AN IMPROVED AND DIVERGENT INTRODUCTION OF THE STREPTONIGRIN AND LAVENDAMYCIN QUINOLINE-5,8-QUINONE AB RING SYSTEMS

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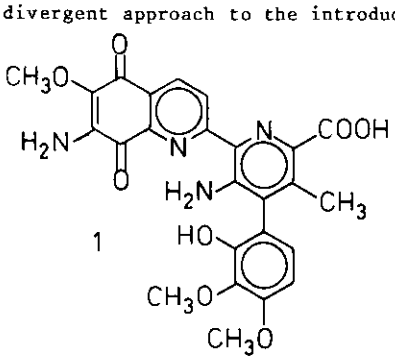
Abstract — An improved and divergent approach to the introduction of the streptonigrin and lavendamycin quinoline-5,8-quinone AB ring systems is detailed and is based on the selective and controlled nucleophilic substitution of common 7-bromoquinoline-5,8-quinone intermediates derived from the Friedländer condensation products of 2-amino-3-benzyloxy-4-bromobenzaldehyde.

Streptonigrin (**1**),[2] lavendamycin (**2**),[3] and streptonigrone (**3**),[4] three structurally and biosynthetically related natural products isolated from Streptomyces flocculus and Streptomyces lavendulae, each possess a characteristic and functionalized quinoline-5,8-quinone AB ring system.[4] Early efforts on streptonigrin[5,6] and more recent efforts on lavendamycin[5,7] have confirmed that the minimal structural component of the naturally occurring antitumor-antibiotics necessary for observed in vitro cytotoxic and antimicrobial activity consists of this substituted quinoline-5,8-quinone AB ring system. In conjunction with synthetic efforts on the total synthesis of streptonigrin,[8] streptonigrone[9] and lavendamycin[10] and in efforts designed to delineate the structural features of the naturally-occurring antitumor-antibiotics which potentiate the antitumor and antimicrobial activity of the quinoline-5,8-quinones we have devised an improved, divergent approach to the introduction of the required quinoline-5,8-quinone systems.[11]



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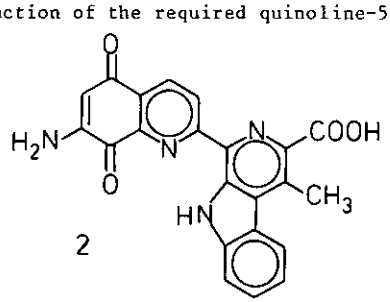

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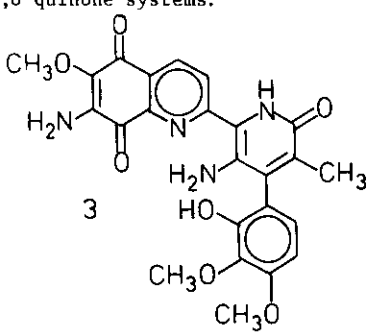

