Synthetic Approaches to the Quinolinequinone System of Streptonigrin

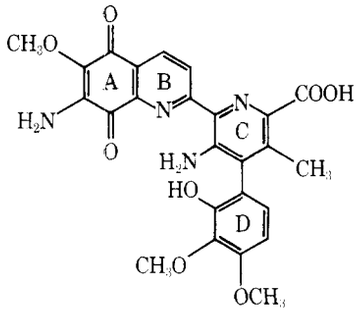
Satoshi Hibino and Steven M. Weinreb*[1]

Department of Chemistry, Fordham University, Bronx, New York 10458

Received July 1, 1976

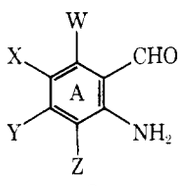
Model studies directed toward synthesis of the quinolinoquinone AB ring system of streptonigrin (1) using approaches based upon Friedlander quinoline synthesis are described. Aldehyde **6** has been prepared from *o*-vanillin, and several unsuccessful attempts were made to convert it to the model quinolinequinone **36.** A successful route to **36** was developed using the *o*-aminobenzaldehyde **30.** Friedlander condensation of **30** with 2-acetylpyridine produced quinoline **31,** which can be transformed in a few simple steps to quinolinequinone **36.** This last route should be applicable to a total synthesis of streptonigrin.

Streptonigrin, a complex antitumor antibiotic isolated[2] from *Streptomyces flocculus,* was shown by chemical studies[3] to have structure **1.** This structure was recently confirmed by

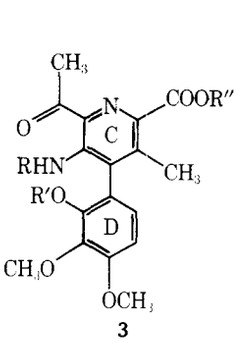


1

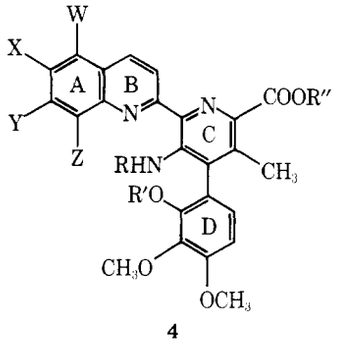
both x-ray analysis[4] and ^{13}C NMR.[5] Streptonigrin shows a broad spectrum of inhibition of several types of tumors,[6] and its mode of action has received considerable attention.[7] Efforts directed toward total synthesis,[8] as well as the synthesis of analogues[9] of the quinolinequinone portion of **1,** have appeared. We are attempting to develop a convergent total synthesis based on the Friedlander condensation of a appropriately substituted 2-acetylpyridine derivative **3** with a



2



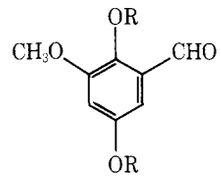
3



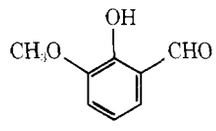
4

substituted *o*-aminobenzaldehyde **2** to provide streptonigrin via a quinoline **4.** Using a model series, we have tested such a synthetic strategy.

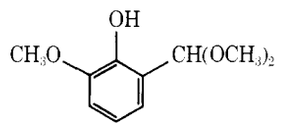
Initial studies were aimed at the incorporation of as many substituents as possible of the A ring of **1** into the *o*-aminobenzaldehyde **2.** An appropriate starting material, hydroquinone **5,** can be prepared in 15% yield by potassium persulfate oxidation of *o*-vanillin (**7**),[10] but a better route to **5** was developed. Fremy's salt oxidation of *o*-vanillin (**7**) gave no



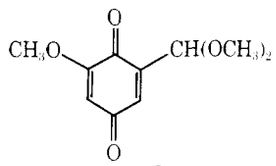
5, R = H
6, R = $CH_2C_6H_5$



7



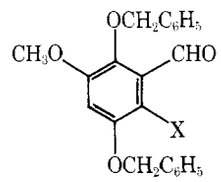
8



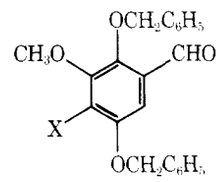
9

isolable quinone products, but the derived acetal **8** could be oxidized to quinone **9** in 61% yield. However, in view of the inconvenience in preparing and storing large amounts of Fremy's salt, along with the disadvantage of needing large volumes of solvent for this oxidation, an alternate procedure for conversion of **8** to **9** was developed. The oxidation of phenols to quinones using molecular oxygen catalyzed by bis(salicylidene)ethylenediiminocobalt(II) (salcomine) has been reported[11] but has not found wide use in synthesis. Oxidation of **8** in DMF by this method was very clean and produced quinone **9** (91% yield), which could be reduced using sodium hydrosulfite with concomitant hydrolysis of the acetal to give hydroquinone aldehyde **5.** Benzylation of **5** as described afforded the known dibenzyl ether **6.**[12]

Compound **6** was quite reactive toward electrophilic reagents, and upon treatment with cupric nitrate in acetic anhydride gave a single mononitro product, formulated initially as either **10** or **12.** It was not possible at this stage to assign a



