# Synthesis of 9,10,11,12,12a,13-Hexahydro-2,3-dimethoxy-7*H*-naphtho[1,2-*b*]quinolizine Hydrobromide. A Cell Growth Inhibitor Related to Cryptopleurine



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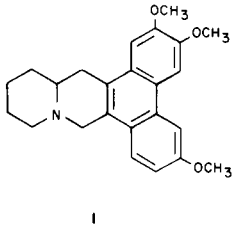
Received January 10, 1983

9,10,11,12,12a,13-Hexahydro-2,3-dimethoxy-7*H*-naphtho[1,2-*b*]quinolizine hydrobromide (**4**), which has structural similarity to cell growth inhibitory alkaloid cryptopleurine (**1**), was found to inhibit the growth of HeLa cells by 50% versus control at a concentration of 0.6 μg/ml. An expeditious synthesis of the title compound was based on hydrogenation of quinolizinium salt **10**, available through Friedel-Crafts cyclization of aldoxime **9**.

*J. Heterocyclic Chem.*, **21**, 261 (1984).

Cryptopleurine (**1**) first isolated from *Cryptocarya pleurosperma (Lauraceae)* [1] has been reported to inhibit the growth of Ehrlich ascites tumor cells by blocking incorporation of leucine [2]. This alkaloid along with the related tylophorine (**2**) and tylocrebrine (**3**) are thought to inhibit protein synthesis in both yeast and Chinese hamster ovary (CHO) cells by a common mechanism of action [3]. Tylocrebrine has shown activity against Lymphoid Leukemia L1210 in mice [4]. A Spanish group has published a recent synthesis of cryptopleurine [3b] and has prepared a series of simplified analogs to study which portions of the ring system are required for protein synthesis inhibitory activity [5].

During routine screening of compounds for antiviral activity in cell culture we found that structurally similar 9,10,11,12,12a,13-hexahydro-2,3-dimethoxy-7*H*-naphtho-[1,2-*b*]quinolizine hydrobromide (**4**) inhibited the growth of HeLa cell colonies by 50% at 0.6 μg/ml, while a 10-fold greater concentration was needed to show signs of cell toxicity. A 25-gram sample was required by the Development Therapeutics Program of the National Cancer Institute for further evaluation. Reduced forms of the naphtho[1,2-*b*]-quinolizine nucleus have not to our knowledge been described. We report a convenient synthesis of **4**, suitable for the preparation of useful quantities.



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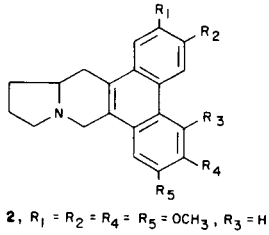
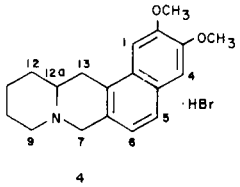


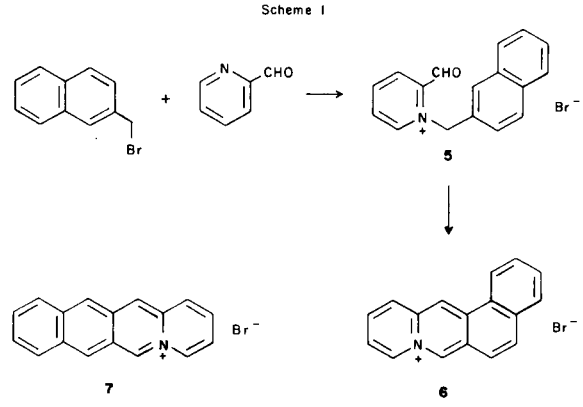
**2**, $R_1 = R_2 = R_4 = R_5 = OCH_3$, $R_3 = H$

**3**, $R_1 = R_2 = R_3 = R_4 = OCH_3$, $R_5 = H$



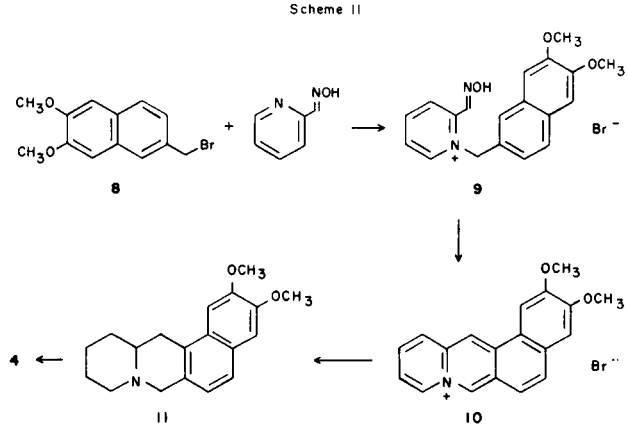
4

Scheme I



Bradsher and Beavers have described the synthesis of the parent unsaturated nucleus **6** (Scheme I) [6]. These authors prepared the pyridinium salt **5** and allowed it to cyclize in boiling concentrated hydrobromic acid. They provided uv evidence that the product had the angular structure **6** rather than the linear structure **7**. Our synthesis was carried out along similar lines (Scheme II).