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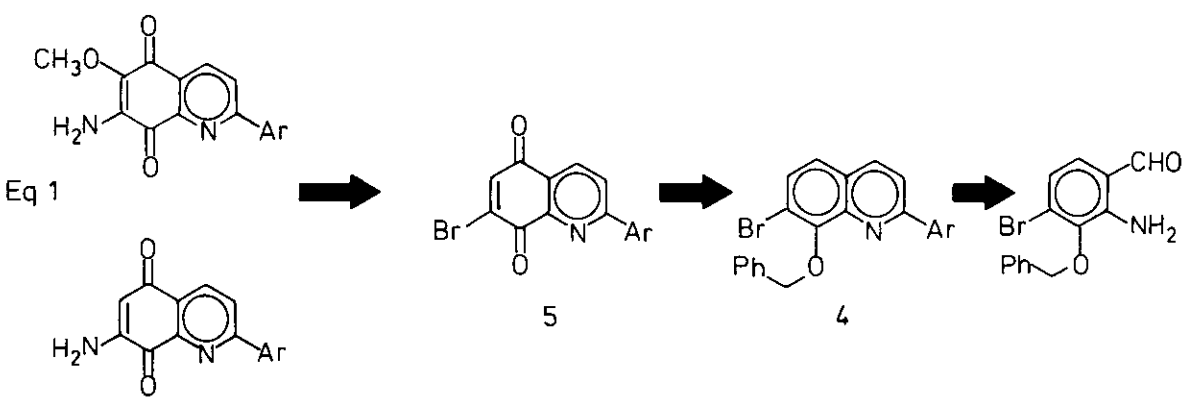
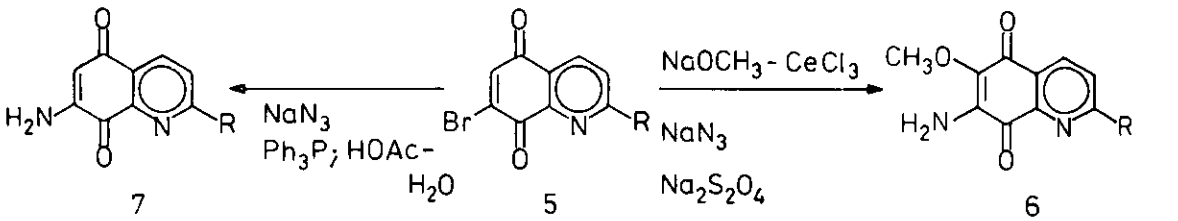
The approach which has been implemented in efforts required for the introduction of the lavendamycin 7-aminoquinoline-5,8-quinone AB ring system[10b] has been extended as detailed herein to provide an improved method for the introduction of the streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone AB ring system and is based on the selective and controlled nucleophilic substitution of common 7-bromoquinoline-5,8-quinone intermediates derived from the Friedländer condensation products of 2-amino-3-benzyloxy-4-bromobenzaldehyde,[10b] equation 1.[12] Consequently the approach permits the introduction of the streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone or the lavendamycin 7-aminoquinoline-5,8-quinone AB ring systems from common intermediates.



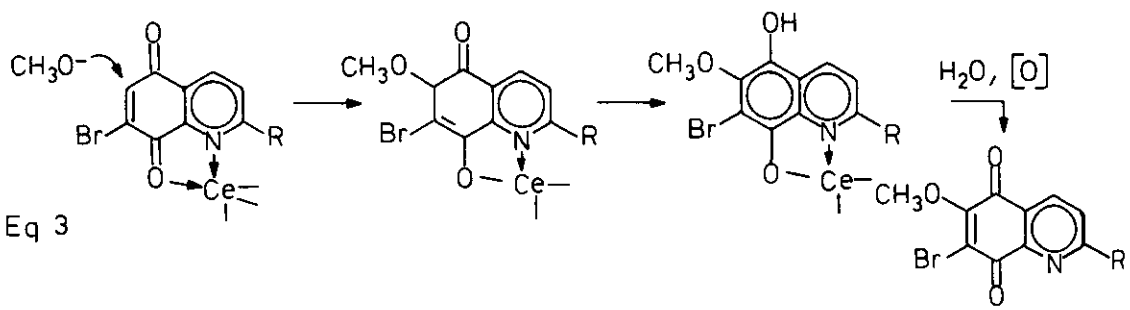
As detailed in earlier work,[10] direct azide displacement at C-7 of 7-bromoquinoline-5,8-quinones under carefully controlled conditions followed by subsequent triphenylphosphine mediated azide reduction, which proceeds without competing quinone to hydroquinone reduction and with the generation of a stable and isolable triphenylphosphine imine,[10b] permits the introduction of the 7-aminoquinoline-5,8-quinone system, equation 2.[13] In a complementary sequence, treatment of 7-bromoquinoline-5,8-quinones with cerium(III) methoxide in methanol leads to C-6 methoxy substitution in which cerium(III) cation coordination with the quinoline substrate serves to direct nucleophilic attack to C-6 and which proceeds with the apparent subsequent stabilization of the initial addition product, equation 2 - 3. This stabilization of the hydroquinone addition product prevents subsequent elimination - addition reactions observed when conventional conditions (sodium methoxide - methanol) are employed for the reaction. Table I summarizes a representative series of experimental results of this C-6 directed nucleophilic substitution of 7-bromoquinoline-5,8-quinones. The nucleophilic substitution reaction of methoxide does proceed at a decelerated and controlled rate in the presence of cerium(III) and the cerium(III) cation coordination does not, in these instances,[14] accelerate the apparent rate of nucleophilic addition.



