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Stobbe condensation of 2,3-dimethoxybenzaldehyde with diethyl succinate, followed by reduction and cyclization, gave 3-carbethoxy-5,6-dimethoxy-1-tetralone (**7a**). Subsequent reduction, aromatization and side chain conversion yielded the key intermediate 7,8-dimethoxy-2-naphthalenecarboxaldehyde (**8c**). 6,7-Dimethoxybenz[*g*]isoquinoline (**1**) was prepared from **8c** *via* condensation with nitromethane, reduction, formylation, cyclization, and aromatization reactions; the isomeric 8,9-dimethoxybenz[*g*]isoquinoline (**2**) was obtained by the condensation of **8c** with the diethyl acetal of aminoacetaldehyde (**12**) followed by reduction, tosylation, cyclization and aromatization. The methiodides of both compounds were also prepared.

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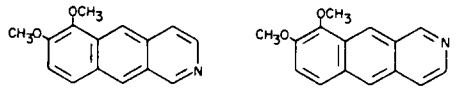
A planar tricyclic compound containing two methoxyl groups and a ring nitrogen, 6,7-dimethoxybenz[*g*]isoquinoline (**1**), was suggested by Adamson (1) for additional study of the relationship between N-O-O triangulation feature and antileukemic activity (2). The present work reports the synthesis of **1** and the isomeric 8,9-dimethoxybenz[*g*]isoquinoline (**2**).

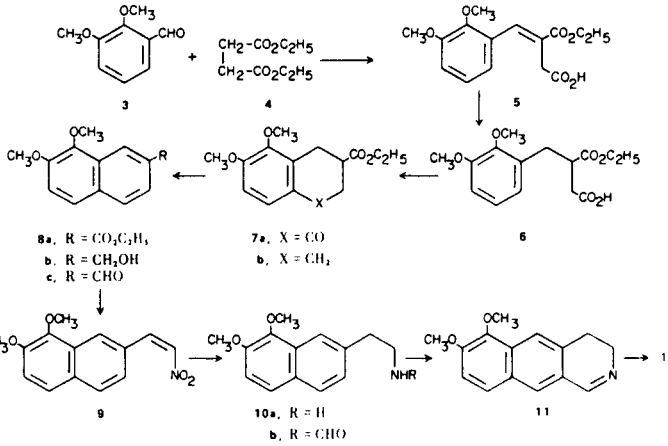


1 **2**

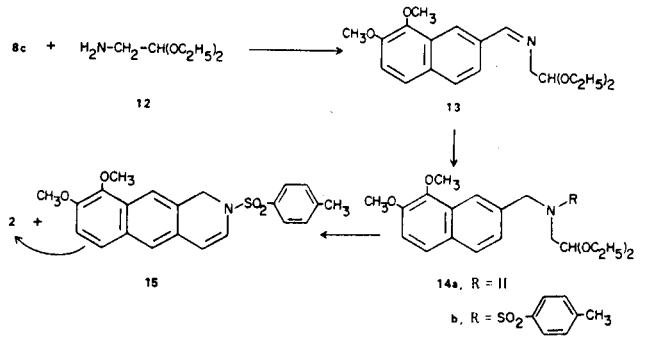
The Stobbe condensation (3) of the aldehyde **3** with diethyl succinate (**4**) yielded the unsaturated half ester **5**. Catalytic hydrogenation of **5** gave the half ester **6**, which was cyclized with a mixture of phosphorus pentachloride and stannic chloride in chloroform to the ketoester **7a** (4). Catalytic reduction of **7a**, according to the general reaction conditions of Cason and Phillips (5), afforded the ester **7b**.

Attempted aromatization of **7b** with (a) 10% palladium-on-charcoal in either refluxing *p*-cymene or refluxing tetralin, (b) chloranil in refluxing benzene, or (c) powdered sulfur, only resulted in the recovery of starting material. Finally, it was found that by refluxing a mixture of **7b** and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene, a high yield of the naphthalenecarboxylate **8a** was obtained.

Reduction of the ester **8a** to the alcohol **8b** was carried out with lithium aluminum hydride in equal volumes of benzene and ether. Activated manganese dioxide in refluxing xylene oxidized **8b** to the aldehyde **8c**. The nitrostyrene **9** was obtained by condensation of **8c** with nitromethane in the presence of ammonium acetate (6). Reduction of **9** to the amine **10a** can be achieved with either zinc-hydrochloric acid or catalytic hydrogenation in glacial acetic acid; but the best yield (almost quantitative) of the amine was obtained by aluminum hydride reduction (7,8) in tetrahydrofuran. Treatment of **10a** with acetic-formic anhydride yielded the formylated derivative **10b**. Bischler-Napieralski cyclization of **10b** afforded the hydrochloride salt of dihydrobenz[*g*]isoquinoline **11**, which, in turn, gave the desired compound **1** with palladium-on-charcoal in refluxing *p*-cymene. The methiodide of **1** was prepared from **1** and methyl iodide in chloroform.



