

Synthesis of 8,9-Dialkoxy-substituted Tetrahydrobenz[*h*]isoquinolines

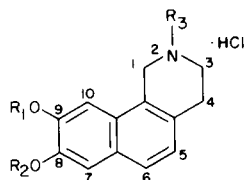
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6,7-Dimethoxy-2-naphthylethylamine, prepared by the diborane reduction of 6,7-dimethoxy-2-naphthaleneacetamide, underwent a Pictet-Spengler cyclization to form 8,9-dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline. This compound is identical with that obtained by reduction of the corresponding dihydrobenzisoquinoline prepared from formamide cyclization. 6,7-Dialkoxy-2-naphthaleneacetic acids, the key intermediates for the preparation of these amides, were obtained from 6,7-dialkoxy-2-acetonaphthones by a modified Willgerodt reaction.

During the course of our structure-activity relationship study on various oncolytic agents, a common structural feature was noted among a wide variety of antileukemic agents. It consists of a triangulation composed of one nitrogen and two oxygen atoms with definite interatomic distance between the atoms. It has been suggested that this structural feature may contribute to the *in vivo* binding to one of the biologically pertinent sites (1). For the purpose of gaining more information on this postulation, several compounds whose structures are designed to accommodate these electronegative centers with appropriate interatomic distances were synthesized and will be evaluated. In order to minimize the *in vivo* conformational changes as well as the *in vivo* transport problems, compounds initially selected in this and the following paper are relatively small in size and of comparably rigid molecular structure. These compounds may provide certain information on the minimum steric and electronic requirements as well as other physical chemical parameters related to biological activity. Synthesis of 8,9-dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinolines (Ia-c) as well as a corresponding 8,9-methylenedioxy analog Id is reported in this paper.



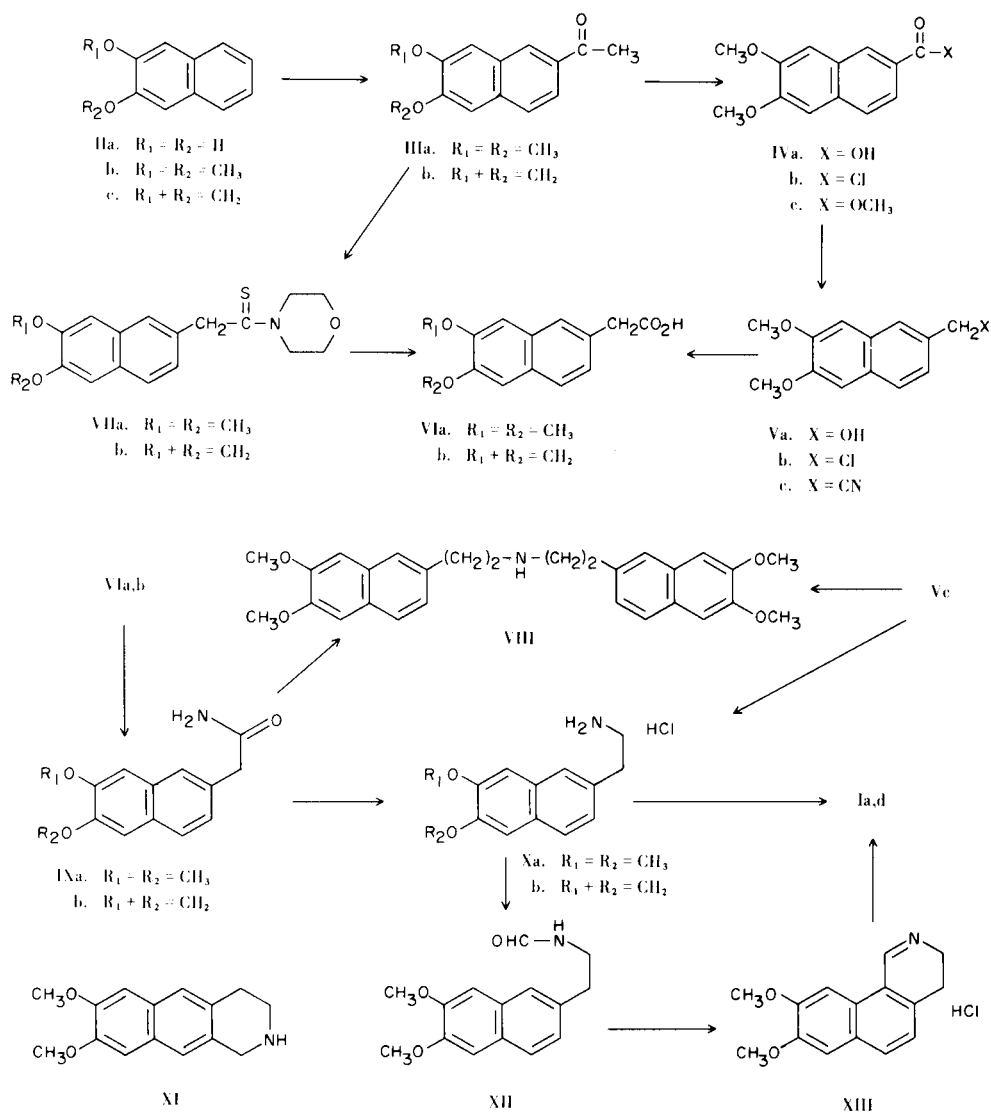
- Ia.  $R_1, R_2 = \text{CH}_3; R_3 = \text{H}$   
 Ib.  $R_1, R_2 = \text{CH}_3; R_3 = \text{CH}_3$   
 Ic.  $R_1, R_2 = \text{CH}_3; R_3 = \text{CH}_2\text{C}_6\text{H}_5$   
 Id.  $R_1 + R_2 = \text{CH}_2; R_3 = \text{H}$

