tetrahydrofuran, 25°, 0.7 hour, 60% **8**.

[33] The reaction was run in a 2.0 ml resealable Kontes vial equipped with a Teflon seal/liner (50 mg, 1.5 ml, methylene chloride) or a 20 ml, thick-walled resealable, glass tube internally threaded on one end and sealed with a threaded, solid Teflon plug (273 mg, 7 ml methylene chloride). The vessels are available from Ace Glass Company.

[34] H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, **71**, 229 (1971).

[35] S. Hibino, and S. M. Weinreb, *J. Org. Chem.*, **42**, 232 (1977).

[36] K. V. Rao, *J. Heterocyclic Chem.*, **14**, 653 (1977).

[37] A. S. Kende, and F. H. Ebetino, *Tetrahedron Letters*, **25**, 923 (1984); A. S. Kende, F. H. Ebetino, R. Battista, D. P. Lorah, and E. Lodge, *Heterocycles*, **21**, 91 (1984).

[38] S. Hibino, M. Okazaki, M. Ichikawa, K. Sato, and T. Ishizu, *Heterocycles*, **23**, 261 (1985).

[39] J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).

[40] Treatment of **9** with lithium hydroxide provided 7-bromo-8-hydroxy-2-(2'-pyridyl)quinoline-6'-carboxylic acid (93%). Fremy's salt oxidation of the free carboxylic acid failed to provide the corresponding 7-bromoquinoline-5,8-quinone.

[41] E. J. Corey, and M. J. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965); A. I. Meyers, J. L. Durandetta, and R. Marava, *J. Org. Chem.*, **40**, 2025 (1975).

[42] A. R. MacKenzie, C. J. Moody, and C. W. Rees, *Tetrahedron*, **42**, 3259 (1986).

[43] K. V. Rao, *J. Heterocyclic Chem.*, **12**, 725 (1975).

[44] W. S. Mungall, G. L. Greene, G. A. Heavner, and R. L. Letsinger, *J. Org. Chem.*, **40**, 1659 (1975). E. J. Corey, B. Samuelsson, and F. A. Luzzio, *J. Am. Chem. Soc.*, **106**, 3682 (1984).

[45] Minimum Inhibitory Concentration (MIC μg/ml) were determined using the agar dilution/streak method, *cf.* L. A. Mitscher, R.-P. Leu, M. S. Bathala, W.-N. Wu, J. L. Beal, and R. White, *Lloydia*, **35**, 157 (1972), by Mr. Steven D. Drake, Department of Medicinal Chemistry, University of Kansas, IC_{50} (μg/ml, Inhibitory Concentration for 50% cell growth relative to untreated control) values for B-16 mouse melanoma [47] and Pro-

fessor P. Kitos, Department of Biochemistry, University of Kansas, using a previously detailed procedure, *cf.* D. L. Boger, L. A. Mitscher, M. D. Mullican, S. D. Drake, and P. A. Kitos, *J. Med. Chem.*, **28**, 1543 (1985); IC_{50} (μg/ml) values for P388 mouse leukemia (9PS) and human epidermoid carcinoma of the nasopharynx (9KB) were determined under the supervision of Linda Jacobsen, Purdue Cancer Center Cell Culture Lab, Purdue University, following the protocols [46] established by the National Institute of Health, National Cancer Institute.

[46] R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3** (2), 17-20, 59-61 (1972).

[47] J. A. Donoso, and R. H. Himes, *Cancer Biochem. Biophys.*, **7**, 133 (1984).