Scheme II



Excess pyridine-2-aldoxime was allowed to react with the bromomethylnaphthalene **8** *(vide infra)* to afford the pyridinium salt **9** in 92% yield. Attempts at cyclization of **9** in boiling concentrated hydrobromic acid (5 minutes, 110°) gave the desired bright orange naphtho[1,2-*b*]quinolizinium bromide **10** in only modest yield. Initially, this was attributed to good water solubility of the bromide salt, and much effort was expended on finding a more suitable counter ion to effect quantitative precipitation of the cation from aqueous solution. These attempts failed, possibly due to demethylation which occurred under the vigorous reaction conditions and gave rise to water soluble phenolic products. When constant-boiling hydrochloric acid (6.01 *M*) was subtituted, an orange product analogous to **10** was isolated in much improved yield. It was reduced over platinum oxide in aqueous acetic acid to furnish the free base **11** [7]. The overall yield of **11** from the pyridinium salt **9** was 59%. That the quinolizinium salt **10** had the desired angular structure was verified from the nmr spectrum of **11**, which exhibited a pair of doublets for the coupled adjacent protons H-5 (7.49 δ, J = 8 Hz) and H-6 (7.02 δ, J = 8 Hz). The desired product **4** was obtained quantitatively by precipitation from a methanol solution of **11** with concentrated hydrobromic acid.

Attempts to prepare the required starting material, 6-bromomethyl-2,3-dimethoxynaphthalene (**8**), *via* selective 6-hydroxymethylation or 6-formylation of 2,3-dimethoxynaphthalene were not successful. Therefore, 2,3-dimethoxy-6-hydroxymethylnaphthalene was prepared according to the literature procedure [8]. When stirred briefly with concentrated hydrobromic acid, it was converted to **8** in good yield. The overall yield of **4** from commercially available 2,3-dihydroxynaphthalene was 12%.

Although **4** is a fairly potent cell growth inhibitor *in vitro*, it failed to exhibit significant *in vivo* activity in the P-388 pre-screen or against a panel of eight tumors in standard tests performed at the National Cancer Institute.

## EXPERIMENTAL

The $^1$H nmr spectra were obtained on a Perkin-Elmer Model R-32 spectrometer at 90 MHz and are reported in parts per million downfield from tetramethylsilane internal standard (δ). Mass spectra were obtained on a Finnigan 4000 spectrometer interfaced to an Incos 2000 data system. Infrared spectra were recorded on a Beckman Model 4020 instrument. Elemental analyses were performed by the Analytical Laboratory, Dow Chemical Co., 1602 Building, Midland, MI. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected.

6-Bromomethyl-2,3-dimethoxynaphthalene (**8**).

To a magnetically stirred solution of 123.4 g (0.57 mole) of 2,3-dimethoxy-6-hydroxymethylnaphthalene [8] in 2000 ml of dichloromethane was added 400 ml of 48% hydrobromic acid. After 1 hour at 20°, the layers were separated and the lower aqueous layer was extracted with dichloromethane. The combined dichloromethane layers were washed with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo* to a tan solid. Recrystallization from ethyl acetate/hexane afforded 121.8 g (77%) of off-white crystals, mp 120-121°; nmr (deuteriochloroform): δ 7.79 (d, 1H, J ≅ 2 Hz, H-5), 7.64 (d, 1H, J ≅ 9 Hz, H-8), 7.35 (dd, 1H, $J_1$ ≅ 9 Hz, $J_2$ ≅ 2 Hz, H-7), 7.08 (s, 2H, H-1 and H-4), 4.63 (s, 2H, $CH_2Br$), 3.97 (s, 6H, 2 × $OCH_3$); ms: (CI, methane) 283, 281 (M + H, 40), 201 (M − Br, 100).

*Anal.* Calcd. for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.6; H, 4.67.

1-((6,7-Dimethoxy-2-naphthalenyl)methyl)-2-((hydroxyimino)methyl)pyridinium Bromide (**9**).

To a mechanically stirred solution of 85.5 g (0.7 mole) of pyridine-2-aldoxime in 575 ml of *N,N*-dimethylformamide was added 120.0 g (0.43 mole) of **8** and the mixture was warmed to 40° under nitrogen for 18 hours, then heated at 65° for an additional hour. After cooling to 20°, the precipitated product was filtered off and washed with dichloromethane, then was dried *in vacuo* to afford 159.5 g (92%) of white powder, mp 225-227° dec; nmr (hexadeuteriodimethyl sulfoxide): δ 12.00 (s, 1H, OH), 9.30 (d, 1H, J ≅ 8 Hz, H-6′ of pyridine ring), 8.75 (s, 1H, aldoxime CH), 8.71 (d, 1H, J ≅ 7 Hz, H-3′), 8.2-8.6 (m, 2H, H-4′ and H-5′), 7.81 (d, 1H, J ≅ 10 Hz, H-4), 7.15-7.40 (m, 3H, H-3, H-5, H-8), 6.20 (s, 2H, $CH_2$), 3.87 (s, 6H, 2 × $OCH_3$); ir (potassium bromide): 1655 $cm^{-1}$ (aldoxime).