Preparation of 6,7-dimethoxy-2-naphthaleneacetic acid (VIa), a key intermediate for the synthesis of Ia and several benzo[*a*]naphtho[1,2-*g*]quinolizines in the sub-

sequent paper, was initially studied as follows: Friedel-Craft acylation of 2,3-dimethoxynaphthalene (IIb) gave 6,7-dimethoxy-2-acetophenone (IIIa) in 75% yield. The position of acylation of IIIa was confirmed by nmr study. Hypochlorite oxidation (2) of IIIa yielded the 2-naphthoic acid IVa. Since the general conditions for hypochlorite reaction were rather difficult to control and the yield uncertain, commercial Clorox was subsequently used and the yield of IVa was consistent and good (90%). Lithium aluminum hydride reduction of the ester IVc, which was obtained from the acid IVa through its acid chloride IVb, gave 2-hydroxymethyl-6,7-dimethoxynaphthalene (Va). The latter was converted to the acetonitrile Vc via the chloride Vb, subsequent base hydrolysis of Vc gave the desired intermediate VIa. The overall yield of VIa from IIa was 25%.

The number of steps involved and the relative low yield of compound VIa by the aforementioned process prompted a search for other synthetic routes. The Willgerodt reaction, which consists of the conversion of a ketone to the amide of an  $\omega$ -acid, has been known for many years (3). The sealed tube or pressurized equipment required for carrying out the reaction and the generally low yields had prevented this reaction from being considered of synthetic value. However, with the adaptation of a newly modified method, wherein morpholine was used in the presence of *p*-toluenesulfonic acid (4), the thioamide VIIa was readily prepared from IIIa in 80% yield. Subsequent hydrolysis of VIIa gave 95% yield of the acid VIa. The shortcut in the reaction sequence and an improvement of the overall yield (45% from IIa) has rendered the second route as the method of choice.

For the synthesis of compounds I, an initial study was conducted on the preparation of the intermediate 6,7-dimethoxy-2-naphthylethylamine (Xa) by the reduc-

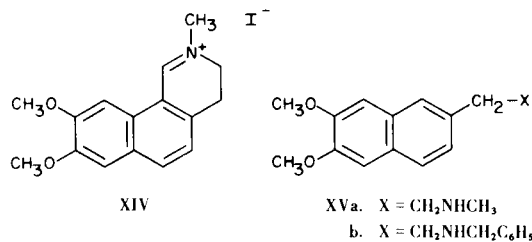


tion of 6,7-dimethoxy-2-naphthylacetonitrile (Vc). Lithium aluminum hydride reduction of Vc in tetrahydrofuran (5) gave a mixture of Xa (as the minor product) and the secondary amine VIII (major product), even under a variety of reaction conditions including variation of the amount of the reducing agents, amount of solvent, and reaction time. Catalytic hydrogenation of the acetonitrile VIc in ethanolic ammonia in the presence of rhodium-on-alumina (6) was not successful and only starting material was recovered even after shaking the reaction mixture for 30 hours. Lithium aluminum hydride reduction of the corresponding amide IXa, prepared from 6,7-dimethoxy-2-naphthaleneacetic acid (VIa) *via* the corresponding acid chloride, gave a mixture of products which were difficult to purify. The desired primary amine Xa was finally obtained in good yield by diborane reduction (7,8) of either the nitrile Vc or the amide IXa.

Pictet-Spengler cyclization of Xa with formaldehyde afforded the desired 8,9-dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline (Ia) in 30% yield. The product was isolated as its hydrochloride salt, m.p. 283-285°. Nmr spectra of Ia ruled out the possibility of structure XI for the product which could have resulted by an alternate ring closure. Some minor by-products (Ib, XIII), which were present in the reaction mixture, were identified.

Since the yield of Ia from Xa was comparatively low, an alternate approach was also studied. Treatment of Xa with acetic-formic anhydride gave the formylated product XII. Bischler-Napieralski cyclization (9) of XII with phosphorus pentachloride in chloroform yielded the dihydrobenz[*h*]isoquinoline XIII, which was reduced in a mixture of zinc and aqueous acetic acid to give Ia. The product was found to be identical with that prepared by the Pictet-Spengler cyclization. The overall yield of the

second method, however, was not higher than that of the first route. Compound Ib was obtained by sodium borohydride reduction of 8,9-dimethoxy-3,4-dihydrobenz[*h*]isoquinoline methiodide (XIV) in 72% yield. The *N*-substituted tetrahydrobenz[*h*]isoquinolines Ib and Ic have been prepared, albeit in low yields, in a similar fashion from XVa and XVb (prepared by diborane reduction of the corresponding amides), respectively, by a Pictet-Spengler synthesis.