Eq 2

Table I. C-6 Nucleophilic Substitution of 7-Bromoquinoline-5,8-quinones.

Substrate	Conditions		Product	% Yield
	equiv of NaOMe (equiv of $CeCl_3$)	temp, °C (time, h)		
5a[10b]	2-3	0 (0.1-0.3)	**8a**	0
	1.1	0 (1 min)		25
	2 (1, $Ce(NO_3)_3 \cdot 6H_2O$)	0 (2)		33
	3 (1, $CeCl_3 \cdot 7H_2O$)	0 (2), 25 (1)		40
	2 $LiOCH_3$ (1, $CuCl_2$)	25 (0.5)		21
	3 (1)	0 (0.5)		20
	2 (1)	0 (0.5), 25 (1)		45
5b[10b]	2 (1)	0 (1), 25 (5.5)	**8b**	39
	2 (1)	0 (1), 25 (10)		60



Eq 3

a, R = H b, R = Py 8

Implementation of this work in the preparation of the naturally occurring antitumor-antibiotics and related, synthetic quinoline-5,8-quinones is in progress.

EXPERIMENTAL

General Procedure for the Preparation of 7-Bromo-6-methoxyquinoline-5,8-quinones. Table I: A stirred solution of anhydrous cerous chloride and sodium methoxide in methanol was treated with substrate (**5a/5b**, 0.1 mmole) at 0 °C under a N_2 atmosphere and the mixture was stirred at 25 °C. The solution was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were washed with saturated aqueous NaCl (1 x 20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography (SiO_2, 1 x 8 cm, 40% EtOAc-hexane eluant) afforded the 7-bromo-6-methoxyquinoline-5,8-quinones **8a/8b** as yellow solids. For 7-bromo-6-methoxyquinoline-5,8-quinone (**8a**): mp 183-185 °C (lit.[13a] mp 185-187 °C dec.): ^1H NMR ($CDCl_3$) δ 9.04 (1H, dd, J = 4.7 Hz, 1.7 Hz, C-2 H), 8.43 (1H, dd, J = 7.9 Hz, 1.7 Hz, C-4 H), 7.69 (1H, dd, J = 7.9 Hz, 4.7 Hz, C-3 H), 4.35 (3H, s, OCH_3).

For 7-Bromo-6-methoxy-2-(2'-pyridyl)quinoline-5,8-quinone (**8b**): mp 178-179 °C dec.; ^1H NMR ($CDCl_3$) δ 8.84 (1H, d, J = 8.3 Hz, C-4 H) 8.59-8.78 (2H, m, C-3' H and C-6' H), 8.50 (1H, d, J = 8.3 Hz, C-3 H), 7.90 (1H, dt, J = 7.9 Hz, 1.6 Hz, C-4' H), 7.29-7.48 (1H, m, C-5' H), 4.36 (3H, s, OCH_3); IR(KBr) ν_{max} 3080, 2930, 1674, 1586, 1563, 1452, 1435, 1334, 1307, 1250, 1143, 1078 cm^{-1}; CIMS *m/z* (rel. intensity) 345/347 (M + 1, 1/1, base), 333(2.5), 267(4); HRMS *m/z* for $C_{15}H_9N_2O_3Br$ requires 343.9797; found 343.9789.

7-Amino-6-methoxyquinoline-5,8-quinone (6a): A stirred suspension of 7-bromo-6-methoxyquinoline-5,8-quinone (**8a**, 33 mg, 0.123 mmol) in 0.6 ml of THF was treated with a solution of sodium azide (8.8 mg, 0.135 mmol, 1.1 equiv) in 0.08 ml of H_2O at 25 °C under a N_2 atmosphere and the mixture was stirred at 25 °C for 15 h with protection from light. The suspension was poured onto 20 ml of H_2O and extracted with CH_2Cl_2 (3 x 15 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (SiO_2, 1 x 20 cm, 50% EtOAc-hexane eluant) afforded 23.0 mg (28.3 mg theor., 81%) of 7-azido-6-methoxyquinoline-5,8-quinone as an orange-yellow solid: mp 132-133 °C dec. (lit.[13a] mp 131.5-132 °C dec.); ^1H NMR ($CDCl_3$) δ 8.99 (1H, dd, J = 4.7 Hz, 1.6 Hz, C-2 H), 8.40 (1H, dd, J = 7.8 Hz, 1.6 Hz, C-4 H), 7.66 (1H, dd, J = 7.8 Hz, 4.7 Hz, C-3 H), 4.24 (3H, s, OCH_3).

