A Practical Synthesis of Pyoluteorin

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A convenient, large-scale synthesis of the antibiotic pyoluteorin, 2,3-dichloro-5-(2',6'-dihydroxybenzoyl)-pyrrole (**1**), is described. A key step in the synthesis involved a Friedel-Crafts aroylation of pyrrole with 2,6-dimethoxybenzoyl chloride (**3**) in methylene chloride. The desired intermediate, 2-(2',6'-dimethoxybenzoyl)pyrrole (**4**), was obtained as the major product, along with a product of beta substitution (**6**). Compound **4** was converted to pyoluteorin (**1**) in four steps in an overall yield of 51%.

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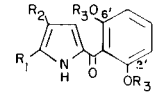
Pyoluteorin, 2,3-dichloro-5-[2',6'-dihydroxybenzoyl]pyrrole (**1**) is a naturally-occurring antibiotic produced by several strains of *Pseudomonas aeruginosa* (1-3). Since its discovery by Takeda in 1958 (1), it has been the object of numerous synthetic efforts (4-7), culminating with the synthesis of Davies and Hodge (8). In principle, all of these syntheses involve coupling a pyrrole moiety with a dihydroxybenzoic acid derivative. While this concept is straightforward, the yields of products resembling pyoluteorin usually were quite low. To obtain large amounts of this antibiotic for evaluation in our animal health screens, we have developed an improved synthesis of **1**, which is the topic of this paper.

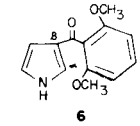
The molecular skeleton of **1** was constructed by a Friedel-Crafts aroylation of pyrrole (**2**) with 2,6-dimethoxybenzoyl chloride (**3**). Previously, this reaction had been studied by Durham, Hughes and Rees (9), who obtained 2-[2',6'-dimethoxybenzoyl]pyrrole (**4**) as the major product, along with a more polar product which they tentatively characterized as **5**, the product of disubstitution. We repeated the original work and obtained **4** as the major product along with the more polar product, which proved to be **6**, the product of beta substitution.

The isomeric pyrroles **4** and **6** were obtained in ratios which varied between 85:15 and 95:5 (α/β) in 58% overall yield. Numerous attempts to improve the yield of the α-isomer were unsuccessful. Heating pyrrole and 2,6-dimethoxybenzoyl chloride in refluxing xylenes in the absence of a Lewis acid catalyst led to extensive decomposition, with little **4** detected (10). However, during this study we found that omitting the catalyst and carrying out the reaction in methylene chloride at room temperature gave yields and ratios which were similar to what we saw with the catalyst present. This modification greatly simplified the isolation and purification of **4** and **6**. Although it has been reported that the Vilsmeier-Haack aroylation of pyrrole afforded a high yield of isomerically pure 2-benzoyl-pyrrole (11), we were unable to effect a reaction between pyrrole and the complex derived from *N*-2,6-dimethoxybenzoyl morpholide and phosphorusoxychloride.

Chlorination of **4** leads to incorporation of chlorine into the phenyl ring as well as the pyrrole ring (9). To circumvent this side reaction, **4** was demethylated using three equivalents of aluminum bromide (99% pure) in benzene at 25° to give **7** in 85% yield. Previous workers (8) had used a large excess of aluminum chloride in refluxing chlorobenzene to effect the **4** → **7** conversion, but in our hands, these conditions led to the formation of a small but significant amount of the monodealkylated product along with **7**. The demethylation of **4** was also accomplished, albeit in lower (55%) yield, by heating an intimate mixture of **4** and ten equivalents of freshly purified pyridine hydrochloride at 210° for two hours.