The corresponding methylenedioxy analog of Ia, 8,9-methylenedioxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline hydrochloride (Id), was prepared in a parallel manner *via* the route IIa → IIc → IIIb → VIIb → VIb → IXb → Xb → Id. Biological activity of these compounds is currently being evaluated.

## EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus. The nmr spectra were determined on a Varian A-60 spectrometer. The mass spectra data were obtained with a Varian Mat CH-4B mass Spectrometer. Infrared spectra were taken on a Perkin Elmer Infracord. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrometer.

### 2,3-Dimethoxynaphthalene (IIb).

Preparations of this compound and compound IIIa were originally described by Buu-Hoi<sup>1</sup> and Lavit (10). The following modified procedure as well as that for compound IIIa were found to be practical for large-scale preparations. To a stirred suspension of 350 g. (2.18 moles) of 2,3-dihydroxynaphthalene (IIa) in 1700 ml. of water cooled in a cold water bath was simultaneously added, through separate dropping funnels, 670 g. (5.30 moles) of dimethyl sulfate and an aqueous solution of potassium hydroxide (prepared by dissolving 390 g. of potassium hydroxide in 1200 ml. of water). The addition took *ca.* 30 minutes. A solution was initially formed followed by precipitation of a white solid. The mixture was stirred overnight at room temperature. The solid was collected by filtration and washed thoroughly with water until the filtrate became neutral. The product was dried at 60° *in vacuo* to give 370 g. (91%) of IIb, m.p. 113-116°. An analytical sample melted at 117-118° (lit. (10), b.p. 182°/17 mm).

### 2,3-Methylenedioxy-naphthalene (IIIc).

Originally reported (11) procedure is not practical for large-scale synthesis. The following procedure was a modified synthesis based on the method of Tomita and Aoyagi (12). A stirred mixture of 320 g. (2 moles) of 2,3-dihydroxynaphthalene (IIa), 788 g. (2.95 moles) of diiodomethane, 20 g. of finely powdered cupric

oxide, 500 g. (3.62 moles) of anhydrous potassium carbonate in 2 l. of dimethylformamide was refluxed under nitrogen for 3 hours. The reaction mixture was cooled and poured into 3 l. of ice water. The resulting solid was collected by filtration, triturated with 2 l. of 2% sodium hydroxide and again filtered. It was then washed twice with water and dried. The crude solid product was then extracted continuously with ether for 3 days to give 218 g. (63.5% yield) of IIIc, m.p. 97-99° (lit. (11), m.p. 99-100°).

### 6,7-Dimethoxy-2-acetonaphthone (IIIa).

To a stirred mixture of 248 g. (1.86 moles) of anhydrous aluminum chloride in 420 ml. of nitrobenzene in a round bottom flask equipped with a stirrer, addition funnel and a drying tube and immersed in an ice bath was added 162 g. (2.05 moles) of acetyl chloride during 20 minutes. To the ice-cooled mixture was then added, during 35 minutes, a solution of 310 g. (1.64 moles) of anhydrous 2,3-dimethoxynaphthalene (IIb) in 1 l. of nitrobenzene (the nitrobenzene mixture was initially warmed to 45° to affect solution, then cooled to 25° before addition). Stirring was continued for 2 hours at 5° and then at room temperature for 18 hours during which time the color of the reaction mixture changed from brown to dark green. The mixture was then cautiously poured, with vigorous stirring, into 2.5 l. of 10% hydrochloric acid containing 500 g. of crushed ice. The upper aqueous layer was separated and extracted with chloroform (4 x 600 ml.). The organic layer and the chloroform extract were combined and washed successively with water (3 x 800 ml.), 5% sodium hydroxide (3 x 600 ml.) and water (3 x 800 ml.). The washings were extracted with chloroform (3 x 300 ml.). The combined organic solution was dried (Celite-sodium sulfate). Chloroform was removed under reduced pressure and nitrobenzene was distilled *in vacuo* through a short Vigreux column. The product was then rapidly distilled at 205-220°/2 mm without a column using a direct flame to give 320 g. of product which solidified on standing. Recrystallization from 800 ml. of ethanol gave 284 g. (75% yield) of pure product, m.p. 104-106°. An analytical sample was obtained by an additional recrystallization from ethanol, m.p. 107-109° (lit. (10), m.p. 109°).

The following derivatives of 6,7-dimethoxy-2-acetonaphthone were prepared: The *oxime*, m.p. 206-208° (93% yield). Calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.47; H, 6.30; N, 5.79. The *thiosemicarbazone*, m.p. 238-239° (86% yield). Calcd. for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>S: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.57; H, 5.86; N, 13.75. The *formylhydrazone*, m.p. 248-250° (90% yield). Calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.38; H, 5.98; N, 10.02. The *azine*, m.p. 295-297° (81% yield). Calcd. for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>: C, 73.66; H, 6.18; N, 6.14. Found: C, 74.00; H, 6.30; N, 6.25.

