A Novel Synthesis of the Tetracyclic Ring System Present in Streptonigrin

Mark Cushman* and Jacob Mathew

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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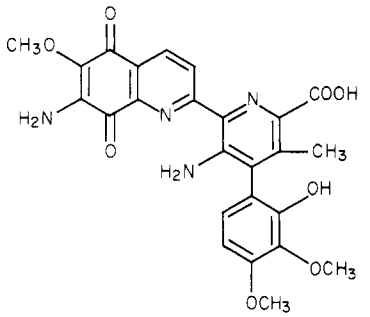
The reaction of the substituted (dicyanomethylene)benzopyran **6** with ammonia to afford the pyridine **7** has been utilized as the key step in the synthesis of the streptonigrin model compound **9**.

Streptonigrin is an antitumor antibiotic which was first isolated from the broth filtrates of *Streptomyces flocculus*.[1] It is identical with a substance known as bruneomycin which was subsequently obtained from *Actinomyces albus*.[2] The structure **1** of streptonigrin was established by



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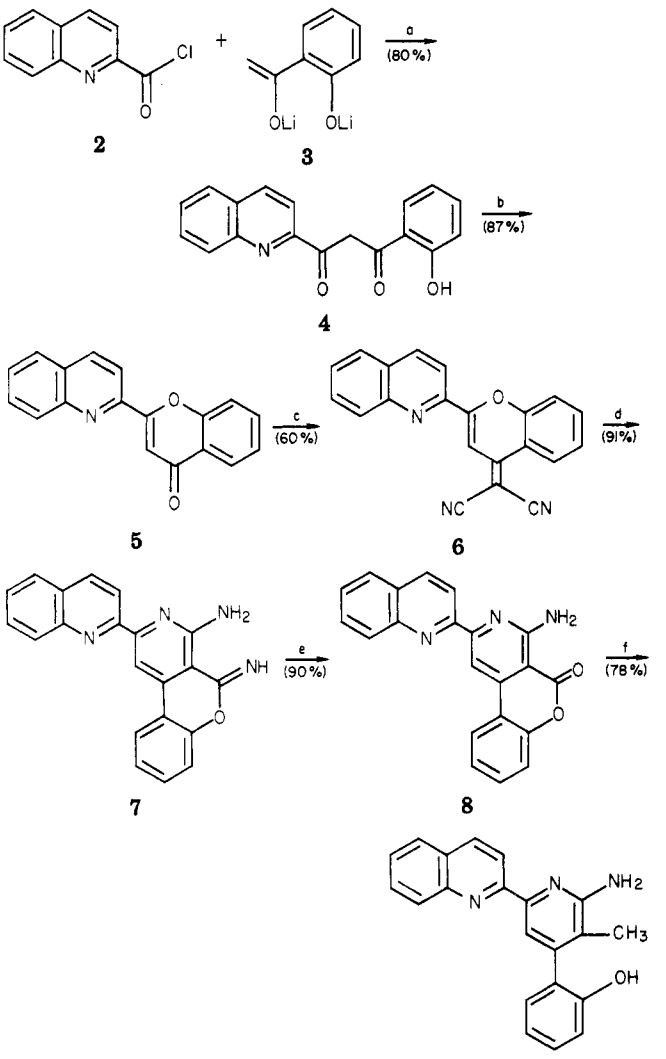
extensive chemical degradation studies[3] and confirmed by X-ray analysis[4] and ^{13}C NMR.[5] Its mode of action,[6] structure–activity relationships,[7] and metal binding properties[8] have been studied. At least 26 papers to date have focused on streptonigrin synthesis[9] and two total syntheses have now been reported.[10,11] Popular strategies have been based on the Ullmann coupling of aryl halides[12] and the Friedländer quinoline synthesis.[13] New strategies for streptonigrin synthesis remain of interest because they might lead to shorter and more practical routes. In addition, the preparation of structural analogues which may display a more favorable therapeutic index will also remain a significant objective because the suppression of hematopoietic tissue caused by streptonigrin itself precludes its clinical use. We now report a short route to the streptonigrin skeleton which utilizes the extension of a known conversion of flavones to pyridines.[14]