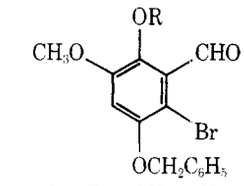
10, X = NO_2
11, X = NH_2



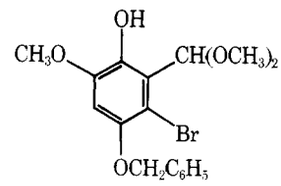
12, X = NO_2
13, X = NH_2

structure to the compound, but either **10** or **12** could be useful in preparing a substituted *o*-aminobenzaldehyde, since it is necessary to eventually introduce nitrogen into both unsubstituted positions of **6.** We were discouraged by the finding that this mononitro compound could not be reduced successfully to the amino aldehyde **11** or **13.**

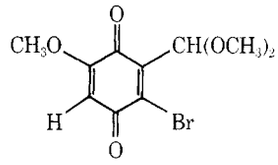
Bromination of aldehyde **6** was also facile and position selective, but proceeded with some ether cleavage to give a mixture of two monobromo products which were proved to have structures **14** and **15,** respectively. Conversion of **15** to the acetal **16,** followed by oxidation with silver(II) oxide,[13]



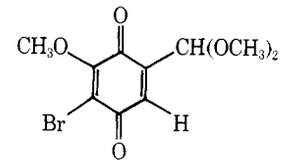
14, R = $CH_2C_6H_5$
15, R = H



16



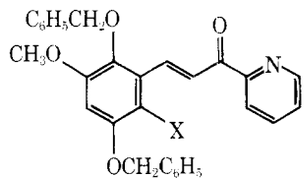
17



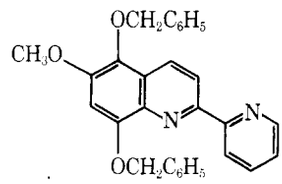
18

afforded a *p*-quinone which could be assigned structure **17** on the basis of its NMR spectrum. The acetal and vinyl protons in quinone **17** appeared as sharp singlets. In the isomeric quinone **18**, one would expect to observe a coupling between the same two hydrogens.[14] Although conditions could not be found for the bromination which prevented ether cleavage, phenol **15** could easily be rebenzylated to give diether **14.**

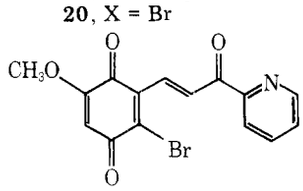
By analogy with the bromination product, it was reasonable to assign structure **10** to the mononitration product of aldehyde **6,** and we attempted a modification of the Friedlander synthesis[15] on this nitro aldehyde. Condensation of **10** with 2-acetylpyridine in the presence of sodium hydroxide gave chalcone derivative **19,** but all attempts at reduction of **19** to give pyridylquinoline **21** were unsuccessful.



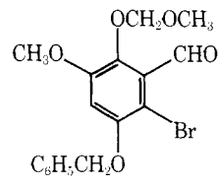
19, X = NO_2
20, X = Br



21

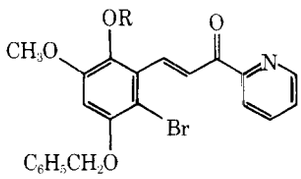


22

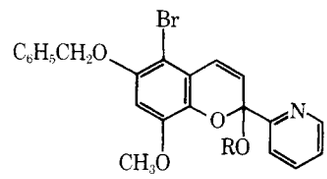


23

Similarly, bromoaldehyde **14** was condensed with 2-acetylpyridine to give chalcone **20.** We intended to convert this compound to quinone **22,** which on treatment with ammonia might go directly to pyridylquinone **33.** All attempts to remove the benzyl ether protecting groups of **22** to provide the corresponding hydroquinone failed. In an effort to circumvent this problem, hydroxy aldehyde **15** was converted to the methoxymethyl ether **23** and condensed with 2-acetylpyridine to give chalcone **24.** Hydrolysis of the methoxymethyl protecting group with dilute hydrochloric acid gave some of the desired phenol **25,** but primarily yielded the chromene **27.** This mixture of products was acetylated with acetic anhydride in pyridine and separated to afford acetates **26** and **28** in a 1:2 ratio. Although we had hoped to convert phenol **25** to quinone **22,** these difficulties prompted us to seek a different route to the streptonigrin quinolinequinone system.

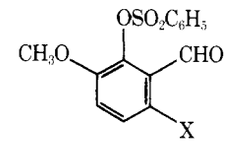


24, R = CH_2OCH_3
25, R = H
26, R = $COCH_3$

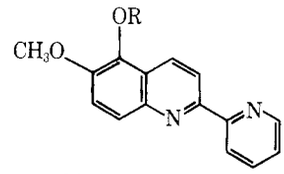


27, R = H
28, R = $COCH_3$

It was decided to use a simpler *o*-aminobenzaldehyde in the Friedlander reaction, and to later introduce the remaining A-ring substituents. The known nitroaldehyde **29,** prepared



29, X = NO_2
30, X = NH_2

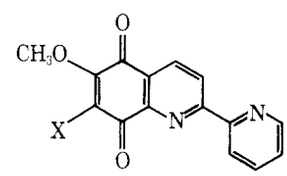


31, R = $SO_2C_6H_5$
32, R = H

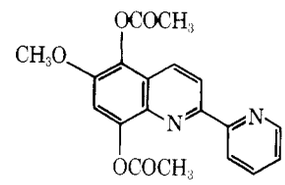
in two steps from *o*-vanillin (**7**), was reduced as described[16] to *o*-aminoaldehyde **30.** Condensation of this compound with 2-acetylpyridine using Triton B as catalyst gave a 1:4 mixture of pyridylquinolines **31** and **32,** respectively, which was separated by preparative TLC. Sulfonate **31** could be easily saponified to phenol **32,** but, from a preparative viewpoint, it was found easier to combine several steps, and it was possible to go directly from nitroaldehyde **29** to pyridylquinoline **32** without purification of intermediates in 33% overall yield.