A stirred suspension of the azodiquinoline-5,8-quinone (7.0 mg, 0.0304 mmol) in 0.15 ml of THF was treated with a solution of sodium hydrosulfite (18.5 mg. 0.106 mmol, 3.5 equiv) in 0.08 ml of H_2O at 25 °C under a N_2 atmosphere and the mixture was stirred at 25 °C for 2 h. The mixture was poured onto H_2O (15 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (SiO_2, 1 x 12 cm, 60% EtOAc-hexane eluant)

afforded 3.6 mg (6.2 mg theor., 58%) of **6a** as a purple solid: mp 201-202 °C dec. (lit.[13a] mp 202-203 °C dec.); ^{1}H NMR ($CDCl_3$) δ 8.88 (1H, dd, J = 4.7 Hz, 1.7 Hz, C-2 H), 8.37 (1H, dd, J = 7.8 Hz, 1.7 Hz, C-4 H), 7.60 (1H, dd, J = 7.8 Hz, 4.8 Hz, C-3 H), 5.21 (2H, br s, NH_2), 4.07 (3H, s, OCH_3).

7-Amino-6-methoxy-2-(2'-pyridyl)quinoline-5,8-quinone (6b). A stirred suspension of 7-bromo-6-methoxy-2-(2'-pyridyl)quinoline-5,8-quinone (**8b**, 11.5 mg, 0.0333 mmol) in 0.5 ml of DMF and 0.5 ml of methanol was treated with powdered sodium azide (2.4 mg, 0.0366 mmol, 1.1 equiv) at 25 °C under a N_2 atmosphere and the mixture was stirred at 25 °C for 16 h with protection from light. The crystals were collected, washed with 50% methanol, dried *in vacuo* to give the azidoquinoline-5,8-quinone as an orange solid (6.2 mg, 10.2 mg theor., 61%). The filtrate was extracted with CH_2Cl_2 (1 x 15 ml) and the extract was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (SiO_2, 1 x 9.5 cm, 50% EtOAc-hexane eluant) afforded an additional 3.9 mg (10.1 mg total, 99%) of the azidoquinoline-5,8-quinone as an orange solid: mp 136-138 °C (lit.[15a] mp 137-139 °C); ^{1}H NMR ($CDCl_3$) δ 8.82 (1H, d, J = 8.3 Hz, C-4 H), 8.60-8.83 (2H, m, C-3' H and C-6' H), 8.48 (1H, d, J = 8.3 Hz, C-3 H), 7.89 (1H, dt, J = 8.0 Hz, 1.6 Hz, C-4' H), 7.32-8.00 (1H, m, C-5' H), 4.26 (3H, s, OCH_3).

A stirred suspension of the azidoquinoline-5,8-quinone (7.0 mg, 0.0228 mmol) in 50% aqueous methanol (0.8 ml) was treated with sodium hydrosulfite (13.9 mg, 0.0798 mmol, 3.5 equiv) under a N_2 atmosphere at 25 °C for 21 h. The mixture was diluted with H_2O (20 ml) and extracted with EtOAc (3 x 15 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (SiO_2, 1 x 8.5 cm, 80% EtOAc-hexane eluant) afforded 4.2 mg (6.4 mg theor., 65%) of **6b** as a purple solid: mp 172-173.5 °C (lit.[15b] mp 172-174 °C); ^{1}H NMR ($CDCl_3$) δ 8.75 (1H, d, J = 8.2 Hz, C-4 H), 8.57-8.76 (2H, m, C-3' H and C-6' H), 8.46 (1H, d, J = 8.2 Hz, C-3 H), 7.87 (1H, dt, J = 7.7 Hz, 1.8 Hz, C-4' H), 7.34-7.97 (1H, m, C-5' H), 5.20 (2H, br s, NH_2), 4.10 (3H, s, OCH_3).

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11. For studies on the introduction of the streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone AB ring system, see: reference 5, 8 and 13, and references cited therein. For studies detailing the introduction of the lavendamycin 7-aminoquinoline-5,8-quinone AB ring system, see: reference 10, 13 and references cited therein.