*Anal.* Calcd. for $C_{19}H_{19}BrN_2O_3$: C, 56.59; H, 4.75; N, 6.95. Found: C, 56.5; H, 4.86; N, 7.16.

2,3-Dimethoxynaphtho[1,2-*b*]quinolizinium Bromide (**10**).

To 150 ml of mechanically stirred 48% hydrobromic acid at 105° was added 19.8 g (49.2 mmoles) of pulverized pyridinium salt **9**. The mixture immediately became deep red. After 5 minutes, the mixture was cooled to 5° in ice, then poured into 1000 ml of ice-cold dioxane. The resulting orange-red precipitate was collected by filtration, washed with ether, and dried *in vacuo* to yield 8.7 g (45%) of orange-yellow solid, mp 295-297° dec; nmr (trifluoroacetic acid): δ 9.72 (s, 1H, H-13), 9.44 (s, 1H, H-7), 9.05 (d, 1H, J ≅ 8 Hz, H-9 or H-12), 8.55 (d, 1H, J ≅ 10 Hz, H-12 or H-9), 8.37 (s, 1H, H-1), 7.7-8.2 (m, 4H, H-10, H-11, H-5, H-6), 7.52 (s, 1H, H-4), 4.30 (s, 3H, $OCH_3$), 4.22 (s, 3H, $OCH_3$).

*Anal.* Calcd. for $C_{19}H_{16}BrNO_2 \cdot H_2O$: C, 58.77; H, 4.67; N, 3.61. Found: C, 58.6; H, 4.33; N, 3.63.

Cyclization of 1-((6,7-Dimethoxy-2-naphthalenyl)methyl)-2-((hydroxyimino)methyl)pyridinium Bromide (**9**) in Constant-boiling Hydrochloric Acid.

A solution of 200 ml of water and 252 ml of concentrated hydrochloric acid was heated to 110° and 60.13 g (0.15 mole) of **9** was added. After 330 minutes, the rapidly stirred reaction mixture was homogeneous and dark red. It was cooled to 5° and poured into 1500 ml of ice-cold tetrahydrofuran. The resulting precipitate was filtered off, washed with ether, and dried *in vacuo* to afford 47.0 g of an orange solid which exhibited identical spectral characteristics with **10**.

9,10,11,12,12a,13-Hexahydro-2,3-dimethoxy-7*H*-naphtho[1,2-*b*]quinolizine Hydrobromide (**4**).

To a solution of 13.4 g of the crude naphthoquinolizinium product from hydrochloric acid cyclization in a mixture of 400 ml of acetic acid and 200 ml of water was added 1.5 g of platinum oxide and the magnetically stirred mixture was placed under 1 atmosphere of hydrogen. The progress of the hydrogenation was monitored by removal of a small aliquot by syringe and addition to a vial containing a mixture of ethyl acetate and 1*N* sodium hydroxide. The vial was shaken and the ethyl acetate layer was checked by tlc (silica gel, 10% methanol in dichloromethane). After 43 hours, only one spot was present. The reaction mixture was filtered through celite, diluted with crushed ice, and made basic by addition of solid potassium hydroxide. The precipitated product was extracted into dichloromethane and the product solution was boiled with carbon, filtered through celite, and concentrated to a pale tan solid. Recrystallization from 2-propanol yielded 6.02 g of white crystals, mp 173-174°. The reaction was repeated several times giving a total of 38.15 g of **11** from 68.4 g of naphthoquinolizinium salt; nmr (deuteriochloroform): δ

7.49 (d, 1H, J ≅ 9 Hz, H-5, or H-6), 7.12 (s, 2H, H-1 and H-4), 7.02 (d, 1H, J ≅ 9 Hz, H-6 or H-5), 4.01 (s, 6H, methoxy groups), 2.68-3.7 (complex pattern, 5H, protons adjacent to N), 1.1-2.5 (complex pattern, 8H, protons on C-10, C-11, C-12, and C-13); ms: 297 ($M^+$, 30), 296 (M − H, 20), 214 (M − $C_5H_9N$, 100); hydrobromide salt, mp 288-290°.

*Anal.* Calcd. for $C_{19}H_{23}NO_2 \cdot HBr$: C, 60.32; H, 6.39; N, 3.70. Found: C, 60.7; H, 6.53; N, 3.89.

Acknowledgements.

The authors thank Robert Barbuch of the Analytical Dept., Merrell Dow, for aid with spectral interpretations, and Ken Paull of the National Cancer Institute for communicating the cancer testing results to us.

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