Compound **32** could be oxidized to the quinolinequinone **33** by either Fremy's salt[9] or by the salcomine/oxygen procedure. In this case, Fremy's salt was the oxidant of choice, providing quinone **33** in 74% yield, whereas the salcomine/oxygen method gave only a 39% yield of **33.** The structure of **33** was confirmed by hydrogenation to the hydroquinone and acetylation to afford the quinoline diacetate **37.**

Treatment of **33** with chlorine in chloroform at 0 °C provided the chloroquinone **34** (78% yield).[17] Replacement of the



33, X = H
34, X = Cl
35 X = N_3
36, X = NH_2



37

chlorine of **34** by azide was a clean reaction, and azidoquinone **35** could be isolated in 88% yield. Reduction of the azide group of **35** with sodium hydrosulfite[18] afforded the purple aminoquinone **36** which had been previously prepared by Rao[9] via a different route.

This last sequence of reactions appears quite promising for constructing the AB system of streptonigrin and we feel that it is also compatible with substituents present in the C and D rings of **1.** Work is now in progress on synthesis of an acetylpyridine such as **3** in order to complete a total synthesis of streptonigrin.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrometer. NMR spectra were at 60 MHz on Varian A-60A or Perkin-Elmer R-12 spectrometers. Elemental analysis were done by Microtech Laboratories, Skokie, Ill. Merck silica gel 60 was used for column chromatography, and Merck PF_{254} silica gel was used for both analytical and preparative TLC. NMR spectra were determined in deuteriochloroform.

***o*-Vanillin Dimethyl Acetal (8).** A solution of *o*-vanillin (25 g, 0.16 mol), trimethyl orthoformate (120 g, 1.13 mol), and a catalytic amount of *p*-toluenesulfonic acid in absolute methanol was gently refluxed and stirred for 8 h. After removal of solvent, the residue was dissolved in ether, which was washed with brine twice, dried over Na_2SO_4, and

evaporated under reduced pressure. The residue was crystallized from ethyl acetate/hexane to give *o*-vanillin acetal **8** as colorless prisms (25.8 g, 79%): mp 73–74 °C; NMR δ 3.42 (s, 6 H), 3.88 (s, 3 H), 5.67 (s, 1 H), 6.7–7.1 (m, 3 H).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60,59; H, 7.12. Found: C, 60.87; H, 7.19.

2-Dimethoxymethyl-6-methoxy-*p*-benzoquinone (9). A. Oxidation of 8 with Salcomine/Oxygen. To a stirred mixture of *o*-vanillin acetal **8** (5 g, 25.3 mmol) and salcomine[11] (310 mg, 1 mmol) in DMF (40 ml) was introduced oxygen gas for 18 h. The mixture was poured onto crushed ice, and the crystals which precipitated were collected. The mother liquors were extracted with ether, and the organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crystalline material and the residue from the extraction were combined, the recrystallized from hexane to give the quinone **9** as yellow crystals (5 g, 91%): mp 86–87 °C; IR (Nujol) 1675, 1650 cm^{-1}; NMR δ 3.45 (s, 6 H), 3.87 (s, 3 H), 5.42 (broad s, 1 H), 5.92 (d, J = 2.5 Hz, 1 H), 6.82 (broad d, J = 2.5 Hz, 1 H).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.45; H, 5.71.

B. Oxidation of 8 with Fremy's Salt. A solution of *o*-vanillin acetal **8** (3 g, 15.2 mmol) in methanol (300 ml) was added to a solution of Fremy's salt[19] (13.8 g in 750 ml of 0.05 M KH_2PO_4). The mixture was stirred at room temperature for 2 h and extracted with ether. The ether layer was separated, washed with brine, dried over Na_2SO_4, and evaporated to dryness to give a dark, reddish solid (2 g, 61%). Recrystallization from hexane gave the same yellow quinone as in part A, mp 86–87 °C.

2,5-Dihydroxy-3-methoxybenzaldehyde (5). A solution of quinone **9** (4 g, 18.9 mmol) in ether (100 ml) was added to the solution of $Na_2S_2O_4$ (16 g, 92.0 mmol) in water (100 ml), which was stirred at room temperature for 2 h. The water layer was separated, acidified with concentrated HCl (60 ml), and extracted with ether, which was washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from benzene to give the hydroquinone **5** (1.5 g, 47%), mp 142–143 °C. This product was identical with an authentic sample prepared by the method of Merchant et al.[10]

2,5-Dibenzyloxy-3-methoxy-6-nitrobenzaldehyde (10). To a solution of 2,5-dibenzyloxy-3-methoxybenzaldehyde (**6**, 1.4 g, 4 mmol) in acetic anhydride was added cupric nitrate (1.5 g, 8 mmol) and then the solution was heated at 50–65 °C for 15 min. The mixture was poured onto ice, and was extracted with benzene. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel (60 g), which was eluted with benzene/hexane (3/1) to give the nitroaldehyde **10** (0.7 g, 44%). Recrystallization from chloroform/hexane gave pale yellow needles: mp 130–131 °C; IR (Nujol) 1670 cm^{-1}; NMR δ 3.90 (s, 3 H), 5.12 (s, 2 H), 5.19 (s, 2 H), 6.85 (s, 1 H), 7.43 (s, 10 H), 10.16 (s, 1 H).

Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87. Found: C, 67.05; H, 4.77.