### 6,7-Methylenedioxy-2-acetonaphthone (IIIb).

To a stirred mixture of 114 g. of anhydrous aluminum chloride in 200 ml. of nitrobenzene was added 81 g. of acetyl chloride over 20 minutes. Stirring was continued for an additional 20 minutes and to this was added a solution of 141 g. of IIIc in 140 ml. of cold nitrobenzene (heating of the mixture of affect solution of IIIc should be avoided). The reaction mixture was allowed to warm up slightly without external cooling. After 5 hours the mixture was added, with vigorous stirring, to a mixture of 500 ml. of concentrated hydrochloric acid in 1.5 kg. of ice. The organic layer was separated and the aqueous layer extracted with chloroform (5 x 250 ml.). The combined organic solution was washed with water (3 x 400 ml.) and extracted quickly with a solution of 50 g. of potassium hydroxide in 1 l. of water. (When sodium hydroxide

solution was used, an emulsion was formed which was difficult to separate. Prolonged contact of the organic layer with alkaline solution drastically lowered the yield of IIIb). The separated aqueous layer was again extracted with chloroform (2 x 200 ml.), the combined organic solution was dried (sodium sulfate), and the solvent and nitrobenzene removed by distillation. The product was rapidly distilled over an open flame to give 110 g. (62% yield) of a white solid m.p. 115-118°. Recrystallization from aqueous ethanol yielded white crystals, m.p. 122-124°.

*Anal.* Calcd. for  $C_{13}H_{10}O_3$ : C, 72.89; H, 4.71. Found: C, 72.95; H, 4.51.

#### 6,7-Dimethoxy-2-naphthalenecarboxylic Acid (IVa).

An aqueous solution of 54 g. of sodium hydroxide in 160 ml. of water was slowly added, with stirring, to 1600 ml. of commercial Clorox (containing ca. 5.3% sodium hypochlorite with a pH of 11.2) in a 3 l. three-necked, round bottom flask equipped with a stirrer, a condenser and a thermometer. The pH of the resulting mixture was 13.5. The solution was heated to 45° on a steam bath and to this was added 75 g. of IIIa. The mixture was then carefully heated with stirring and the steam was turned off when the temperature of the reaction mixture reached 62°. The spontaneous reaction began and the temperature rose slowly. External cooling with cold water was used from time to time in order to keep the reaction temperature at 72-73° as overheating would cause chloroform, which was formed during the course of reaction, to escape rapidly through the condenser. A clear solution resulted in about 30 minutes. The reaction mixture was then maintained between 60-70° without further heating for another 30 minutes. It was cooled to 30° and a solution of 20% sodium bisulfite (ca. 20 ml.) was added to remove excess chlorine (potassium iodide paper was used). The reaction mixture was cleared by filtration, cooled, and cautiously acidified with concentrated hydrochloric acid (ca. 130-140 ml.) in a hood. It was then allowed to stand overnight and the resulting solid collected by filtration. The solid was washed twice with water and dried to yield crude IVa, m.p. 240-243°. Recrystallization from ethanol gave 68 g. (90% yield) of pure product, m.p. 246-248°. The product was found to be identical with that prepared by the condensation of ethyl  $\gamma$ -veratrylbutyrate and isoamyl formate followed by aromatization (13).

#### 6,7-Dimethoxy-2-naphthalenemethanol (Va).

A solution of 13 g. (0.053 mole) of the methyl ester of 6,7-dimethoxy-2-naphthalenecarboxylic acid (13) (IVc) in 120 ml. of redistilled tetrahydrofuran was added dropwise, at 0°, into a stirred suspension of 9.5 g. (0.25 mole) of lithium aluminum hydride in 200 ml. of the same solvent. After the addition was complete, the mixture was stirred in an ice bath for 1 hour and at room temperature for another hour. It was then refluxed for 3 hours. After being allowed to stand overnight at room temperature, the reaction mixture was worked up as usual and extracted with chloroform to give 10.9 g. (95% yield) of Va, m.p. 106-108°. An analytical sample was prepared by recrystallization from a mixture of ethanol and petroleum ether, m.p. 108-110°.

*Anal.* Calcd. for  $C_{13}H_{14}O_3$ : C, 71.54; H, 6.57. Found: C, 71.64; H, 6.15.

#### 6,7-Dimethoxy-2-naphthaleneacetonitrile (Vc).

To a stirred solution of 35 g. (0.16 mole) of Va in 450 ml. of chloroform was added 60 g. (0.50 mole) of thionyl chloride. The mixture was heated at 45-50° for 2 hours and evaporated at <50° *in vacuo* to dryness to yield ca. 38 g. of crude product Vb. This was added in small portions, with cooling, to a stirred mixture of

20 g. (0.41 mole) of sodium cyanide in 220 ml. of dimethyl sulfoxide. The resulting syrupy mixture was vigorously stirred at room temperature for 2 days and then poured into 350 ml. of ice water with rapid stirring. The light yellow solid was collected by filtration, washed cold water (2 x 50 ml.) to give 8 g. of the acetonitrile Vc. The filtrate and washings were combined and extracted with ether (4 x 800 ml.). The ether extract was washed with water (4 x 100 ml.) and dried (sodium sulfate). The solvent was removed *in vacuo* to afford an additional 25.5 g. of Vc, m.p. 84-87°. Total yield was 92%. An analytical sample was obtained by recrystallization from a 1:2 mixture of ethanol and petroleum ether, m.p. 90-92°.