The C-acylation of the dilithium dianion **3**, derived from *o*-hydroxyacetophenone, with quinaldic acid chloride (**2**) yielded the β-diketone **4** (Scheme I).[15] Compound **4** underwent cyclodehydration to afford the chromone **5**. This preparation of the chromone **5** represents a substantial improvement over the published procedure which proceeds in only 11% yield from the acid chloride **2** and *o*-hydroxyacetophenone.[16] Although the chromone **5** did

Scheme I



2 **3** **4** **5** **6** **7** **8** **9**

[a] (1) THF, −78 °C (3 h); (2) 10% aqueous CH_3COOH. [b] H_2SO_4, $CHCl_3$, room temperature (15 min). [c] $H_2C(CN)_2$, $SOCl_2$, room temperature (6 h). [d] 30% aqueous NH_4OH, pyridine, reflux (15 min). [e] Concentrated HCl, CH_3COOH, reflux (2 h). [f] $NaAl(OCH_2CH_2OCH_3)_2H_2$, xylene–toluene, reflux (2.5 h).

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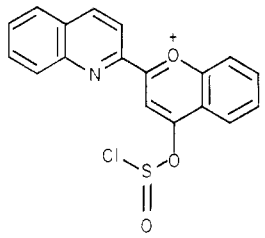
not react with malononitrile under a variety of basic conditions, the dicyanomethylene derivative **6** was obtained directly by using malononitrile in thionyl chloride. This reaction may proceed through intermediates **10** and **11**.



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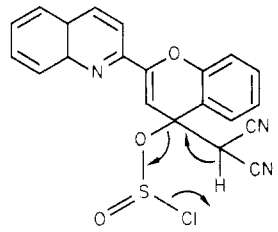

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The pyridine **7** was obtained on treatment of intermediate **6** with hot ammonium hydroxide.[14] Acid hydrolysis of the imino group of **7** afforded the lactone **8**, which was converted directly to the desired model compound **9** by using sodium bis(2-methoxyethoxy)aluminum hydride in refluxing xylene.[17] The methyl group of **9** is produced during hydride reduction under these conditions due to facilitation by the electron-donating ortho amino group.[18] The direct conversion of **8** to **9** could not be performed either with lithium aluminum hydride[18] or diborane.[19]

We are presently attempting to extend this approach to the synthesis of biologically active nitrogen analogues of streptonigrin as well as the natural product itself.

Experimental Section

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. The high-resolution 470-MHz spectra were obtained with a Nicolet NTC-470 spectrometer and the data accumulated by using 32 K free induction decays. Except where noted, the samples for NMR analyses were dissolved in $CDCl_3$. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Preparative thin-layer chromatography (TLC) was performed on Merck, silica gel 60 F-254. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a CEC 21-110 or a Du Pont 21-492 B double-focusing spectrometer using an ion-source temperature of 150–270 °C and an ionization potential of 70 eV. Organic solutions were dried over $MgSO_4$.

1-(2-Hydroxyphenyl)-3-(2-quinolyl)propane-1,3-dione (4). A solution of *o*-hydroxyacetophenone (13.62 g, 0.1 mol) in dry THF (200 mL) was added to a stirred solution of lithium diisopropylamide (0.25 mol, prepared in situ from diisopropylamine and *n*-butyllithium) in THF (50 mL) at −25 °C under a nitrogen atmosphere. The mixture was stirred at −25 °C for 1 h before it was cooled to −78 °C. A solution of freshly crystallized quinaldic acid chloride (18.00 g, 0.094 mol) in THF (100 mL) was added. Stirring was continued for 3 h at −78 °C followed by 12 h at room temperature. The THF was evaporated. The residue was diluted with 10% aqueous acetic acid and extracted with $CHCl_3$. The organic layer was washed with water and dried. Evaporation gave a brown powder which was triturated with dry acetone to yield the yellow diketone **4** (22 g, 80%): mp 147–148 °C (lit.[16] mp 148–149 °C).