2,5-Dibenzyloxy-3-methoxy-6-bromobenzaldehyde (14) and 2-Hydroxy-3-methoxy-5-benzyloxy-6-bromobenzaldehyde (15). To a stirred solution of 2,5-dibenzyloxy-3-methoxybenzaldehyde (**6**, 190 mg, 0.55 mmol) in chloroform (20 ml) was added dropwise a solution of an excess of bromine in chloroform (2 ml) at room temperature. After stirring for 1.5 h, the excess bromine was removed by washing with a solution of sodium bisulfite. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting mixture was separated by preparative TLC using benzene as development solvent to give 2,5-dibenzyloxy-3-methoxy-6-bromobenzaldehyde (**14**, 76.4 mg, 33%) and 2-hydroxy-3-methoxybenzyloxy-6-bromobenzaldehyde (**15**, 83.5 mg, 45%).

14. Recrystallization from ether/hexane gave pale yellow needles: mp 97–98 °C; IR (Nujol) 1680 cm^{-1}; NMR δ 3.85 (s, 3 H), 5.06 (s, 2 H), 5.18 (s, 2 H), 6.82 (s, 1 H), 7.3–7.7 (m, 10 H).

Anal. Calcd for $C_{24}H_{19}O_4Br$: m/e 426.0466. Found: m/e 426.0461.

15. Recrystallization from ether/hexane gave golden yellow needles: mp 86–87 °C; IR (Nujol) 1640 cm^{-1}; NMR δ 3.87 (s, 3 H), 5.17 (s, 2 H), 6.86 (s, 1 H), 7.53 (s, 5 H), 10.50 (s, 1 H).

Anal. Calcd for $C_{15}H_{13}O_4Br$: C, 53.43; H, 3.89. Found: C, 53.38; H, 3.88.

2-Hydroxy-3-methoxy-5-benzyloxy-6-bromobenzaldehyde Dimethly Acetal (16). A mixture of hydroxy aldehyde **15** (83.5 mg, 0.25 mmol), trimethyl orthoformate (1.8 g, 16.98 mmol), and a catalytic amount of *p*-toluenesulfonic acid in absolute methanol (10 ml) was gently refluxed overnight. After removal of solvent, the residue was dissolved in benzene, which was washed with brine, dried over $MgSO_4$, and evaporated to give dimethyl acetal **16** (83.3 mg, 87%). Recrystallization from ether gave pale yellow needles: mp 70–71 °C; NMR δ 3.53 (s, 1 H), 3.84 (s, 3 H), 5.11 (s, 2 H), 5.95 (s, 1 H), 6.67 (s, 1 H), 7.3–7.7 (m, 5 H).

Anal. Calcd for $C_{17}H_{19}O_5Br$: C, 53.28; H, 5.00. Found: C, 53.45; H, 5.11.

2-Dimethoxymethyl-3-bromo-6-methoxy-*p*-benzoquinone (17). A mixture of dimethyl acetal **16** (231 mg, 0.6 mmol), argentic oxide (1.489 g, 12 mmol), and 85% H_3PO_4 (1.5 ml) in dioxane (30 ml) was stirred at room temperature for 1 h.[13] The mixture was filtered, diluted with water, and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue was extracted with hexane, which was evaporated and the residue was purified by preparative TLC using benzene/acetone (95/5) as development solvent to give quinone **17.** Recrystallization from hexane gave yellowish-brown crystals (29.1 mg, 16.6%): mp 50–52 °C; IR ($CHCl_3$) 1635, 1650 cm^{-1}; NMR δ 3.53 (s, 6 H), 3.89 (s, 3 H), 5.67 (s, 1 H), 6.18 (s, 1 H).

Preparation of Chalcone 19. To a stirred solution of 2-acetylpyridine (31 mg, 0.26 mmol) in DME (1 ml) and 10% NaOH (1 ml) was added a solution of 2,5-dibenzyloxy-3-methoxy-5-nitrobenzaldehyde (**10**, 80 mg, 0.20 mmol) in DME (5 ml). The solution was stirred at room temperature for 2.5 h, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/ethyl acetate (9:1) as development solvent to give the chalcone **19** (24.1 mg, 24%). Recrystallization from chloroform/hexane gave pale yellow needles: mp 113–114 °C; IR (Nujol) 1610, 1575, 1520, 1320 cm^{-1}; NMR δ 3.88 (s, 3 H), 4.98 (s, 2 H), 5.21 (s, 2H), 6.67 (s, 1 H), 7.2–8.8 (m, 16 H).

Anal. Calcd for $C_{29}H_{24}N_2O_6$: m/e 496.16530. Found: m/e 496.16343.

Preparation of Chalcone 20. A solution of bromoaldehyde **14** (197.3 mg, 0.46 mmol), 2-acetylpyridine (121 mg, 1 mmol), and 10% NaOH (2 ml) in DME (10 ml) was stirred at room temperature for 18 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC using benzene/acetone (98/2) as development solvent to give chalcone **20.** Recrystallization from benzene/hexane gave yellow needles (159.2 mg, 67%): mp 127–128 °C; IR (Nujol) 1620, 1580 cm^{-1}; NMR δ 3.85 (s, 3 H), 4.97 (s, 2 H), 5.18 (s, 2 H), 6.70 (s, 1 H), 7.9–8.9 (m, 16 H).

Anal. Calcd for $C_{29}H_{24}NO_4Br$: C, 65.69; H, 4.53. Found: C, 65.38; H, 4.67.

