# Synthesis of 5-Phenyl-2,3,8,9-tetramethoxy-11*H*-indeno[1,2-*c*]isoquinoline



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A novel approach to the title compound **10** starting with a conveniently available cinnamic acid is proposed. It involves a Friedel-Crafts reaction followed by the synthesis of the amide and subsequent cyclodehydration *via* a Bischler-Napieralski reaction.

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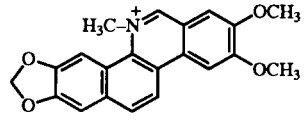
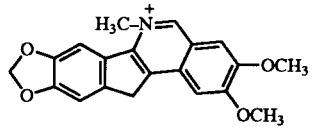
In a recent paper [1] Cushman reported the preparation and biological activity of indenoisoquinoline compound **1** as a structural analogue of the anticancer benzo[*c*]phenanthridine alkaloid nitidine chloride, **2**. Analogue **1** has displayed higher activity against leukemia L1210 than that reported for the natural product itself, and has also shown activity against M5076 sarcoma, while nitidine is inactive in this system. These results stimulated the synthesis of structurally related compounds that might have a more favorable therapeutic index. The fact that we are working in the synthesis of indane and isoquinoline structures encouraged us to propose an alternative synthesis of the indenoisoquinoline system. Two main objectives were outlined: a) increase the overall yield and b) employ simple and readily available materials which provides different substituent-incorporation in the indanoisoquinoline structure. Scheme 1 shows the route proposed, reminded us of the sequence developed by Robinson [2] for the synthesis of benzo[*c*]phenanthridine alkaloids.

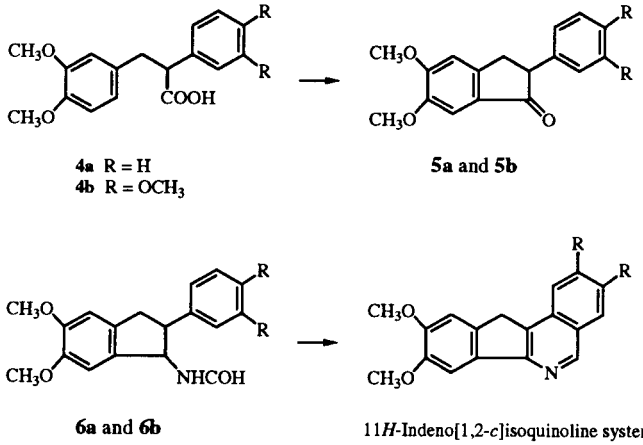


**2**



**1**

Scheme 1




**4a** R = H
**4b** R = $OCH_3$

**5a** and **5b**

**6a** and **6b**

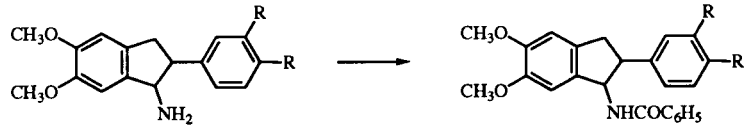
11*H*-Indeno[1,2-*c*]isoquinoline system

In the synthetic sequence, catalytic reduction of the respective propenoic acids **3** provided 2,3-diarylpropanoic acids **4**. Synthesis of indanones **5** involved an internal Friedel-Crafts reaction of **4** which was carried out in good yields with polyphosphoric acid [5]. Indanones **5** should be transformed into 2-aryl-2,3-dihydro-1-formylaminoindene **6**. Having in mind that this step is one of the major obstacles in this sequence we examined two methods: a) direct conversion of the ketone function into a formamide group by means of the Leuckart reaction [3] and b) acylation of the 2-aryl-2,3-dihydroindenamines **8** obtained by reduction of the 2-aryl-2,3-dihydroindene 1-oximes, **7**, [4] derived from the respective 2-aryl-2,3-dihydroinden-1-ones **5** [5], Scheme 2. Efforts to obtain the formamides **6** by means of Leuckart reaction always led to disappointing results, yielding in all cases polymerization by-products, presumably due to β-elimination reactions [6]. In order to circumvent this difficulty, the synthesis of the amides was performed *via* the oxime intermediate (Scheme 2). Chromatographic and nmr behaviour of amines obtained by catalytic reduction on 10% palladium on charcoal [9] or with *in situ* activated Raney nickel amalgam [8], was the same. We assumed, bearing in mind the stereochemistry of the catalytic reduction along with the nmr data, that the main product obtained was the *cis*-amine. There was chemical evidence that similar *cis* amides would preferably undergo the β-elimination process [6]. Thus, in order to easily recognize the desamidation by-product the acylation was carried out with benzoyl chloride. The benzoyl derivatives **9** were treated with ethyl polyphosphate, EPP [7]. The indenoisoquinoline **10** system was obtained in good yield from **9a** by the Bischler-Napieralski reaction. In contrast, **9b** yielded the *retro*-Ritter reaction products: the indene **11** and the benzonitrile **12**, (Scheme 3). The