2-(2-Quinoyl)chromone (5). Concentrated H_2SO_4 (18 mL) was added slowly to an ice-cooled, stirred solution of the diketone **4** (12.00 g, 41.2 mmol) in $CHCl_3$ (70 mL). The orange solution was stirred at room temperature for 15 min and then diluted with cold 10% aqueous KOH until the pH was 8–9. The mixture was extracted with $CHCl_3$ (3 × 150 mL). The combined extracts were washed with water (2 × 20 mL) and dried. Evaporation of the $CHCl_3$ gave a tan powder which was crystallized from acetonitrile (200 mL) to yield the chromone **5** (9.80 g, 87%): mp 201–202 °C (lit.[16] mp 200 °C).

4-(Dicyanomethylene)-2-(2-quinolyl)-4*H*-1-benzopyran (6). A mixture of the chromone **5** (8.22 g, 30.1 mmol) and freshly distilled malononitrile (2.10 g, 31.8 mmol) in thionyl chloride (70 mL) was stirred at room temperature for 6 h under a nitrogen atmosphere. The solution was then concentrated under vacuum. The residue was poured into 5% aqueous $NaHCO_3$ (300 mL) and the mixture diluted with water (100 mL). The brown solid was filtered and dried. Trituration with $CHCl_3$ (20 mL) and filtration gave a pale brown powder (7 g). This material was purified by column chromatography on silica gel (200 g), eluting with $CHCl_3$, to yield the dinitrile **6** (5.80 g, 60%): mp 288–289 °C; IR (KBr) 2200, 1620, 1500 cm^{-1}; NMR (470 MHz) δ 8.94 (d, 1 H, J = 9 Hz), 8.31 (d, 1 H, J = 9 Hz), 8.22 (s, 1 H), 8.18 (d, 1 H, J = 8 Hz), 8.11 (d, 1 H, J = 9 Hz), 7.84 (d, 1 H, J = 8 Hz), 7.75 (d of q, 2 H, J = 1, 8 Hz), 7.61 (m, 2 H), 7.46 (d of t, 1 H, J = 1, 8 Hz); mass spectrum, m/e (relative intensity) 321 (M^+, 100), 295 (38), 278 (20), 203 (28), 140 (25).

Anal. Calcd for $C_{21}H_{11}N_3O$: C, 78.49; H, 3.45; N, 13.08. Found: C, 78.22; H, 3.68; N, 13.14.

4-Amino-5-imino-2-(2-quinolyl)-4*H*-[1]benzopyrano[3,4-*c*]pyridine (7). A mixture of the dinitrile **6** (2.75 g, 8.56 mmol) and pyridine (50 mL) was heated on the steam bath for 5 min before addition of 30% aqueous NH_4OH (10 mL). The mixture was heated at reflux 15 min. Additional aqueous NH_4OH (10 mL) was then added and heating at reflux continued for 15 min. The mixture was cooled and filtered to yield a yellow powder. Crystallization from 2-ethoxyethanol yielded the pyridine **7** (2.65 g, 91%): mp 242–243 °C; IR (KBr) 3400, 3200, 1620, 1600 cm^{-1}; NMR (470 MHz) δ 8.57 (d, 1 H, J = 9 Hz), 8.48 (s, 1 H), 8.29 (d, 1 H, J = 9 Hz), 8.25 (d, 1 H, J = 8 Hz), 8.22 (d of d, 1 H, J = 1, 9 Hz), 7.87 (d, 1 H, J = 10 Hz), 7.77 (d of t, 1 H, J = 1, 7 Hz), 7.70 (br s, 1 H), 7.58 (d of t, 1 H, J = 1, 7 Hz), 7.46 (d of t, 1 H, J = 1, 7 Hz), 7.28 (d of t, 1 H, J = 1, 8 Hz), 7.14 (d of d, 1 H, J = 1, 8 Hz), 1.65 (br s, 2 H); mass spectrum, m/e (relative intensity) 338 (M^+, 100), 312 (30), 210 (6), 169 (8).

Anal. Calcd for $C_{21}H_{14}N_4O$: C, 74.54; H, 4.17; N, 16.56. Found: C, 74.36; H, 4.37; N, 16.71.