*Anal.* Calcd. for  $C_{14}H_{13}NO_2$ : C, 73.99; H, 5.77; N, 6.16. Found: C, 74.21; H, 5.54; N, 5.96.

#### 4-[(6,7-Dimethoxy-2-naphthyl)thioacetyl]morpholine (VIIa).

A stirred mixture of 116 g. (0.50 mole) of 6,7-dimethoxy-2-acetonaphthone (IIIa), 18 g. (0.56 g-atom) of sulfur, 3 g. of *p*-toluenesulfonic acid, and 94 ml. of morpholine was vigorously refluxed for 3 hours. It was then cooled to <100° and, with continuous stirring, 200 ml. of ethanol was carefully added in order to disperse the crystals in the reaction mixture. After being allowed to stand overnight at room temperature, the yellow solid product was collected by filtration, washed with cold ethanol, petroleum ether, and dried to give 133 g. (80% yield) of product. An analytical sample was prepared by recrystallization from methanol, m.p. 173-175°.

*Anal.* Calcd. for  $C_{18}H_{21}NO_3S$ : C, 65.23; H, 6.39; N, 4.23. Found: C, 65.01; H, 6.34; N, 4.14.

#### 4-[(6,7-Methylenedioxy-2-naphthyl)thioacetyl]morpholine (VIIb).

This compound was prepared from 180 g. of IIIa, 18 g. of sulfur, 3 g. of *p*-toluenesulfonic acid and 94 ml. of morpholine in a similar manner as that for the synthesis of VIIa. The product was isolated (101 g., 64% yield) from the reaction mixture m.p. 156-160°. Recrystallization from ethanol afforded an analytical sample as white crystals, m.p. 161-163°.

*Anal.* Calcd. for  $C_{17}H_{17}NO_3S$ : C, 64.74; H, 5.43; N, 4.44. Found: C, 64.49; H, 5.21; N, 4.21.

#### 6,7-Dimethoxy-2-naphthaleneacetic Acid (VIa).

##### Method 1.

A mixture of 3 g. of 6,7-dimethoxy-2-naphthaleneacetonitrile (Vc), 2 g. of sodium hydroxide, 18 ml. of water and 8 ml. of ethanol was refluxed with stirring for 9 hours. Solvent was removed *in vacuo* and the residue dissolved in 150 ml. of water. The aqueous solution was extracted repeatedly with ether and the ether extracts discarded. The aqueous layer was filtered from small amounts of insoluble material and the filtrate acidified (to pH 1) with 10% of hydrochloric acid to give 2.67 g. (82% yield) of VIa, m.p. 140-143°. An analytical sample was obtained by recrystallization from ethanol-water, m.p. 144-145°.

*Anal.* Calcd. for  $C_{14}H_{14}O_4$ : C, 68.28; H, 5.73. Found: C, 68.47; H, 5.40.

##### Method 2.

A mixture of 116 g. of 4-[(6,7-dimethoxy-2-naphthyl)thioacetyl]morpholine VIIa, 78 g. of sodium hydroxide, 740 ml. of water and 250 ml. of ethanol was refluxed on a steam bath for 7 hours. The solvent was removed *in vacuo* and the residue was worked up as described in Method 1 to give 81.8 g. (95% yield) of VIa. An analytical sample was prepared by recrystallization from ethanol-water, m.p. 144-145°. The product was found to be identical with that prepared by Method 1.

## 6,7-Methylenedioxy-2-naphthaleneacetic Acid (VIb).

A mixture of 76 g. (0.24 mole) of VIIIb, 54 g. of sodium hydroxide, 500 ml. of water and 250 ml. of ethanol was refluxed on a steam bath for 5 hours. The reaction mixture was cooled and extracted with ether and the ether extraction discarded. The aqueous layer was filtered from small amounts of an insoluble substance and the filtrate acidified with concentrated hydrochloric acid to pH 1. The mixture was allowed to stand overnight and the solid product collected by filtration to give 46 g. (81.5% yield) of VIb, m.p. 156-160°. Recrystallization from methanol-water afforded analytically pure product, m.p. 161-162°.

*Anal.* Calcd. for  $C_{13}H_{10}O_4$ : C, 67.82; H, 4.38. Found: C, 67.54; H, 4.28.