Preparation of Methoxymethyl Ether 23. To a stirred mixture of 50% NaH (220 mg, 4.6 mmol, washed with absolute benzene to remove the mineral oil) and hydroxybenzaldehyde **15** (746.4 mg, 2.2 mmol) in DME (5 ml) was added a solution of excess chloromethyl methyl ether. After stirring for 0.5 h at room temperature, the mixture was basified with 5% NaOH and extracted with benzene. The benzene layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue crystallized from chloroform/hexane as pale yellow needles (667.4 mg, 76%): mp 87–88 °C; IR (Nujol) 1680 cm^{-1}; NMR δ 3.56 (s, 3 H), 3.72 (s, 3 H), 5.12 (s, 2 H), 5.18 (s, 2 H), 6.80 (s 1 H), 7.3–7.7 (m, 5 H), 10.47 (s 1 H).

Anal. Calcd for $C_{17}H_{17}O_5Br$: C, 53.56; H, 4.49. Found: C, 53.65; H, 4.46.

Preparation of Chalcone 24. A solution of bromoaldehyde **23** (667 mg, 1.7 mmol) in DME (15 ml) was added to a solution of 2-acetylpyridine (424 mg, 3.5 mmol) and 10% NaOH (4 ml) in DME (10 ml). The resulting solution was stirred at room temperature for 18 h and extracted with chloroform. The chloroform extract was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/ethyl acetate (95/5) as development solvent to give chalcone **24,** which was recrystallized from hexane as pale yellow prisms: mp 144–145 °C; NMR δ 3.50 (3 H, s), 7.79 (s, 3 H), 5.04 (s, 2 H), 5.14 (s, 2 H), 6.62 (s, 1 H), 7.3–8.9 (m, 11 H).

Anal. Calcd for $C_{24}H_{22}NO_5Br$: m/e 483.0679. Found: m/e 483.0667.

Chalcone 26 and Chromene 28. A solution of chalcone **24** (196 mg, 0.42 mmol) and 10% HCl (3 ml) in THF (10 ml) was stirred at room temperature for 1 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with brine, dried over Na_2SO_4, and evaporated to afford 151 mg of residue. This crude material was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) to give a mixture of **26** and **28** in a ratio of 1:2. This mixture was separated by preparative TLC using chloroform/ethyl acetate (95/5) as development solvent to give chalcone **26** (48 mg, 24%, R_f 0.40) and chromene **28** (90 mg, 45% R_f 0.24), respectively.

26. Recrystallization from ether gave pale yellow needles: mp 145 °C; IR (Nujol) 1760 cm^{-1}; NMR δ 2.37 (s, 3 H), 3.80 (s, 3 H), 5.17 (s, 2 H), 6.17 (s, 1 H), 8.18 (d, 1 H, J = 6 Hz), 7.3–8.8 (m, 10 H).

Anal. Calcd for $C_{24}H_{20}NO_5Br$: *m/e* 481.0522. Found: *m/e* 481.0498.

28. Recrystallized from ether/hexane: mp 155–157 °C; IR (Nujol) 1750 cm^{-1}; NMR δ 2.37 (s, 3 H), 3.80 (s, 3 H), 5.17 (s, 2 H), 6.17 (s, 1 H), 6.89 (d, 1 H, J = 12 Hz), 7.3–8.9 (m, 10 H).

5-Benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (31) and 5-Hydroxy-6-methoxy-2,2-pyridylquinoline (32). A solution of *o*-nitroaldehyde **29** (336 mg, 1 mmol) in THF was hydrogenated over 5% Pd/C (150 mg).[16] After absorbtion of the theoretical amount of hydrogen, the catalyst was removed and the filtrate was used in the Friedlander condensation immediately. To a stirred solution of 2-acetylpyridine (181 mg, 1.5 mmol) and 10 drops of Triton B was added a solution of the *o*-aminoaldehyde **30** in THF under a nitrogen atmosphere. The solution was stirred at room temperature for 15 h, diluted with water, neutralized with dilute hydrochloric acid, and extracted with chloroform. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude mixture was purified by preparative TLC using chloroform/methanol (98/2) as development solvent to give 5-benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31** 30 mg, 7.6% from nitro aldehyde **29**) and 5-hydroxy-6-methoxy-2,2-pyridylquinoline (**32,** 72 mg, 28.6% from nitro aldehyde **29**).

5-Benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31**): mp 93–95 °C (recrystallized from chloroform/hexane); NMR δ 3.71 (s, 3 H), 7.2–8.8 (m, 13 H); λ_{max} (MeOH) 346, 335, 275, 261 nm (log ϵ 4.81, 4.88, 5.37, 5.47).

Anal. Calcd for $C_{21}H_{16}N_2O_4S$: *m/e* 393.08584. Found: *m/e* 393.08643.

5-Hydroxy-6-methoxy-2,2-pyridylquinoline (**32**): mp 184–185 °C (recrystallized from ethanol); NMR δ 3.96 (s, 3 H), 7.39 (d, J = 9 Hz, 1 H), 7.74 (d, J = 9 Hz, 1 H), 7.2–8.7 (m, 6 H); λ_{max} (MeOH) 284, 271 nm (log ϵ 5.49, 5.44).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42, H, 4.79. Found: C, 71.55, H, 4.82.