1, $R_1 = R_2 = Cl$; $R_3 = H$
4, $R_1 = R_2 = H$; $R_3 = CH_3$
5, $R_1 = H$; $R_2 = 2,6\text{-}(OCH_3)_2C_6H_3CO$; $R_3 = CH_3$
7, $R_1 = R_2 = R_3 = H$
8, $R_1 = R_2 = H$; $R_3 = COCH_3$
9, $R_1 = R_2 = Cl$; $R_3 = COCH_3$



6

After acylating **7**, using a procedure very similar to that previously reported (8), we were able to cleanly introduce two chlorine atoms into the pyrrole nucleus of **8**, using slightly more than two equivalents of *N*-chlorosuccinimide in refluxing chloroform. The combined yield of these two steps is *ca.* 60%. The pyrrole **9** which we obtained from the chlorination of **8** was identical in all respects (ir, nmr, uv, mass spectrum, m.p.) with the product obtained by Takeda from the acylation of pyoluteorin (1). The liberation of pyoluteorin (**1**) from **9** was accomplished in quantitative yield by simply warming a methanolic solution of **9**

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containing a drop of concentrated hydrochloric acid for a few hours.

EXPERIMENTAL (12)

2-[2',6'-Dimethoxybenzoyl]pyrrole (**4**) and 3-[2',6'-dimethoxybenzoyl]-pyrrole (**6**).

Under an atmosphere of dry nitrogen, thionyl chloride (445 g., 3.74 mole) was cooled to 15°, stirred and treated portionwise with 2,6-dimethoxybenzoic acid (200 g., 1.10 mole), then stirred at 25° for 1 hour. The excess thionyl chloride was evaporated *in vacuo* to give the crude 2,6-dimethoxybenzoyl chloride which was dissolved in methylene chloride (1.6 l.) and added to a solution of stannic chloride (647 g., 2.48 moles) in dry methylene chloride (1.6 l.) at 25°. Next, a solution of pyrrole (74.2 g., 1.10 moles) in methylene chloride (1.6 l.) was added slowly over 1 hour while maintaining the temperature at 15° with an ice-water bath. Following the addition, the reaction mixture was heated at reflux for 2 hours, and then cooled in an ice-water bath to 10° while 1*N* sulfuric acid (1.6 l.) was added over a 2 hour period. The organic layer was separated, the aqueous layer was washed with methylene chloride (850 ml.) and the combined organic layers were dried thoroughly over anhydrous magnesium sulfate. Evaporation of the dried solution gave a tan solid (216 g.) which contained the isomeric pyrroles **4** and **6**. This solid was dissolved in a minimum volume of chloroform and introduced onto a silica gel column (5 kg., 70-230 mesh). Elution with chloroform gave **4** (131.8 g., 52%); m.p. 192-195° [lit. (9) m.p. 191-193°]; ir (potassium bromide): 6.05 μ; nmr (DMSO-d_6): δ 10.59 (br s, NH), 7.36 (t, H_4'), 7.20 (d of d, H_5, $J_{4,5}$ = 2.6 Hz, $J_{3,5}$ = 1.1 Hz), 6.76 (d, H_3' and H_5'), 6.34 (d of d, H_3, $J_{3,5}$ = 1.1 Hz, $J_{3,4}$ = 3.4 Hz), 6.12 (d of d, H_4, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 2.6 Hz) and 3.68 (s, OCH_3); uv (ethanol): λ max 296 (ϵ 16,000) (13); ms: (70 eV) m/e 231 (M+), 165 [$(MeO)_2C_6H_3CO^+$].

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.62; N, 6.06. Found: C, 67.46; H, 5.51; N, 6.10.

Further elution with chloroform gave **6** (9.6 g., 4%), m.p. 200-202° (ethanol); ir (potassium bromide): 6.15 μ; nmr (DMSO-d_6): δ 10.57 (br s, NH), 7.32 (t, H_4') 7.00 (d of d, H_5, $J_{2,5}$ = 2.2 Hz), 6.80 (d of d, H_2, $J_{2,4}$ = 1.1 Hz, $J_{2,5}$ = 2.2 Hz), 6.65 (d, H_3' and H_5'), 6.40 (d of d, H_4, $J_{2,4}$ = 1.1 Hz, $J_{4,5}$ = 2.6 Hz) and 3.65 (s, OCH_3); uv (methanol): δ max: 249 (ϵ 10,000), 274 (ϵ 8,200)] (13); ms: (70 eV) m/e 231 (M+), 165.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.62; N, 6.06.Found: C, 67.31; H, 5.55; N, 5.96.