Scheme 2

**5a** R = H
**5b** R = $OCH_3$

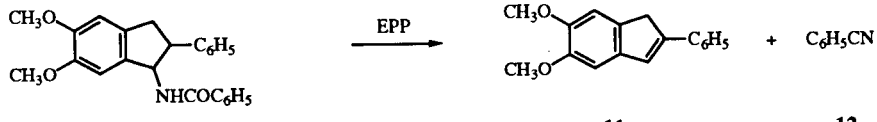
**7a** and **7b**



**8a** and **8b**

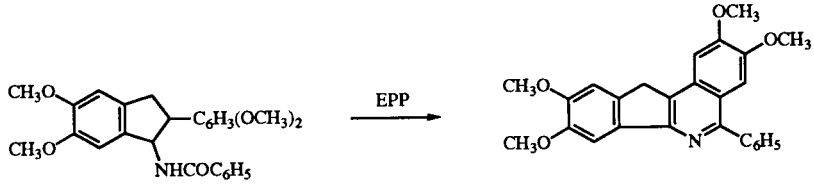
**9a** and **9b**

Scheme 3



**9a**

**11** **12**



**9b**

**10**

last result confirms once more the importance of the presence of an electron donor group in the *para* cyclization position [7].

The good yield obtained for these reactions makes it possible to consider generalization of this method for the synthesis of indenoisoquinolines bearing other substituents capable of providing interesting biological properties.

## EXPERIMENTAL

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and were uncorrected. The nmr spectra were recorded on a Varian FT 80A spectrometer or on a Bruker AW80. Chemical shifts are given in ppm ($\delta$) relative to tetramethylsilane. Elemental analyses were performed with a Coleman analyzer. Infrared spectra were performed on a Jasco A-200 as mulls.

2,3-bis(3,4-Dimethoxyphenyl)propenoic Acid (**3a**).

This compound was obtained by a published procedure [5] as pale yellow crystals from ethanol, mp 201-203° (lit 202°, [5]) in 77% yield.

3-(3,4-Dimethoxyphenyl)-2-phenylpropenoic Acid (**3b**).

This compound was obtained by a published procedure [5] as colorless crystals from ethanol, mp 268-269° in 71% yield; pmr: 3.40 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.50 (s, 1H, Ar), 7.20-7.60 (m, 7H, Ar), 7.80 (s, 1H, CH); ir: $\nu$ 1680 (C=O), 3400 (OH) $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.80; H, 5.70.

2,3-bis(3,4-Dimethoxy)propanoic Acid (**4a**).

This compound was obtained by a published procedure [5] as colorless crystals from ethanol, mp 140-141° (lit 141°, [5]) in 83% yield.

3-(3,4-Dimethoxyphenyl)-2-phenylpropanoic Acid (**4b**).

This compound was obtained by a published procedure [5] as colorless crystals from ethanol, mp 113-114° in 71% yield; pmr: 2.80-3.90 (m, 3H, CH-$CH_2$), 3.60 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 6.70 (m, 3H, Ar), 7.20 (m, 5H, Ar); ir: $\nu$ 1710 (C=O), 3500 (OH) $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.30; H, 6.30.

2,3-Dihydro-5,6-dimethoxy-2-(3,4-dimethoxyphenyl)inden-1-one (**5a**).

This compound was obtained by a published procedure [5] as pale yellow crystals from benzene-hexane, mp 128-130° (lit 130°, [5]) in 68% yield.

2,3-Dihydro-2-phenyl-5,6-dimethoxyinden-1-one (**5b**).

This compound was obtained by a published procedure [5] as white crystals from ethanol, mp 150-151° in 55% yield; pmr: 3.10 (broad d, 1H, $CH_2$), 3.80 (m, 2H, CH-CH), 3.90 (s, 3H, $OCH_3$), 4.00 (s, 3H, $OCH_3$), 6.90 (s, 1H, Ar), 7.10 (s, 1H, Ar), 7.30 (m, 5H, Ar); ir: $\nu$ 1720 (C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.10; H, 6.00.

2,3-Dihydro-5,6-dimethoxy-2-(3,4-dimethoxyphenyl)inden-1-amine (**8a**).