4-Amino-2-(2-quinolyl)-5*H*-[1]benzopyran[3,4-*c*]pyridin-5-one (8). A mixture of the pyridine **7** (2.65 g, 7.83 mmol), glacial acetic acid (26 mL), and concentrated HCl (2.6 mL) was heated on a steam bath under a nitrogen atmosphere for 2 h. It was then poured into a mixture of ice and 5% aqueous $NaHCO_3$. The yellow solid was filtered, washed with water, and dried. Crystallization from pyridine (25 mL) gave the lactone **8** (2.40 g, 90%): mp 276–277 °C; IR (KBr) 3400, 3300, 1700, 1600 cm^{-1}; NMR (470 MHz) δ 8.61 (s, 1 H), 8.57 (d, 1 H, J = 9 Hz), 8.30 (d, 2 H, J = 9 Hz), 8.26 (d, 1 H, J = 9 Hz), 7.87 (d, 1 H, J = 9 Hz), 7.77 (d of t, 1 H, J = 1, 7 Hz), 7.58 (q, 2 H, J = 8 Hz), 7.41 (d of t, 1 H, J = 1, 8 Hz), 7.37 (d, 1 H, J = 9 Hz), 1.55 (br s, 2 H), mass spectrum, m/e (relative intensity) 339 (M^+, 100), 310 (8), 169 (10), 129 (14).

Anal. Calcd for $C_{21}H_{13}N_3O_2$: C, 74.33; H, 3.86; N, 12.38. Found: C, 74.17; H, 3.97; N, 12.30.

2-Amino-3-methyl-4-(2-hydroxyphenyl)-6-(2-quinolyl)-pyridine (9). A suspension of the lactone **8** (0.25 g, 0.74 mmol) in xylene (6 mL) was treated dropwise with a 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride (1.20 g, 4.15 mmol) in toluene. A clear yellow solution resulted after vigorous gas evolution and was then heated for 2 h at reflux under a nitrogen atmosphere. The black solution was poured into 20% aqueous H_2SO_4 (2 mL) and the mixture was stirred for 5 min. It was then diluted with cold water (25 mL) and filtered. The orange powder was washed with water and Et_2O. It was then stirred with 10% aqueous KOH (20 mL) and filtered. The yellow filtrate was acidified with 2 N acetic acid to pH 5–6. The yellow powder which separated was extracted with Et_2O (2 × 25 mL). The extract was washed with water (2 × 10 mL), 5% aqueous $NaHCO_3$ (2 × 10 mL), and finally water (2 × 5 mL). The extract was dried and the solvent evaporated. The pale yellow powder was crystallized from Et_2O–hexane (1:1) to obtain the target molecule **9** (0.19 g, 78%): mp 172–173 °C; IR (KBr) 3480, 3400, 3050, 2925, 1600, 1550, 1500, 1430, 1270, 810, 730 cm^{-1}; NMR (470

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MHz) δ 8.33 (br d, 1 H, J = 9 Hz), 8.18 (d, 1 H, J = 9 Hz), 8.05 (d, 1 H, J = 9 Hz), 7.80 (m, 2 H), 7.66 (t, 1 H, J = 8 Hz), 7.51 (t, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 7.13 (d, 1 H, J = 9 Hz), 7.05 (s, 1 H), 7.03 (d, 1 H, J = 9 Hz), 6.98 (t, 1 H, J = 8 Hz), 1.92 (s, 3 H), 1.24 (s, 2 H); mass spectrum, m/e (relative intensity) 327 (M^+, 72), 312 (100), 149 (22).

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.83. Found: C, 76.93; H, 5.20; N, 12.54.

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Synthesis and Stereochemistry of Perhydrobenzo[*b*]thiophene Derivatives