Hydrolysis of 31 to 32. A stirred mixture of 5-benzenesulfonyloxy-6-methoxy-2,2-pyridylquinoline (**31,** 121.8 mg, 0.321 mmol) in 15% NaOH (5 ml) and ethanol (5 ml) was refluxed overnight. The mixture was cooled, diluted with water, and neutralized with dilute HCl. The aqueous solution was extracted with chloroform, which was washed with brine, dried over $MgSO_4$, and evaporated to dryness. Recrystallization from ethanol gave pyridylquinoline **32** as pale yellow needles, mp 184–185 °C. This product was identical with a sample prepared above.

Direct Synthesis of 5-Hydroxy-6-methoxy-2,2-pyridylquinoline (32). A stirred solution of *o*-nitroaldehyde **29** (5 g, 14.8 mmol) in THF was hydrogenated over 5% Pd/C (2.5 g).[16] After absorption of the theoretical amount of hydrogen, the mixture was filtered and the filtrate was used in the Friedlander condensation immediately. To a stirred solution of 2-acetylpyridine (2.7 g, 22.3 mmol) and 10 drops of Triton B was added a solution of the aminoaldehyde **30** in THF under an atmosphere of nitrogen. The solution was stirred at room temperature for 15 h, during which additional Triton B was added (10 drops, eight times). The reaction mixture was neutralized with dilute HCl and extracted with chloroform. The chloroform extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. A stirred mixture of the residue and 15% NaOH (100 ml) in ethanol (100 ml) was refluxed overnight. The solution was cooled, diluted with water, and washed with chloroform. The aqueous layer was separated, neutralized with dilute HCl, and extracted with chloroform. The chloroform extract was washed with brine, dried over Na_2SO_4, and evaporated to dryness. Recrystallization from ethanol gave pyridylquinoline **32** as pale yellow needles (1.22 g, 33%).

Preparation of 6-Methoxy-2,2-pyridylquinoline-5,8-dione (33). A solution of pyridylquinoline (**32,** 450 mg, 1.79 mmol) in methanol (250 ml) was added to a stirred solution of Fremy's salt[19] (6.5 g in 250 ml of 0.05 M KH_2PO_4). The solution was stirred for 15 h and diluted with water (500 ml), and the crystalline solid which separated was collected. Recrystallization from benzene/chloroform gave quinolinequinone **33** as yellow needles (350 mg, 74%): mp 260 °C dec; IR (Nujol) 1680, 1610 cm^{-1}; λ_{max} (MeOH) 298, 254 nm (log ϵ 5.44, 5.35); NMR δ 3.98 (s, 3 H), 6.49 (s, 1 H), 8.79 (d, J = 8 Hz, 1 H), 8.88 (d, J = 8 Hz, 1 H), 7.3–8.9 (m, 4 H).

Anal. Calcd for $C_{15}H_{10}N_2O_3$: *m/e* 281.0798. Found: *m/e* 281.0799.

B. Oxidation with Salcomine and Oxygen.[11] Into a stirred mixture of pyridylquinoline (**32,** 73 mg, 0.29 mmol) and salcomine[11] (35 mg, 0.11 mmol) in DMF (20 ml) was bubbled oxygen overnight at room temperature. The mixture was poured onto ice, and was extracted with chloroform. The chloroform layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by preparative TLC using chloroform/methanol (95/5) as development solvent to give quinolinequinone **33** (30 mg, 39%).

5,8-Diacetoxy-6-methoxy-2,2-pyridylquinoline (37). A suspension of 6-methoxy-2,2-pyridylquinoline-5,8-dione (**33,** 83.2 mg, 0.031 mmol) in ethanol (4 ml) and THF (6 ml) was hydrogenated over 5% Pd/$BaSO_4$ (40 mg). After absorption of the theoretical amount of hydrogen, the mixture was filtered, evaporated to dryness, and acetylated with acetic anhydride (5 ml) in pyridine (5 ml). After removal of the solvent, the residue was crystallized from ethanol/chloroform to give colorless needles (92 mg, 84%): mp 199–200 °C; IR (Nujol) 1770, 1750 cm^{-1}; NMR δ 2.50 (s, 3 H), 2.71 (s, 3 H), 4.01 (s, 3 H), 8.32 (d, J = 8.6 Hz, 1 H), 8.73 (d, J = 8.6 Hz, 1 H), 7.3–9.0 (m, 4 H).

Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58. Found: C, 64.71; H, 4.72.

7-Chloro-6-methoxy-2,2-pyridylquinoline-5,8-dione (34). To a stirred cold (0–5 °C) solution of quinolinequinone (**33,** 200 mg, 0.75 mmol) in chloroform (20 ml) was added a solution of ice-cold chloroform saturated with chlorine.[17] The solution was kept at 0–5 °C for 2 h with stirring. The solution was washed with water and dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was recrystallized from chloroform/hexane to give chloroquinolinequinone **34** as small yellow needles (175 mg, 78%): mp 188–191 °C; IR (Nujol) 1660 cm^{-1}; NMR δ 4.35 (s, 3 H), 8.51 (d, J = 8 Hz, 1 H), 8.78 (d, J = 8 Hz, 1 H), 7.3–8.8 (m, 4 H).

Anal. Calcd for $C_{15}H_9N_2O_3Cl$: *m/e* 300.0300. Found: *m/e* 300.0301.