## 6,7-Dimethoxy-2-naphthaleneacetamide (IXa).

To a stirred and ice-cooled solution of 39.5 g. (0.16 mole) of 6,7-dimethoxy-2-naphthaleneacetic acid (VIa) in 260 ml. of dry chloroform was added dropwise 100 g. (0.84 mole) of thionyl chloride. The mixture was allowed to warm to room temperature in 30 minutes after which was heated on a water bath at 45-50° for 2 hours, then allowed to remain at room temperature overnight. Solvent and excess thionyl chloride were removed under reduced pressure at <50° and the acid chloride residue was dissolved in 1 l. of anhydrous ether. The ethereal solution was added dropwise to 1 l. of rapidly stirred, ice-cooled solution of 20% aqueous ammonia. After addition was complete, the mixture was stirred in an ice bath for 2 hours and the solid were collected by filtration. This was washed with ice water and dried to give 38 g. (96% yield) of IXa, m.p. 199-201°. An analytical sample was prepared by recrystallization from aqueous methanol, m.p. 203-205°.

*Anal.* Calcd. for  $C_{14}H_{15}NO_3$ : C, 68.56; H, 6.16; N, 5.71. Found: C, 68.65; H, 6.09; N, 5.50.

*N*-Methyl-6,7-dimethoxy-2-naphthaleneacetamide.

This compound was prepared in a similar fashion from the acid chloride and methylamine, 98% yield, m.p. 168-170°.

*Anal.* Calcd. for  $C_{15}H_{17}NO_3$ : C, 69.48; H, 6.61; N, 5.40. Found: C, 69.43; H, 6.41; N, 5.27.

*N*-Benzyl-6,7-dimethoxy-2-naphthaleneacetamide.

This compound was obtained in a similar manner, 93% yield, m.p. 150-151°.

*Anal.* Calcd. for  $C_{21}H_{21}NO_3$ : C, 75.20; H, 6.31; N, 4.18. Found: C, 74.95; H, 6.42; N, 4.28.

## 6,7-Dimethoxy-2-naphthylethylamine Hydrochloride (Xa).

To a stirred suspension of 18 g. (0.073 mole) of IXa in 650 ml. of dry tetrahydrofuran was added dropwise, with cooling, 230 ml. of 1 *M* borane in tetrahydrofuran. The resulting mixture was stirred in the ice bath for 2 hours, at room temperature for 18 hours, and finally refluxed for 6 hours. The reaction mixture was then decomposed cautiously by dropwise addition of 60 ml. of ethanol followed by 140 ml. of 30% ethanolic hydrogen chloride. It was then stirred in the ice bath for 4 hours. The resulting product was collected by filtration, washed with ether and dried to yield 15.8 g., m.p. 238-240°. An additional 2.5 g. of product was obtained by treatment of the concentrated filtrate with ethanol and ether to raise the total yield to 93%. An analytical sample was obtained as shiny plates by recrystallization from butanol, m.p. 243-245°.

*Anal.* Calcd. for  $C_{14}H_{17}NO_2 \cdot HCl$ : C, 62.80; H, 6.78; N, 5.23. Found: C, 62.88; H, 6.56; N, 4.95.

Similarly prepared were the hydrochloride salt of *N*-methyl-6,7-dimethoxy-2-naphthylethylamine (XVa), 79% yield, m.p. 229-231°. *Anal.* Calcd. for  $C_{15}H_{19}NO_2 \cdot HCl$ : C, 63.94; H, 7.15; N, 4.97. Found: C, 63.81; H, 7.16; N, 5.09 and the hydrochloride salt of *N*-benzyl-6,7-dimethoxy-2-naphthylamine (XVb), 90% yield, m.p. 241-243°. *Anal.* Calcd. for  $C_{21}H_{23}NO_2 \cdot HCl$ : C, 70.48; H, 6.76; N, 3.91. Found: C, 70.09; H, 6.76; N, 3.85.

*N*-(6,7-Dimethoxy-2-naphthylethyl)formamide (XII).

To the free base of Xa (prepared by adding excess dilute sodium carbonate solution to the hydrochloride salt of 1.8 g. (6.7 mmoles) of Xa, followed by chloroform extraction and evaporation) at 0-5° was added 35 ml. of acetic-formic anhydride. The resulting mixture was stirred overnight at room temperature, heated at 45-50° for 4 hours, then at 85-90° for 1 hour. The mixture was cooled and excess anhydride was decomposed by addition of 30 ml. of methanol. It was then evaporated to dryness *in vacuo* and the syrupy residue dissolved in 100 ml. of chloroform. The chloroform solution was washed with dilute sodium carbonate, water and dried (sodium sulfate). Evaporation of the solvent yielded a solid residue which, upon crystallization from water, gave 1.2 g. (69% yield) of XII as white needles, m.p. 104-106°.

*Anal.* Calcd. for  $C_{15}H_{17}NO_3$ : C, 69.48; H, 6.61; N, 5.40. Found: C, 69.77; H, 6.73; N, 5.22.

8,9-Dimethoxy-3,4-dihydrobenz[*h*]isoquinoline Hydrochloride (XIII).

To a stirred mixture of 1.5 g. of phosphorus pentachloride in 5 ml. of dry chloroform was added, with cooling, 0.9 g. (3.5 mmoles) of XII in 20 ml. of chloroform. The resulting mixture was stirred at room temperature for 3 days. To this was added 200 ml. of ether and the precipitated hydrochloride salt was collected by filtration. The solid was redissolved in 30 ml. of chloroform and reprecipitated with ether to give 0.6 g. (60% yield) of XIII, m.p. 237-240° dec. An analytical sample was prepared by recrystallization from propanol-ether, greenish yellow crystals, m.p. 248-250° dec.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2 \cdot HCl$ : C, 64.86; H, 5.81; N, 5.04; mol. wt., 241.3 + 36.5. Found: C, 64.64; H, 5.78; N, 4.93; m/e: 241 ( $M^+ \cdot HCl$ ).