P. N. Confalone,*[1] E. Baggiolini, B. Hennessy, G. Pizzolato, and M. R. Uskoković

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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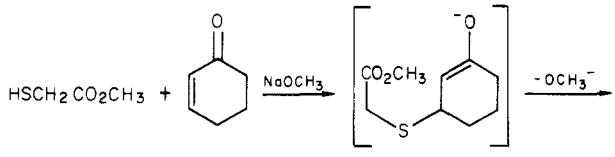
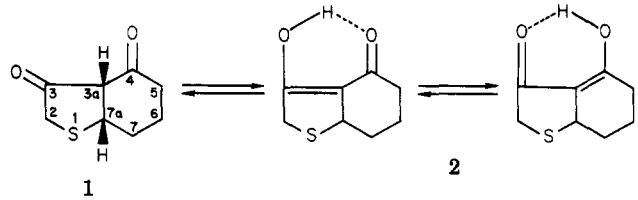
The synthesis of 2,3a,5,6,7,7a-hexahydro-3*H*,4*H*-benzothiophene-3,4-dione (1) and several of its transformation products is discussed. The stereochemistry of various intermediates containing up to four asymmetric centers is assigned on a mechanistic and spectroscopic basis and confirmed unequivocally by a full three-dimensional X-ray determination of 4α-acetamido-3aβ,4,5,6,7,7aβ-hexahydrobenzothiophen-3(2*H*)-one *anti*-oxime (**19**). The thermodynamic stability of the cis ring fusion in this bicyclic system is demonstrated by equilibration studies on the amido ketones **6** and **7**.

In connection with our program directed toward the total synthesis of the growth promotant biotin, we required the preparation of certain derivatives of perhydrobenzo[*b*]thiophene. This effort resulted in several important observations regarding the synthesis and stereochemistry of this class of compounds. We report these results which we believe to be of general interest.

Representatives of this system were found to be easily available from the crystalline diketone **1**, which is the major product of the base-catalyzed reaction between cyclohexenone and methyl mercaptoacetate. The presumed initial product of a Michael addition, the enolate anion **1a**, underwent a spontaneous cyclization with concomitant loss of methoxide to afford the observed product **1**. Spectroscopic data indicated that the diketone **1** is highly enolized and is best represented as the equilibrium mixture of ketone-enol tautomers **2**.

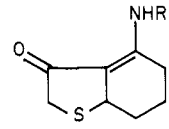


1a

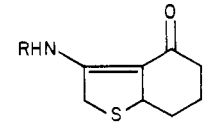


1 2

The diketone **1** reacted with nitrogenous nucleophiles such as ammonia and urethane to afford the keto-enamines **3** and **4**, respectively. Although spectroscopic data indicated that the reaction occurred regiospecifically at the cyclohexanone carbonyl, the evidence at this point did not exclude entirely the alternative structures **3a**. Catalytic hydrogenation of the keto-enamines **3** and **4** could not be cleanly effected. However, acylation of compound **3** with trifluoroacetic anhydride yielded the vinylogous imide **5**.

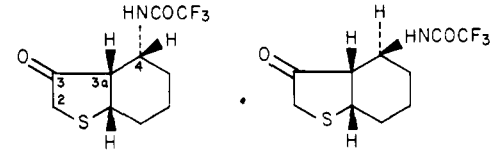


3, R = H
4, R = CO_2Et
5, R = $COCF_3$



3a, R = H, CO_2Et

The presence of the strongly electron withdrawing group on nitrogen deactivated its influence, and hydrogenation of **5** proceeded smoothly to afford the two C(4) epimeric ketones **6** and **7**. These assignments were in part based



6 **7**

upon the following NMR experiment. In CD_3ONa/CD_3OD both ketonic products exchanged exactly three protons. However, the ketones **6** and **7** were shown *not* to interconvert under these conditions. Therefore, the products are clearly epimeric at C(4) and not at the ring fusion, since a facile cis ⇌ trans equilibration would have occurred in the NMR tube if they were C(3a) epimers. The appearance of a two-proton singlet at δ 3.4 corresponding to the C(2) protons in the NMR spectra of **6** and **7** further supports the presence of the ketone at C(3). These conclusions were rigorously confirmed by an X-ray analysis on a later intermediate.

An interesting reaction of the diketone **1** and hydroxylamine was observed. The product was found to be the pseudo oxime **8**. This compound could be easily converted to either the pseudo oxime ether **9** by methanol/HCl or the pseudo oxime acetate **10** by acetic anhydride, respectively.

LAH reduction of the pseudo oxime **8** produced two crystalline amino alcohols **11** and **12** in a ratio of 6:1, respectively. These compounds were characterized as their

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