7-Azido-6-methoxy-2,2-pyridylquinoline-5,8-dione (35). To a stirred mixture of 7-chloro-6-methoxy-2,2-pyridyl-5,8-quinolinedione (**34,** 150 mg, 0.5 mmol) in methanol (10 ml) and DMF (10 ml) was added powdered sodium azide at room temperature. After a few minutes, orange crystals began to separate. The stirred mixture was kept at room temperature for 16 h with protection from light. The crystals were collected, washed with 50% methanol, dried over $CaCl_2$ in a vacuum desiccator, and recrystallized from methanol/chloroform to give azidoquinolinequinone **35** as orange needles (143 mg, 88%): mp 137–139 °C; IR (Nujol) 2145, 1660 cm^{-1}; NMR δ 4.30 (s, 3 H), 8.55 (d, J = 8 Hz, 1 H), 8.76 (d, J = 8 Hz, 1 H), 7.3–8.8 (m, 4 H); λ_{max} (MeOH) 310, 279, 250 nm (log ϵ 5.16, 5.07, 5.14).

Anal. Calcd for $C_{15}H_9O_3$: C, 58.63; H, 2.95. Found: C, 58.72; H, 3.11.

7-Amino-6-methoxy-2,2-pyridylquinoline-5,8-dione (36). A stirred mixture of 7-azido-6-methoxy-2,2-pyridylquinoline-5,8-dione (**35,** 76.9 mg, 9.24 mmol) in 50% aqueous methanol (10 ml) was heated with sodium hydrosulfite (150 mg, 0.86 mmol) for 4 h. The mixture was cooled, diluted with water, and extracted with ethyl acetate. Evaporation of the solvent gave a dark, reddish solid which was recrystallized from chloroform/hexane to give 7-amino-6-methoxy-2,2-pyridylquinoline-5,8-dione (**36**) as a purple solid (30 mg, 44%): mp 173–175 °C (lit.[9] mp 172–174 °C); IR ($CHCl_3$) 3370, 3480, 1675, 1630 cm^{-1}; NMR δ 4.12 (s, 3 H), 5.30 (broad s, 2 H, disappeared on D_2O exchange), 8.48 (d, J = 8 Hz, 1 H), 8.78 (d, J = 8 Hz, 1 H), 7.3–8.9 (m, 4 H); λ_{max} (MeOH) 315, 274, 250 nm (log ϵ 5.26, 5.22, 5.43).

Anal. Calcd for $C_{15}H_{11}N_3O_3$: *m/e* 281.0798. Found: *m/e* 281.0799.

Acknowledgment. This work was supported by the National Science Foundation (MPS75-01558) and by Eli Lilly and Co. We are grateful to Professor R. K. Boeckman for bringing the salcomine/oxygen procedure to our attention. We thank Dr. C. E. Costello, MIT, for high-resolution mass spectra.

Registry No.—**5,** 2179-22-8; **6,** 2011-05-4; **8,** 60582-30-1; **9,** 60582-31-2; **10,** 60582-32-3; **14,** 60582-33-4; **15,** 60582-34-5; **16,** 60582-35-6; **17,** 60582-36-7; **19,** 60582-37-8; **20,** 60582-38-9; **23,** 60582-39-0; **24,** 60582-40-3; **26,** 60582-41-4; **28,** 60582-42-5; **29,** 2426-60-0; **30,** 60582-43-6; **31,** 60582-44-7; **32,** 60582-45-8; **33,** 60582-46-9; **34,** 60582-47-0; **35,** 60582-48-1; **36,** 57179-31-4; **37,** 60582-49-2; trimethyl orthoformate, 149-73-5; *o*-vanillin, 148-53-8; salcomine, 14167-18-1; Fremy's salt, 14293-70-0; 2-acetylpyridine, 1122-62-9; chloromethyl methyl ether, 107-30-2.

References and Notes

(1) Fellow of the A. P. Sloan Foundation, 1975–1977; Career Development Awardee of the National Heart and Lung Institute, 1975–1980.
(2) K. V. Rao and W. P. Cullen, *Antibiot. Annu.*, 950 (1959–1960).
(3) K. V. Rao, K. Biemann, and R. B. Woodward, *J. Am. Chem. Soc.*, **85,** 2532 (1963).
(4) Y.-Y. Chiu and W. N. Lipscomb, *J. Am. Chem. Soc.*, **97,** 2525 (1975).
(5) J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52,** 2331 (1974).