2-[2',6'-Dihydroxybenzoyl]pyrrole (**7**).

A solution of **4** (9.0 g., 0.038 mole) in benzene (1.3 l.) was added rapidly to a vigorously stirred solution of aluminum bromide (32.0 g., 0.12 mole) in benzene (350 ml.) at room temperature. The solution was then stirred for 5 hours. The reaction mixture was poured into a stirring mixture of ethyl acetate (350 ml.) and 3*N* hydrochloric acid (1.5 l.) and stirred for 30 minutes. After separating the organic layer the aqueous layer was washed with ethyl acetate (350 ml.) and the combined organic phase was then washed with two 250 ml. portions of water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give an amber oil. Hexane (500 ml.) was added to this oil to induce crystallization. Filtration of the solid gave **7** (6.62 g., 85%), m.p. 140-142° (lit. (1) m.p. 142-143°); nmr (DMSO-d_6): δ 13.40 (br s, NH), 9.63 (br s, OH), 7.08 (d of d, H-4'), 7.06 (m, pyrrole H), 6.40 (m, pyrrole H), 6.36 (d, H-3' and H-5') and 6.13 (m, pyrrole H).

2-(2',6'-Dihydroxybenzoyl)pyrrole *O,O*-Diacetate (**8**).

Triethylamine (58 ml., 0.42 mole) was added dropwise over a 5 minute period to a stirred solution of **7** (38.6 g., 0.19 mole) in ethyl acetate (2 l.). After 10 minutes, the reaction mixture was cooled in an ice bath, then acetyl chloride (29.7 ml., 0.42 mole) was added dropwise over a 20 minute period. When the addition was complete, the ice bath was removed and the reaction was allowed to continue for 2 hours at 25°. The reaction mixture was poured into ice cold 1*N* hydrochloric acid (2 l.), the organic layer was separated, washed with a saturated solution of sodium chloride, then dried over anhydrous sodium sulfate. After evaporating the solvent *in vacuo* the residue was recrystallized from ether/hexane to give **8** (47.0 g., 86%), m.p. 108-110° [lit. (1) m.p. 110-111°].

Pyoluteorin *O,O*-Diacetate (**9**).

A solution of **8** (52.8 g., 0.184 mole) and *N*-chlorosuccinimide (54.05 g., 0.405 mole) in chloroform (500 ml.) was heated at reflux for 3 hours, allowed to cool to room temperature, and then washed with two 500 ml. portions of saturated aqueous sodium bicarbonate. After removing the solvent *in vacuo*, the residue was recrystallized from ether to give **9** (48.4 g., 74%), m.p. 208-210° [lit. (1) m.p. 207-208°]; nmr (DMSO-d_6): δ 13.45 (br s, NH), 7.65 (d of d, H-4'), 7.20 (d, H-3' and H-5'), 6.40 (d, H-4), and 2.10 (s, $OCOCH_3$).

Pyoluteorin (**1**).

A stirred solution of pyoluteorin *O,O*-diacetate (**9**, 48.4 g., 0.136 mole) in methanol (750 ml.) containing concentrated hydrochloric acid (1 ml.) was heated at reflux for two hours. After allowing the reaction mixture to cool to room temperature the solvent was evaporated *in vacuo*, the residual yellow solid was triturated with water, filtered and air-dried to give pyoluteorin (**1**, 35.3 g., 95%), m.p. 174-176° dec. [lit. (1) m.p. 174-175°]; nmr (DMSO-d_6): δ 13.10 (br s, NH), 9.50 (br s, OH), 7.03 (d of d, H_4'), 6.43 (s, H-4) and 6.38 (d, H_3' and H_5').

Anal. Calcd. for $C_{11}H_7NO_3Cl_2$: C, 48.53; H, 2.57; N, 5.15. Found: C, 48.37; H, 2.88; N, 5.26.

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