Synthesis of Heterocyclic Compounds Related to Fredericamycin A – the Cyclopent[*g*]isoquinoline System

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A synthetic route is described to compounds **9** and **10**, which resemble the cyclopent[*g*]isoquinoline system of the antitumor agent, Fredericamycin A. The method is based upon directed lithiation of the pyridine **6** and conjugate addition to 2-cyclopenten-1-one. Cyclization of the product **7** with base then generates the required skeleton, which can be aromatized and methylated (**7** → **8** → **9**).

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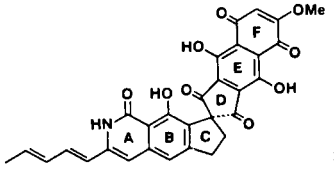
The complex structure **1**, assigned [1] to the antitumor antibiotic [1,2], Fredericamycin A, is attracting attention as a synthetic target [3,4]. The central spiro-unit of this molecule is unique among antitumor agents [1] and, therefore, structure-activity studies may reveal new molecular mechanisms for destroying cancer cells. In this regard, a synthesis of Fredericamycin A is likely to provide a number of analogues that may be helpful in defining the mode of biological action of the compound.



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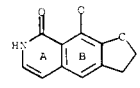
We have recently developed radical-based methodology [4] for synthesis of model spiro-compounds representing rings B-E of Fredericamycin A (see **1**), and we describe here studies related to the heterocyclic ring system (see **1**, rings A, B, C).



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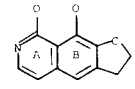

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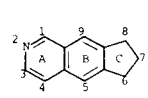

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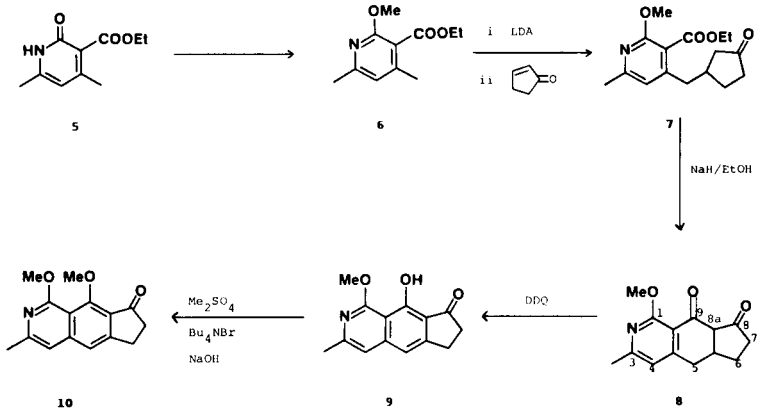
The synthetically equivalent substructures **2** and **3** appear to be extremely rare and, with the oxygenation pattern shown, occur only in Fredericamycin A and some derivatives made from the natural product [5]. Even the cyclopent[*g*]isoquinoline system **4**, lacking nuclear oxygenation, is also not well-known [6]. We have developed a simple route to compounds of type **3** as part of our model studies [4b] for the synthesis of Fredericamycin A. The procedure is summarized in Scheme 1 and was carried out as follows:

The readily accessible pyridone **5**, made by a slight modification of the literature procedure [7], was *O*-methylated with trimethyloxonium fluoroborate to afford **6** (69%). The C-4 methyl group in this compound is easily lithiated [8] by LDA and the resulting carbanion adds to 2-cyclopenten-1-one in a conjugate manner (**6** → **7**, 62-82%).

Scheme 1



We had initially tried the reaction in the presence of cuprous iodide but the results were unpromising and we did not pursue the matter since we found that the organolithium itself was suitable.

Cyclization of **7** in the desired sense (**7** → **8**) was easily achieved (75%) by the action of sodium hydride in the presence of a catalytic amount of ethanol and the diketone **8**, which exists in an enolized form (nmr, ir), could be aromatized by phenylselenation at C-8a and selenoxide fragmentation [9]. However, the same changes could be effected in one step (76%) by the use of DDQ. The phenolic hydroxyl of **9** proved to be resistant to methylation but, under phase transfer conditions, **9** was convertible into **10** in 64% yield.

Compound **10** represents, in protected form, the unusual cyclopent[*g*]isoquinoline substructure that occurs in Fredericamycin A and further work is in progress to incorporate this unit into appropriate spiro-systems.

EXPERIMENTAL

General Information.

Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 eV. Nuclear magnetic resonance spectra were recorded with Bruker WP 80 and AM 300 spectrometers in deuterochloroform with tetramethylsilane as an internal standard.

3-Ethoxycarbonyl-4,6-dimethylpyrid-2-one (**5**).