For the synthesis of the isomeric 8,9-dimethoxybenz[*g*]isoquinoline (**2**) by a modified Pomeranz-Fritsch reaction (9), the aforementioned intermediate 7,8-dimethoxy-2-naphthalenecarboxaldehyde (**8c**) was used as the starting material. Condensation of **8c** and the diethyl acetal of aminoacetaldehyde (**12**) gave a quantitative yield of the anil **13**. Reduction of **13** to the amine **14a** was carried out with sodium borohydride in methanol. Tosylation of **14a** with tosyl chloride yielded **14b**, which was cyclized with 6*N* hydrochloric acid in refluxing dioxane to form a mixture of two products, **15** and **2**. The crude product was treated, without separation and purification,



with potassium *t*-butoxide in boiling *t*-butyl alcohol to yield **2**. Its methiodide was also prepared.

Preliminary biological evaluation of compounds **1**, **2**, and their methiodides failed to show inhibitory activity against leukemia P388 in mice.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover Melting Point apparatus. The nmr spectra were determined on a Varian HA-100 spectrophotometer. The mass spectrum data were obtained with a Varian Mat CH-4B mass spectrometer. The infrared spectra were taken on a Perkin-Elmer Infracord, and the ultraviolet absorption spectra were measured with a Beckman DK-2 spectrophotometer.

3-Carbethoxy-4-(2,3-dimethoxyphenyl)-3-butenoic Acid (**5**).

To a stirred solution of potassium *t*-butoxide in *t*-butyl alcohol (prepared from 60 ml. of *t*-butyl alcohol and 2.5 g. of potassium) was added dropwise, under nitrogen, a solution of 8.3 g. (0.050 mole) of 2,3-dimethoxybenzaldehyde (**3**) and 10.8 g. (0.062 mole) of diethyl succinate (**4**) in 75 ml. of *t*-butyl alcohol at 70-75°. After the addition was complete, the mixture was refluxed for 1 hour. It was then cooled, poured into 500 ml. of cold water, and acidified with dilute hydrochloric acid. The resulting mixture was extracted with ether (2 x 200 ml.). The yellow ether solution was back-extracted with 10% sodium bicarbonate until all the product was removed from the organic layer. The bicarbonate solution was cooled and acidified with dilute hydrochloric acid to *p*H 4 and the product was extracted with ether (2 x 200 ml.). The ether extract was washed with water (2 x 200 ml.) and dried over anhydrous sodium sulfate. Evaporation of ether gave 13.9 g. (94% yield) of **5** as a viscous oil. The product was purified from a mixture of ether and hexane.

Anal. Calcd. for $C_{15}H_{18}O_6 \cdot \frac{1}{2}H_2O$: C, 59.40; H, 6.31. Found: C, 59.69; H, 6.12.

3-Carbethoxy-4-(2,3-dimethoxyphenyl)butanoic Acid (**6**).

A solution of 13.9 g. (0.047 mole) of **5** in 100 ml. of glacial acetic acid was hydrogenated at room temperature with 0.8 g. of 10% palladium-on-charcoal in a Parr Hydrogenator at an initial pressure of 4.2 kg./cm^2 of hydrogen for 3 hours. After filtration, the filtrate was concentrated under reduced pressure and the oily residue was dissolved in 150 ml. of ether, washed with water (2 x 50 ml.), dried over anhydrous sodium sulfate, and evaporated to give 12.2 g. (87% yield) of **6** as a viscous oil.

Anal. Calcd. for $C_{15}H_{20}O_6 \cdot \frac{1}{2}H_2O$: C, 59.01; H, 6.93. Found: C, 59.01; H, 6.93.

Ethyl 7,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (**7a**).