8,9-Dimethoxy-3,4-dihydrobenz[*h*]isoquinoline Methiodide (XIV).

To a solution of 5.3 g. (0.022 mole) of the free base of XIII in 35 ml. of chloroform at 0° in a pressure bottle containing a magnetic stirring bar was added 4.2 g. (0.029 mole) of methyl iodide. The bottle was sealed and stirred for 16 hours at room temperature. The yellow solid, which started to precipitate from the stirred reaction mixture in *ca.* 30 minutes, was collected by filtration. It was washed with chloroform and ether, and dried to give 6.3 g. (75% yield) of XIV, m.p. 228-232°. Recrystallization from ethanol-ether afforded an analytical sample, m.p. 234-236°.

*Anal.* Calcd. for  $C_{16}H_{18}INO_2$ : C, 50.15; H, 4.73; N, 3.66. Found: C, 49.92; H, 4.67; N, 3.83.

8,9-Dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline Hydrochloride (Ia).

## Method A.

To a solution of 3.0 g. (0.011 mole) of the hydrochloride of 6,7-dimethoxy-2-naphthylethylamine (Xa) in 60 ml. of water at 50° was added dropwise 30 ml. of 40% formaldehyde. The pH of the reaction mixture was adjusted to between 1 and 2 by the addition of *ca.* 1 ml. of 15% hydrochloric acid. The resulting

solution was heated on a steam bath with stirring for 2 hours, then allowed to stand at room temperature for 2 days. The pH of the solution was then adjusted to 8 with aqueous ammonia and the basified solution extracted with chloroform (4 x 150 ml.). The chloroform extract was washed with water, dried (potassium carbonate), and evaporated *in vacuo*. The resulting residue was dissolved in 30 ml. of ethanol and acidified with 2 ml. of 30% ethanolic hydrogen chloride. After dilution with 200 ml. of ether, the mixture yielded 2.9 g. of a yellow crystalline solid, m.p. 175-177°. This was recrystallized from 70 ml. of butanol to give 1.2 g. (39% yield) of analytically pure Ia as light yellow crystals, m.p. 283-285°; nmr:  $J_{H_5, H_6}$ : 8 cps.

*Anal.* Calcd. for  $C_{15}H_{17}NO_2 \cdot HCl$ : C, 64.40; H, 6.49; N, 5.01. mol. wt., 243.3 + 36.5. Found: C, 64.47; H, 6.50; N, 4.95; m/e: 243 ( $M^+ \cdot HCl$ ).

Two minor by-products, the hydrochloride salt of *N*-methyl-8,9-dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline (Ib) (ca. 10% yield) and the hydrochloride salt of 8,9-dimethoxy-3,4-dihydrobenz[*h*]isoquinoline (XIII) (ca. 5% yield), were present in the butanol filtrate and identified by thin layer chromatography as well as infrared and mass spectra.

#### Method B.

A solution of 200 mg. of the hydrochloride salt of 8,9-dimethoxy-3,4-dihydrobenz[*h*]isoquinoline (XIII) in 20 ml. of 50% aqueous acetic acid was heated with 800 mg. of zinc dust on a steam bath for 7 hours with stirring. The mixture was filtered and the solid cake was washed with 3 x 15 ml. of hot water. The combined filtrate and washings were adjusted to pH 8 with 30% aqueous ammonia. The resulting solution was extracted with 5 x 50 ml. of chloroform. The chloroform was washed with water, dried (potassium carbonate), and evaporated. The residue was dissolved in 10 ml. of ethanol and to the solution was added 5 drops of saturated ethanolic hydrogen chloride followed by ether. The resulting precipitate was collected by filtration, washed with ether and dried to give 0.15 g. of crude product, m.p. 275-278°. Recrystallization from butanol gave 0.12 g. (60% yield) of Ia, m.p. 283-285°. The product was found to be identical with that prepared by Method A.

#### 8,9-Dimethoxy-2-methyl-1,2,3,4-tetrahydrobenz[*h*]isoquinoline Hydrochloride (Ib).

##### Method A.

To a solution of 3.2 g. (0.011 mole) of the hydrochloride salt of *N*-methyl-6,7-dimethoxy-2-naphthylethylamine (XVa) in 40 ml. of water was added 36 ml. of 40% formaldehyde. The mixture was heated on a steam bath for 6 hours and then allowed to stir at room temperature for 6 days. The pH of the resulting solution was adjusted to 8 with concentrated aqueous ammonia. It was extracted with chloroform and the extract washed, dried and evaporated. The residual product was taken up in ethanolic hydrogen chloride and precipitated with ether to give 3.1 g. of yellow solid, m.p. 186-189° dec. Fractionation of this solid with a mixture of butanol and ether, monitored by thin layer chromatography, gave 0.65 g. (20% yield) of pure Ib, m.p. 273-275° dec.