A mixture of 10 ml (94 mmole) of ethyl cyanoacetate, 9.9 ml (95 mmoles) of 2,4-pentanedione, 10 ml of water and piperidine acetate [10] (from 1.5 ml of 20% w/v acetic acid and sufficient piperidine to bring the *p*H to 9-10) was refluxed for 72 hours and then cooled. The crystalline product (7 g) was collected and washed with a little ether. Concentration of the washings afforded a second crop (1.1 g). The total product weighed 8.1 g (44%) and was suitable for the next stage. A sample was recrystallized from ethyl acetate to afford off-white needles, mp 138-140° lit [7] mp 135-136°; ^{1}H (nmr): δ 1.38 (t, J = 7.25 Hz, 3H), 2.25 (s, 3H), 2.34 (s, 3H), 4.39 (q, J = 7.25 Hz, 2H), 5.93 (s, 1H), 13 (br s, 1H).

Ethyl 2-Methoxy-4,6-dimethyl-3-pyridinecarboxylate (**6**).

To a magnetically stirred solution of 5.0 g (26 mmoles) of the pyridone **5** in 45 ml of anhydrous dichloromethane was added 4.0 g (27 mmoles) of trimethyloxonium fluoroborate. Stirring under an inert atmosphere was continued overnight. The mixture was then cooled in an ice-bath and 50 ml of 10% w/v aqueous sodium hydroxide was added. Stirring was continued for 15 minutes and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with water, dried (sodium sulfate), and evaporated. Flash chromatography of the residue over silica gel with dichloromethane gave 3.7 g (69%) of **6** together with a little starting material. A portion was distilled in a Kugelrohr apparatus, bp 92-93° (1.4 mm); ir (film): 1720, 1595 cm^{-1}; ^{1}H (nmr): δ 1.35 (t, J = 7 Hz, 3H), 2.25 (s, 3H), 2.40 (s, 3H), 3.90 (s, 3H), 4.40 (q, J = 7 Hz, 2H), 6.6 (s, 1H). Exact mass Calcd. for $C_{11}H_{15}NO_3$: 209.1048. Found: 209.1053.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.19; H, 7.13; N, 6.68.

3[4-(3-Ethoxycarbonyl-2-methoxy-6-methylpyridylmethyl)]cyclopent-1-one (**7**).

A solution of LDA was prepared by adding 5.3 ml (8.5 mmoles) of butyllithium in hexane (1.6 *M*) dropwise with stirring to 1.2 ml (8.6 mmoles) of diisopropylamine in 3 ml of THF at -20° and the resulting solution of LDA was transferred by cannula into a cold (-78°), stirred solution of 1.59 g (7.6 mmoles) of **6** in 20 ml of THF. A small portion of THF (*ca.* 1 ml) was used as a wash to transfer residual LDA. Stirring at -78° was continued for 1 hour and then 0.75 ml (9.0 mmoles) of 2-cyclopenten-1-one in 6 ml of THF was injected over 2-3 minutes. The originally orange solution of metallated pyridine changed to a pale yellow. After a further 1 hour at -78° the stirred reaction mixture was quenched by addition of 10 ml of water and allowed to attain room temperature. The layers were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried (sodium sulfate), and evaporated. Flash chromatography of the pale yellow residue over silica gel with 5% v/v ethyl acetate-dichloromethane gave 1.37 g (62%) of **7** as a colourless oil. The experiment was repeated several times and the yields ranged from 62 to 82%. Compound **7** had ir (film): 1742.5, 1731.1, 1600.0; ^{1}H nmr: δ 1.36 (t, J = 7 Hz, 3H), 1.49-1.69 (m, 1H), 1.84-1.96 (m, 1H), 2.02-2.32 (m, 2H), 2.24-2.34 (m, 2H), 2.36-2.56 (m including s, 4H), 2.66 (d, J = 7 Hz, 2H), 3.91 (s, 3H), 4.36 (q, J = 7 Hz, 2H), 6.56 (s, 1H); ^{13}C nmr: (75.469 MHz) δ 14.22 (q), 24.13 (q), 29.19 (t), 37.22 (d), 38.12 (t), 38.20 (t), 44.80 (t), 53.71 (t), 61.36 (t), 114.37 (s), 116.57 (d), 149.17 (s), 157.22 (s), 160.45 (s), 167.34 (s), 218.30 (s). Exact mass Calcd. for $C_{16}H_{21}NO_4$: 291.1463. Found: 291.1474.

Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.19; H, 7.42; N, 4.77.

5,5a,7,8,8a,9a-Hexahydro-1-methoxy-3-methyl-6*H*-cyclopent[*g*]isoquinoline-8,9-dione (**8**).

