Approaches to the Synthesis of Benzo[*c*]phenanthridines

Gábor Blaskó [1] and Geoffrey A. Cordell*

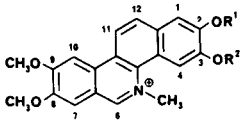
Program for Collaborative Research in the Pharmaceutical Sciences,
College of Pharmacy, University of Illinois at Chicago,
Chicago, Illinois, 60612 U.S.A.

Received March 28, 1989

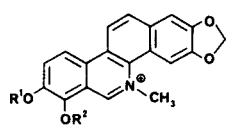
6-Methylbenzo[*c*]phenanthridine derivatives were synthesized *via* an established route and their cytotoxic activity determined. Attempts to synthesize benzo[*c*]phenanthridines lacking the 6-methyl group *via* a 2-benzopyrylium intermediate were unsuccessful.

J. Heterocyclic Chem., **26**, 1601 (1989).

A number of benzo[*c*]phenanthridine alkaloids [2] possess interesting biological activities, for example, nitidine (**1**) and fagaronine (**2**) have shown anticancer activity [3,4], while sanguinarine (**3**) and chelerythrine (**4**) exert antimicrobal activity [5,6]. Recently, sanguinarine (**3**) has become



1 $R^1+R^2 = CH_2$
2 $R^1=H$ $R^2=CH_3$

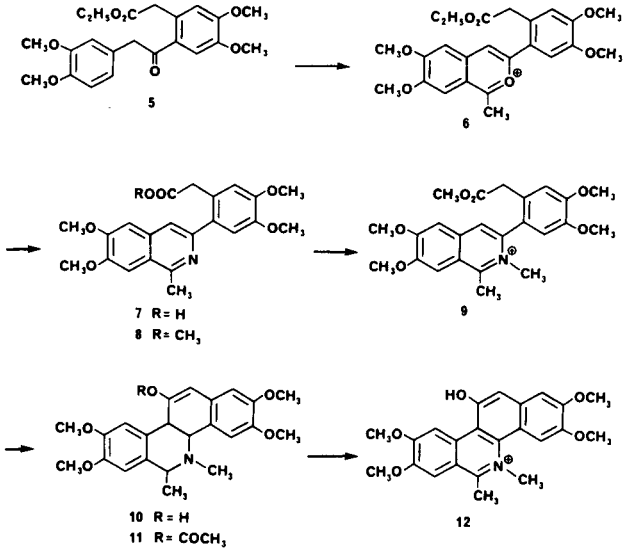


3 $R^1+R^2 = CH_2$
4 $R^1=R^2=CH_3$

a commercial entity as a nematocide. The chemistry, synthesis and pharmacology of benzo[*c*]phenanthridine alkaloids have been reviewed [1,2,7,8]. We became interested in a synthetic strategy to the benzo[*c*]phenanthridines which would permit modification at multiple sites in the molecule and also allow the preparation of potential metabolites. In 1984, a novel approach was published for the preparation of the benzo[*c*]phenanthridine nucleus utilizing a 2-benzopyrylium intermediate in the key reaction step [9]. Thus, treatment of keto ester **5** in acetic anhydride with perchloric acid gave 2-benzopyrylium **6** which, upon reaction with ammonia, afforded isoquinoline **7**. The latter compound was then transformed into benzo[*c*]phenanthridine **12** by simple reaction steps. This novel approach seemed suitable to produce interesting analogues of fagaronine (**2**) and its 2-*O*-methyl derivative in order to study the influence of a C-6 methyl and a C-11 hydroxy or acetoxy group on the cytotoxic activity of these benzo[*c*]phenanthridines.

Initially, we repeated the published [9] reaction sequence (see Scheme 1) to produce 6,7-dimethyl-11-hydroxy-2,3,8,9-tetramethoxybenzo[*c*]phenanthridine (**12**). All of the isoquinoline derivatives synthesized **7-12** were evaluated in the P-388 and KB lymphocytic leukemia test systems *in vitro* according to established protocols [10,11]. With the exception of compound **11**, all of the tested compounds proved to be inactive. Compound **11** displayed an ED_{50} = 3.3 μg/ml against the P-388 and ED_{50} = 2.4 μg/ml against the KB test system. Biological data collected in this series of compounds suggests that substitution at C-6 significantly decreases the cytotoxic activity of the benzo[*c*]phenanthridines.

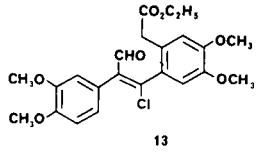
Scheme 1



Synthesis of Benzo[*c*]phenanthridines According to Ref [9].