*Anal.* Calcd. for  $C_{16}H_{19}NO_2 \cdot HCl$ : C, 65.41; H, 6.86; N, 4.77. mol. wt., 257.3 + 36.5. Found: C, 65.09; H, 7.03; N, 4.70; m/e: 257 ( $M^+ \cdot HCl$ ).

##### Method B.

To a stirred suspension of 4.3 g. (0.011 mole) of 8,9-dimethoxy-3,4-dihydrobenz[*h*]isoquinoline methiodide (XIV) in 300 ml. of

ethanol was added 8.2 g., (0.22 mole) of sodium borohydride in three portions (time: ca. 45 minutes). The resulting light yellow solution was stirred at room temperature for 3 hours after which the mixture was evaporated to dryness at room temperature *in vacuo*. The residue was dissolved in 300 ml. of water and extracted with chloroform (4 x 160 ml.). The chloroform extract was washed with water, dried (potassium carbonate), filtered and the filtrate concentrated to 100 ml. This was acidified with 7 ml. of 20% ethanolic hydrogen chloride and the resulting mixture was added, with stirring, to 200 ml. of ether. The solid which separated was collected by filtration, washed with ether and dried to give 2.4 g. (72% yield) of Ib, m.p. 269-271° dec. Recrystallization from ethanol and ether (4:3) afforded pale yellow crystals, m.p. 273-275° dec. The product was found to be identical with that prepared by Method A. The free base of Ib was also prepared, m.p. 150-151°; nmr (deuteriochloroform): 7.50  $\tau$  (s, N-CH<sub>3</sub>);  $J_{H_5, H_6}$ : 8.2 cps,  $J_{H_7, H_{10}}$ : 1.5 cps.

*Anal.* Calcd. for  $C_{16}H_{19}NO_2$ : C, 74.68; H, 7.44; N, 5.44. Found: C, 74.61; H, 7.64; N, 5.49.

#### 2-Benzyl-8,9-dimethoxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline Hydrochloride (Ic).

This compound was prepared from XVb by essentially the same Pictet-Spengler cyclization procedure as that used for the preparation of Ia and Ib, except that dilute aqueous sodium carbonate solution instead of aqueous ammonia was used prior to chloroform extraction. The yield was 48%; m.p. 223-225°.

*Anal.* Calcd. for  $C_{22}H_{23}NO_2 \cdot HCl$ : C, 71.44; H, 6.54; N, 3.79; mol. wt., 353.4 + 36.5. Found: C, 71.23; H, 6.67; N, 3.80; m/e: 353 ( $M^+ \cdot HCl$ ).

#### 6,7-Methylenedioxy-2-naphthaleneacetamide (IXb).

To a mixture of 41 g. (0.17 mole) of 6,7-methylenedioxy-2-naphthalenecarboxylic acid (VIb) in 250 ml. of dry chloroform was added, with stirring and cooling, 100 ml. of thionyl chloride. The mixture was heated at 50° on a water bath for 2 hours, then allowed to stand at room temperature overnight. It was then filtered through a fritted glass funnel and the filtrate evaporated *in vacuo*. After most of the solvent was removed, the syrup was dissolved in 800 ml. of anhydrous ether and the solution was slowly added, with stirring and cooling, to 1 l. of 20% aqueous ammonia. The reaction mixture was stirred for 2 hours. The product was collected by filtration and recrystallized from ethanol to give 31 g. (76% yield) of IXb, m.p. 237-238°.

*Anal.* Calcd. for  $C_{13}H_{11}NO_3$ : C, 68.11; H, 4.84; N, 6.11. Found: C, 68.22; H, 4.91; N, 5.89.

#### 6,7-Methylenedioxy-2-naphthylethylamine Hydrochloride (Xb).

This compound was prepared from 14 g. of IXb, 600 ml. of anhydrous tetrahydrofuran and 230 ml. of 1 *M* borane in tetrahydrofuran by essentially the same method for the preparation of Xa from IXa. Recrystallization from ethanol gave 10.5 g. (68.6% yield) of Xb, m.p. 305° dec.

*Anal.* Calcd. for  $C_{13}H_{13}NO_2 \cdot HCl$ : C, 62.03; H, 5.61; N, 5.56; mol. wt., 215.2 + 36.5. Found: C, 62.48; H, 5.38; N, 5.47; m/e: 215 ( $M^+ \cdot HCl$ ).

#### 8,9-Methylenedioxy-1,2,3,4-tetrahydrobenz[*h*]isoquinoline (Id).

This compound was prepared from 2.77 g. (0.01 mole) of Xb, 250 ml. of water and 30 ml. of 40% formaldehyde by essentially the same procedure for the preparation of Ia from Xa. The product (0.5 g.) was isolated as a yellow-orange solid, m.p. 287° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>·HCl: C, 63.76; H, 5.35; N, 5.31; mol. wt., 227.2 + 36.5. Found: C, 63.84; H, 5.00; N, 5.10; m/e: 227 (M<sup>+</sup>-HCl).

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