12. Less succcessful direct and indirect approaches for the conversion of 7-bromoquinoline-5,8-quinones to the streptonigrin 7-amino-6-methoxyquinoline-5,8-quinone AB ring system are summarized below in Scheme I.

13. For the initial observation that azide will directly displace C-7 halides of 7-haloquinoline-5,8-quinones, see: (a) T. K. Liao, P. J. Wittek, and C. C. Cheng, J. Heterocycl. Chem., **1976**, 13, 1283; T. K. Liao, W. H. Nyberg, and C. C. Cheng, J. Heterocycl. Chem., **1976**, 13, 1063; Idem Angew. Chem. Int. Ed. Engl., **1967**, 6, 82. For further studies on this observation and its

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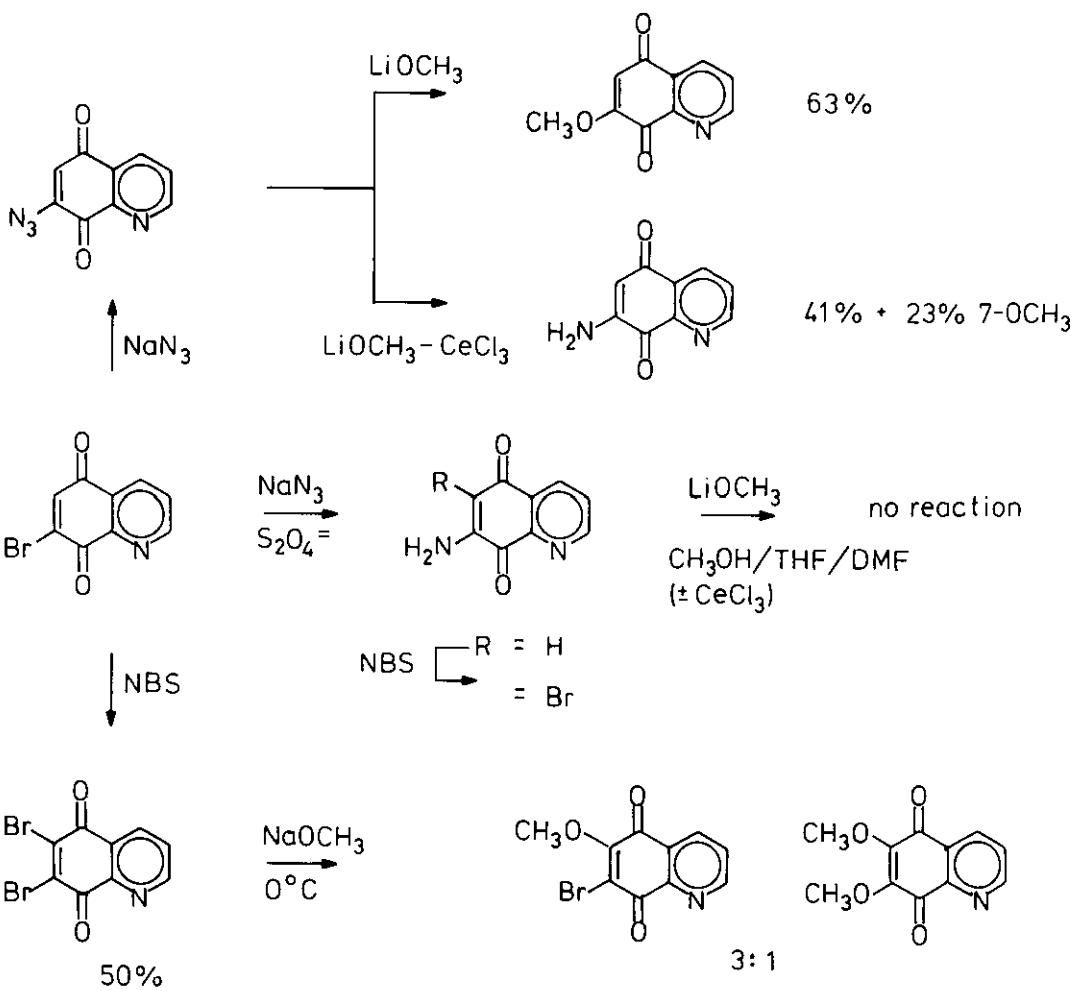
Scheme I



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