(6) J. J. Oleson, L. A. Calderella, K. J. Mjos, A. R. Reith, R. S. Thie, and I. Joplin, *Antibiot. Chemother. (Basel)*, **11**, 158 (1961); W. L. Wilson, C. Labra, and E. Barrist, *ibid.*, **11**, 147 (1961); T. J. McBride, J. J. Olesen, and D. Woolf, *Cancer Res.*, **26A**, 727 (1966).
(7) R. Cone, S. K. Hasan, J. W. Lown, and A. R. Morgan, *Can. J. Biochem.*, **54**, 219 (1976); J. W. Lown and S. Sim, *ibid.*, **54**, 446 (1976); and citations in these articles.
(8) (a) T. Kametani and K. Ogasawara, *Yakugaku Zasshi*, **95**, 985 (1966); (b) *ibid.*, **86**, 55 (1966); (c) T. Kametani, K. Ogasawara, and M. Shio, *ibid.*, **86**, 809 (1966); (d) T. Kametani, K. Ogasawara, and A. Kozuka, *ibid.*, **86**, 815 (1966); (e) T. Kametani, K. Ogasawara, A. Kozuka, and M. Shio, *ibid.*, **87**, 254 (1967); (f) T. Kametani, K. Ogasawara, M. Shio, and A. Kozuka, *ibid.*, **87**, 260 (1967); (g) T. Kametani, K. Ogasawara, A. Kozuka, and K. Nyu, *ibid.*, **87**, 1189 (1967); (h) T. Kametani, K. Ogasawara, and A. Kozuka, *ibid.*, **87**, 1195 (1967); (i) T. Kametani, A. Kozuka, and S. Tanaka, *ibid.*, **90**, 1574 (1970); (j) T. Kametani, S. Tanaka, and A. Kozuka, *ibid.*, **91**, 1068 (1971).
(9) (a) K. V. Rao, *J. Heterocycl. Chem.*, **12**, 725 (1975); K. V. Rao and P. Venkateswarlu, *ibid.*, **12**, 731 (1975).
(10) J. R. Merchant, R. M. Naik and A. J. Mountwalla, *J. Chem. Soc.*, 4142 (1957).
(11) H. M. VanDort and H. J. Geursen, *Recl. Trav. Chim. Pays-Bas*, **86**, 520 (1967).
(12) E. Hardegger, K. Steiner, E. Widmer, H. Corrodi, T. Schmidt, H. P. Knaepfel, W. Rieder, H. J. Meyer, F. Kugler, and H. Gempeler, *Helv. Chim. Acta*, **47**, 1996 (1964).
(13) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 227 (1972).
(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969. p 318.
(15) R. C. Elderfield, "Heterocyclic Compounds", Vol. 4, Wiley, New York, N.Y., 1952, p 73.
(16) W. Reid and H. Schiller, *Chem. Ber.*, **85**, 216 (1952).
(17) H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, **69**, 1133 (1950).
(18) J. L. Hartwell and L. F. Fieser, *J. Am. Chem. Soc.*, **57**, 1483 (1935).
(19) H. Zimmer, D. C. Lankin, and S. W. Horgan, *Chem. Rev.*, **71**, 229 (1971)

o-Chloranil–Azlactone Adducts and Their Conversions to Unsaturated Amino Acid Derivatives

J. M. Riordan,[1] M. Sato, and C. H. Stammer*

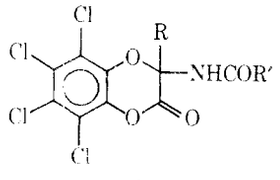
Department of Chemistry, University of Georgia, Athens, Georgia 30602

Received July 6, 1976

The synthesis of a series of tetrachlorodioxinones (1) and their conversions into α-substituted and dehydro amino acid derivatives is discussed. The first synthesis of a dehydro dipeptide derivative from a dipeptide is also reported.

The synthesis of dehydro amino acids and peptides has been of interest to us[2] and to others[3] for some time. In a recent preliminary report,[2c] we described the synthesis of some chlorodioxinones by the reaction of amino acid azlactones with *o*-chloranil. This paper describes that work in more detail and the conversion of the dioxinones into unsaturated amino acid derivatives.

When an acetic anhydride solution of an *N*-benzoyl amino acid was treated with an equimolar amount of *o*-chloranil at room temperature, the dioxinones (**1**, Table I) crystallized from the solution in 60–95% yields. If the azlactone was formed by treatment of the *N*-acyl amino acid with *N,N'*-dicyclohexylcarbodiimide in an inert solvent, the adducts (**1**) were



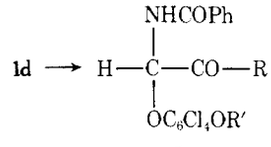
1

a, R = $PhCH_2$; R' = Ph
b, R = $(CH_3)_2CH$; R' = Ph
c, R = CH_3; R' = Ph
d, R = H; R' = Ph
e, R = Ph; R' = Ph
f, R = $(CH_3)_2CHCH_2$; R' = Ph
g, R = $PhCH_2$; R' = CH_3

formed in somewhat lower yields than when acetic anhydride was used. The off-resonance ^{13}C NMR spectra of **1a** and **1d** showed an 88.6-ppm singlet and a 75.2-ppm doublet for C-3 of **1a** and **1d**, respectively. These data along with infrared and ^1H NMR spectra confirmed the dioxinone structure of these compounds.

The chemistry of these compounds was also consistent with the dioxinone structure. They were rapidly converted into α-substituted amino acid derivatives when treated with nucleophiles such as CH_3O^-, $PhNH_2$, and $PhCH_2SH$ and these products are shown in Tables II and III.

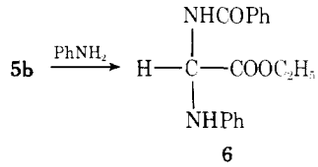
The chemistry of **1d**, formed from *N*-benzoylglycine, was considerably different from that of **1** derived from the other amino acids having an R group larger than hydrogen. The protio compound (**1d**) reacted with water, ethanol, and aniline very rapidly at room temperature giving the α-chlorophenoxy acid salt (**5a**), ester (**5b**), and anilide (**5c**) in excellent yields.



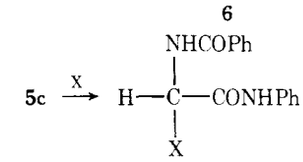
5

a, R = $O^-Et_3\overset{+}{N}H$; R' = H
b, R = OEt; R' = H
c, R = NHPh; R' = H
d, R = OEt; R' = CH_3

Since the α-chlorophenoxy group is an excellent leaving group, compounds of the type **5** could be converted into other α-substituted amino acid derivatives as shown below. In this way



6



7a, X = CH_3O
b, X = PhNH
c, X = $PhCH_2S$

compounds having *different* groups attached to the α- and carbonyl carbon atoms could be prepared. The ether (**5d**), formed by treatment of **5b** with diazomethane, reacted with anhydrous hydrogen fluoride in benzene solution to give an excellent yield of the known phenylglycine derivative **9**. This