The second investigation aimed at the synthesis of C-6 unsubstituted benzo[*c*]phenanthridines *via* a 2-benzopyrylium intermediate unsubstituted at C-1. However, treatment of keto ester **5** in acetic-formic anhydride with perchloric acid uniformly gave 1-methyl-2-benzopyrylium **6**. No C-1 unsubstituted product could be detected, even after transformation of the crude 2-benzopyrylium into the corresponding isoquinoline by treatment with ammonia. We then attempted the direct formylation of keto ester **5** in order to introduce the necessary carbon atom in a separate reaction step prior to the formation of the 2-benzopyrylium moiety. A number of approaches to formylate keto ester **5** in the appropriate position failed, *e.g.* the Wilsmeyer-Haack formylation with phosphorus oxychloride and dimethylformamide, the use of dichloromethyl methyl ether and titanium(IV) chloride, or zinc(II) cyanide and hydrogen chloride as formylating agents. The unsuccess-

ful direct formylation attempts of keto ester **5** were likely due to the presence of the carbonyl group in the molecule. For example, the Wilsmeyer-Haack formylation of **5** resulted in compound **13** according to its ^{1}H-nmr and mass spectral data (see Experimental) instead of the target aromatic electrophilic substitution product. The formation of **13** can be explained by prior α-formylation to the carbonyl of **5**, followed by subsequent chlorination of the enol form of the β-ketoaldehyde intermediate.



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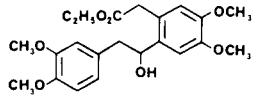

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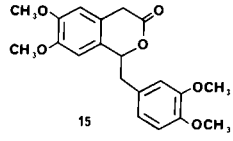

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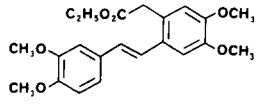

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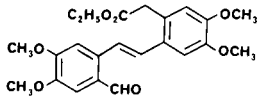

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Successful Wilsmeyer-Haack formylation was performed on olefin **16** lacking the reactive carbonyl group. Compound **16** was prepared either from hydroxy ester **14** or from the corresponding lactone **15** by reflux in ethanol containing hydrogen chloride gas. Wilsmeyer-Haack formylation of **16** with phosphorus oxychloride in dimethylformamide, followed by hydrolysis afforded compound **17**. The presence and position of the C-formyl group in **17** was established by ^{1}H-nmr and mass spectral analysis (see Experimental). Treatment of compound **17** with perchloric acid or triphenylcarbenium perchlorate [12] did not give a 2-benzopyrylium-type product suggesting that the preparation of the target 2-benzopyrylium derivative requires a 1,5-dicarbonyl moiety.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected. Preparative column chromatography was performed on Silica gel 60 (70-230 mesh) (E. Merck). Thin layer chromatography (tlc) was performed on Silica gel GHLF uniplates (Analtech Inc.). The ir spectra were recorded using a Nicolet MX-1 interferometer. The ^{1}H-nmr spectra were obtained on a Varian XL-300 spectrometer operating at 300 MHz. Chemical shifts (δ) are reported in ppm using tetramethylsilane as an internal standard. Mass spectra were determined with a Varian MAT 112S double focusing mass spectrometer operating at 80eV. High resolution mass spectra were determined on a MAT 90 instrument at 70eV. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

Ethyl 2-{2'-[1''-Formyl-2''-chloro-2''-1''-(3,4-dimethoxyphenyl)-vinyl]-4',5'-dimethoxyphenyl}acetic Acid (**13**).

Phosphorus oxychloride (1.1 ml, 0.012 mole) was added to dry dimethylformamide (3.7 ml, 0.048 mole) at 0° and the mixture kept at this temperature for 30 minutes. Ethyl 2-{2'-[1''-(3,4-dimethoxyphenyl)-2''-oxoethyl]-4',5'-dimethoxyphenyl}acetic acid (**5**) (0.4 g, 0.001 mole) in dry dimethylformamide (2 ml) was added and the reaction mixture was stirred for 5 hours at 0° and kept overnight at room temperature. Decomposition of excess reagent with water (10 ml) followed by the usual work up procedure including column chromatography using chloroform-methanol (100:5) as eluent afforded **13** (66 mg, 37%) mp 142-143° (benzene); ir (potassium bromide): ν max 1725 (C=O), 1695 (C=O) and 1610 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.21 (3H, t, J = 8.4 Hz, CH_2-CH_3), 3.65 and 3.78 (1H, 1H, d, d, J_{gem} = 15.5 Hz, CH_2), 3.92 (4 x 3H, s, 4 x OCH_3), 4.11 (2H, q, J = 8.4 Hz, CH_2-CH_3), 6.84 (1H, d, J = 1.2 Hz, 2-H), 6.91 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 6-H), 6.92 and 6.95 (1H, s, each 3'-H and 6'-H), 6.97 (1H, d, J = 8.2 Hz, 5-H), 9.49 (1H, s, CHO); low resolution ms: m/z (relative intensity) 448 (M^+, 61), 413 (12), 385 (7), 361 (100), 339 (9), 311 (44), 298 (12), 281 (8), 253 (7), 224 (6); high resolution ms: Calcd. for $C_{23}H_{25}ClO_7$ 448.12888. Found: 448.12813.

Anal. Calcd. for $C_{23}H_{25}ClO_7$: C, 61.52; H, 5.62; Cl, 7.90. Found: C, 62.20; H, 5.55; Cl, 7.76.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone (**15**).