To 260 mg (55% w/w dispersion in oil, 6.0 mmoles) of sodium hydride was added 5 ml of THF at *ca.* 0° (ice-bath). The mixture was stirred under argon and 800 mg, (2.7 mmoles) of the ketopyridine **7** in 10 ml of THF was added dropwise. After 10 minutes, a catalytic amount (*ca.* 0.025 ml) of ethanol was added. Stirring was continued overnight, during which time the ice-bath attained room temperature. The mixture was quenched by addition of wet ether until effervescence stopped and then saturated aqueous ammonium chloride solution was added. The mixture was extracted with ethyl acetate. (In some experiments an emulsion forms but can be cracked by addition of 6*N* hydrochloric acid to bring the *p*H to 5-6.) The combined organic extracts were dried (sodium sulfate) and evaporated. Flash chromatography of the residual yellow solid over silica gel with 10% v/v ethyl acetate-dichloromethane gave 505 mg (75%) of **8**. For analysis a sample was recrystallized from ether-ethyl acetate, mp 130-133°; ir (cast from chloroform): 1662.3, 1608.4; ^{1}H nmr: δ 1.5-1.7 (m, 1H), 2.25-2.6 (m including s, 7H), 2.90 (dd, J = 6, 15 Hz, 1H), 2.95-3.15 (m, 1H), 4.05 (s, 3H), 6.65 (s, 1H), 11.3 (br s, 1H); ^{13}C nmr: δ 24.34 (q), 28.90 (t), 34.11 (d), 36.84 (t), 37.35 (t), 53.87 (q), 110.37 (s), 111.10 (s), 116.89 (d), 153.40 (s), 159.98 (s), 161.49 (s), 166.59 (s), 200.65 (s). Exact mass Calcd. for $C_{14}H_{15}NO_3$: 245.1049. Found: 245.1050.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.14; H, 6.21; N, 5.64.

1-Methoxy-3-methyl-7,8-dihydro-6*H*-cyclopent[*g*]isoquinolin-9-ol-8-one (**9**).

To a solution of 2.0 g (8.2 mmoles) of **8** in 30 ml of dry benzene was added 2.25 g (9.9 mmoles) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The mixture was stirred for 1 hour at room temperature (tlc control), diluted with dichloromethane, and filtered. The insoluble material was washed with a little warm dichloromethane. The washings were concentrated and filtered through a 2'' bed of silica gel using 20% v/v ethyl acetate-dichloromethane. Appropriate fractions were evaporated and the residual solid was washed with one bed volume of ether to afford 1.5 g (76%) of **9** as an off-white solid. For analysis a sample was recrystallized from ethyl acetate, mp 164-166°; ir: 3360.0, 1701.6, 1659.3, 1637.8, 1623.1 cm^{-1}; ^{1}H nmr: δ 2.50 (s, 3H), 2.75 (m, 2H), 3.15 (m, 2H), 4.20 (s, 3H), 6.95 (s, 1H), 7.00 (s, 1H), 10.65 (br s, 1H); ^{13}C nmr: δ 23.97 (q), 25.18 (t), 36.28 (t), 53.84 (q), 106.22 (s), 112.81 (d), 113.01 (d), 118.23 (s), 145.91 (s), 152.73 (s), 153.64 (s), 157.17 (s), 161.61 (s), 206.90 (s). Exact mass Calcd. for $C_{14}H_{13}NO_3$: 243.0902. Found: 243.0894.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.18; H, 5.48; N, 5.65.

1,9-Dimethoxy-3-methyl-7,8-dihydro-6-*H*-cyclopent[*g*]isoquinoline-8-one (**10**).

A mixture of 1.25 g (5.1 mmoles) of the phenol **9** in 25 ml of dichloromethane, 310 mg (7.8 mmoles) of sodium hydroxide in 25 ml of water, 165 mg (0.51 mmoles) of tetrabutylammonium bromide, and 2.2 ml (23.2 mmoles) of dimethyl sulphate was stirred vigorously overnight at room temperature. The layers were then separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with 10% w/v aqueous sodium hydroxide, dried (sodium sulfate), and evaporated. Flash chromatography of the residue over silica gel with 20% v/v ethyl acetate-dichloromethane gave 840 mg (64%) of **10**, mp 146-148°; ir (cast from chloroform): 1706.5, 1616.6 cm^{-1}; ^1H nmr: δ 2.5 (s, 3H), 2.75 (m, 2H), 3.15 (m, 2H), 4.05 (s, 3H), 4.15 (s, 3H), 6.95 (s, 1H), 7.3 (s, 1H); ^{13}C nmr: δ 24.07 (q), 25.12 (t), 37.28 (t), 53.93 (q), 63.10 (q), 111.98 (s), 112.33 (d), 117.82 (d), 125.74 (s), 145.66 (s), 152.16 (s), 154.40 (s), 158.74 (s), 161.89 (s), 203.28 (s). Exact mass Calcd. for $C_{15}H_{15}NO_3$: 257.1036. Found: 257.1057.

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.30; H, 5.90; N, 5.38.

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