This compound was obtained by a published procedure with Raney nickel [8] or with palladium on charcoal [9] as an oil in 93% yield; pmr: 3.20-4.00 (m, 3H, CH-$CH_2$), 3.70 (s, 6H, $OCH_3$), 4.50 (m, 1H, CH-N), 6.80 (m, 6H, Ar), 1.80 (broad s, 2H, $NH_2$, deuterium oxide-exchangeable).

*Anal.* Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.03; N, 4.25. Found: C, 69.28; H, 7.00; N, 4.24.

2,3-Dihydro-5,6-dimethoxy-2-phenylinden-1-amine (**8b**).

This compound was obtained by a published procedure [8] as an oil in 97% yield; pmr: 3.20-4.20 (m, 3H, CH-$CH_2$), 3.80 (s, 3H, $OCH_3$), 4.60 (m, 1H, CH-N), 6.70 (s, 1H, Ar), 7.20 (m, 5H, Ar), 1.60 (broad s, 2H, $NH_2$, deuterium oxide-exchangeable).

*Anal.* Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.80; H, 7.13; N, 5.20.

*N*-Benzoyl-2,3-dihydro-5,6-dimethoxy-2-(3,4-dimethoxyphenyl)-inden-1-amine (**9a**).

To a solution of indanamine **8a** (1 g, 3 mmoles) and triethylamine (1 ml, 7 mmoles) in methylene chloride (25 ml) was added benzoyl chloride (1 ml, 6 mmoles). The reaction mixture was vigorously shaken and allowed to stand at room temperature one hour and then diluted with methylene chloride (25 ml). The solution was washed with ammonium hydroxyde 25% (2 x 15 ml) and then with water (2 x 15 ml). The organic extract was dried with sodium sulfate and the solvent was evaporated *in vacuo* to afford amide **9a**. This compound was obtained as white crystals from ethanol, mp 140-141° in 82% yield; pmr: 3.20-4.20 (m, 3H, CH-$CH_2$), 3.80 (s, 6H, $OCH_3$), 3.90 (s, 6H, $OCH_3$), 5.80 (m, 1H, NH), 6.00 (q, 1H, CH-N), 6.80 (m, 4H, Ar), 6.95-7.65 (m, 4H, Ar), 8.00 (broad d, 2H, Ar); ir: $\nu$ 3320 (N-H), 1670 (C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{26}H_{27}NO_5$: C, 72.03; H, 6.28; N, 3.23. Found: C, 72.00; H, 6.30; N, 3.23.

*N*-Benzoyl-2,3-dihydro-5,6-dimethoxy-2-phenylinden-1-amine (**9b**).

The benzoyl derivative **9b** was obtained exactly as described for **9a** as white crystals from ethanol, mp 129-130° in 69% yield; pmr: 3.10-4.10 (m, 3H, CH-$CH_2$), 3.60 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 5.80 (m, 1H, NH), 6.00 (q, 1H, CH-N), 6.80 (s, 1H, Ar), 6.90 (s, 1H, Ar), 7.00-7.60 (m, 8H, Ar), 8.00 (broad d, 2H, Ar); ir: $\nu$ 3300 (N-H), 1660 (C=O) $cm^{-1}$.

*Anal.* Calcd. for $C_{24}H_{29}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.20; H, 6.15; N, 3.75.

Reaction of Amides with Ethyl Polyphosphate [7].

The amides **9** were treated with a chloroform solution of EPP (0.86 g/ml) and the products were isolated following the literature procedure [4].

5-Phenyl-2,3,8,9-tetramethoxy-11*H*-indeno[1,2-*c*]isoquinoline **10**.

This compound was obtained as white crystals from ethanol, mp 202-203° in 68% yield; pmr: 3.80 (s, 6H, $OCH_3$), 3.90 (s, 6H, $OCH_3$), 4.40 (s, 2H, $CH_2$), 6.80 (s, 1H, Ar), 6.90 (s, 1H, Ar), 7.10 (s, 1H, Ar), 7.60 (m, 2H, Ar), 7.70 (m, 1H, Ar), 7.80 (m, 1H, Ar).

*Anal.* Calcd. for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.67; H, 5.63; N, 3.38.

5,6-Dimethoxy-2-phenylindene (**11**).

This compound was obtained as colorless crystals from hexane, mp 170-172° in 72% yield; pmr: 3.80 (s, 2H, $CH_2$), 3.90 (s, 6H, $OCH_3$), 6.80 (s, 1H, Ar), 7.00 (s, 1H, Ar), 7.20-8.00 (m, 6H, CH).

*Anal.* Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.90; H, 6.37.

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