To a solution of ethyl 2-{2'-[1''-(3,4-dimethoxyphenyl)-2''-oxoethyl]-4',5'-dimethoxyphenyl}acetic acid (**5**) (0.6 g, 1.5 mmoles) in ethanol (25 ml), sodium borohydride (0.1 g) was added in small portions at 0°. The reaction was monitored by tlc. The reaction mixture was acidified with 10% hydrochloric acid (1 ml) and kept at room temperature for 1 hour. Work up involving extraction with chloroform and crystallization from methanol resulted in **15** (0.4 g, 74%), mp 167-169° (methanol); ir (potassium bromide): ν max 1730 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.57 and 3.30 (1H, 1H, d, d, J_{gem} = 20.0 Hz, 3-H_2), 3.09 and 3.26 (1H, 1H, dd, dd, J_1 = 18.6 Hz, J_2 = 4.5 Hz, CH_2), 3.66 (3H, s, OCH_3), 3.85 (3 x 3H, s, 3 x OCH_3), 5.65 (1H, t, J = 4.5, 1-H), 6.31 (1H, d, J = 2.0 Hz, 2'-H), 6.53 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 6'-H), 6.46 and 6.57 (1H, 1H, s, s, 5-H and 8-H), 6.73 (1H, d, J = 8.4 Hz, 5'-H); low resolution ms: m/z (relative intensity) 358 (M^+, 24), 208 (12), 209 (95), 180 (15), 179 (100), 151 (68), 136 (8); high resolution ms: Calcd. for $C_{20}H_{22}O_6$ 358.14164. Found: 358.14137.

Ethyl 2-{2'-[1''-(3,4-Dimethoxyphenyl)vinyl]-4',5'-dimethoxyphenyl}acetic Acid (**16**).

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone (**15**) (0.5 g, 1.4 mmoles) was refluxed in ethanol (50 ml) containing 5% hydrogen chloride gas for 3 hours. Evaporation to dryness followed by crystallization from ethanol gave **16** (0.45 g, 83%), mp 114-115° (ethanol); ir (potassium bromide): ν max 1720 (C=O), 1620 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.23 (3H, t, J = 6.6 Hz, CH_2-CH_3), 3.71 (2H, s, CH_2), 3.91 (2 x 3H, s, 2 x OCH_3), 3.95 (2 x 3H, s, 2 x OCH_3), 4.15 (2H, q, J = 6.6 Hz, CH_2- CH_3), 6.76 and 7.12 (1H, s, each 3'-H and 6'-H), 6.85 and 7.18 (1H, d, each J = 16.2 Hz, CH=CH), 6.88 (1H, d, J = 2.0 Hz, 2-H), 7.06 (1H, dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 6-H), 7.13 (1H, d, J = 8.2 Hz, 5-H); low resolution ms: m/z (relative intensity) 386 (M^+, 100), 3.72 (121), 313 (14), 282 (13), 267 (4), 235 (5), high resolution ms: Calcd. for $C_{22}H_{26}O_6$ 386.17294. Found: 386.17278.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.36; H, 6.78. Found: C, 68.45; H, 6.56.

Ethyl 2-{2'-[1''-(6-Formyl-3,4-dimethoxyphenyl)vinyl)-4',5'-dimethoxyphenyl}acetic Acid (**17**).

Phosphorus oxychloride (1.1 ml, 0.012 mole) was added to dry dimethylformamide (3.7 ml, 0.0481 mole) at 0° and the mixture was kept at this temperature for 30 minutes. Ethyl 2-{2'-[1''-(3,4-dimethoxyphenyl)vinyl]-4',5'-dimethoxyphenyl}acetic acid (**16**) (0.4 g, 1 mmole) in dry dimethylformamide (2 ml) was added dropwise and the reaction mixture was stirred for 5 hours at 0° and kept overnight at room temperature. Decomposition of the excess of reagent with water (10 ml) followed by usual work up including column chromatography using chloroform-methanol (100:5) as eluent afforded **17** (130 mg, 31%), mp 131-132° (benzene); ir (potassium bromide): ν max 1725 (C=O), 1705 (C=O) and 1615 (C=C) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.21 (3H, t, J = 6.6 Hz, CH_2-C*H*$_3$), 3.71 (2H, s, CH_2), 3.92 (3H, s, OCH_3), 3.96 (2 x 3H, s, 2 x OCH_3), 4.03 (3H, s, OCH_3), 4.14 (2H, q, J = 6.6 Hz, C*H*$_2$-CH_3), 6.78, 7.12, 7.16 and 7.38 (1H, s, each, 2-H, 5-H, 3'-H and 6'-H), 7.18 and 7.67 (1H, d, each J = 15.7 Hz, CH=CH), 10.31 (1H, s, CHO); low resolution ms: m/z (relative intensity) 414 (M^+, 100), 386 (13), 372 (14), 368 (19), 341 (11), 340 (16), 327 (22), 325 (26), 309 (23), 281 (12), 267 (6), 255 (2), 238 (3); high resolution ms: Calcd. for $C_{23}H_{26}O_7$ 414.16785. Found: 414.16762.

Anal. Calcd. for $C_{23}H_{26}O_7$: C, 66.64; H, 6.33. Found: C, 66.63; H, 6.22.

Acknowledgements.

This work was supported, in part, by grant CA-20164 from the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

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