To a stirred suspension of 84 g. of phosphorus pentachloride in 300 ml. of chloroform cooled to 0-3° was added, under nitrogen, a solution of 76.1 g. (0.25 mole) of **6** in 750 ml. of chloroform. After addition, the stirred mixture was allowed to slowly come to room temperature and stirring was continued for 19 hours. The reaction mixture was cooled to 0° and to this was added, with stirring, a solution of 42 ml. of stannic chloride in 250 ml. of chloroform, after which stirring was continued for another 3 hours at 0°. It was then poured, with vigorous stirring, into 800 ml. of cold, 10% hydrochloric acid. The chloroform layer was separated and washed successively with 10% hydrochloric acid (300 ml.), water (2 x 300 ml.), 10% sodium bicarbonate solution (2 x 200 ml.), and water (200 ml.). It was then dried over anhydrous sodium sulfate and evaporated to almost dryness. The residue was dissolved in 100 ml. of ethanol and the solution was again evaporated. Hexane was added to the residue and the product, after trituration, was collected by filtration to give 65.6 g. (92% yield) of **7a**, m.p. 74°. An analytical sample was prepared by recrystallization from ethanol, m.p. 75-76°; ir (Nujol): 1750 cm^{-1} (ester carbonyl), 1700 cm^{-1} (keto carbonyl); uv λ max (ethanol): 230 (log ε 4.39), 280 nm (log ε 4.27).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.69; H, 6.70.

Ethyl 7,8-Dimethoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (**7b**).

Ten g. (0.036 mole) of **7a** was dissolved in 200 ml. of hot absolute ethanol. The solution was cooled to room temperature and hydrogenated with 1 g. of 10% palladium-on-charcoal in a Parr Hydrogenator at 4.2 kg./cm^2 for 5 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness under reduced pressure to give 9.3 g. (97% yield) of **7b** as an oil. An analytical sample was prepared by vacuum distillation, b.p. 120° (0.05 mm).

Anal. Calcd. for $C_{15}H_{20}O_4 \cdot \frac{1}{2}H_2O$: C, 65.91; H, 7.74. Found: C, 65.51; H, 7.87.

Ethyl 7,8-Dimethoxy-2-naphthalenecarboxylate (**8a**).

To a solution of 28 g. (0.11 mole) of **7b** in 1 ℓ of dry benzene was added 60 g. (0.26 mole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The mixture was stirred and refluxed for 4 hours. After standing overnight at room temperature, the precipitated hydroquinone was filtered, washed with dry benzene and recycled (10). The combined benzene filtrate and washings were repeatedly extracted with cold, 5% sodium hydroxide until the aqueous extract was colorless. The benzene solution was again washed with cold water until the aqueous layer was neutral. The resulting orange benzene solution was dried over anhydrous sodium sulfate and evaporated to dryness. The oil residue solidified on standing to give 24 g. (87% yield) of **8a**. Recrystallization from hexane afforded analytically pure **8a** as white crystals, m.p. 65-66°; uv λ max (ethanol): 246.5 (log ε 4.88), 268 (4.17), 285 (4.17), and 350 nm (3.88).

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.05; H, 6.29.

7,8-Dimethoxy-2-naphthalenemethanol (**8b**).

To a stirred suspension of 18 g. (0.47 mole) of powdered lithium aluminum hydride in 800 ml. of anhydrous ether cooled at 0-5° was slowly added, during 1.5 hours, a solution of 23 g. (0.089 mole) of the ester **8a** in 800 ml. of dry benzene. After the addition, the mixture was stirred for another 2 hours at the same temperature, then refluxed for 3 hours. It was cooled and excess reagent was decomposed with cold water. This was followed by dropwise addition of 2*N* sulfuric acid until the slurry settled to the bottom of the reaction flask. The supernatant pale yellow solution was decanted into a separatory funnel. The slurry was extracted with a 1:1 ether-benzene mixture (2 x 250 ml.) and the extract also added to the separatory funnel. The organic solution was washed with 200 ml. of 2*N* sulfuric acid and then with water until the aqueous layer was neutral. After drying over sodium sulfate, the solution was evaporated to give 17 g. (88% yield) of **8b** as a yellow viscous oil, which solidified on standing. Recrystallization from hexane yielded analytically pure **8b**, m.p. 80-81°; uv λ max (ethanol): 283 (log ε 3.94), 294 (3.88), 320 (3.63), and 332 nm (3.62).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.49; H, 6.53.

7,8-Dimethoxy-2-naphthalenecarboxaldehyde (**8c**).

To a solution of 16 g. (0.073 mole) of the alcohol **8b** in 600 ml. of xylene was added 50 g. of active manganese dioxide. The mixture was refluxed with stirring under nitrogen for 4 hours, then cooled to 80° and filtered. The solid filter cake was extracted with hot benzene (2 x 100 ml.). The combined organic solution was dried over sodium sulfate and evaporated to dryness. The residual oily substance (13.5 g.) which solidified on standing, was triturated with a small amount of cold ethanol and filtered to give 10.8 g. (71% yield) of **8c**. Recrystallization from ethanol gave analytically pure **8c**, m.p. 88-89°; uv λ max (ethanol): 255.5 (log ε 4.80), 287.5 (4.19), and 362 nm (3.75).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.64; H, 5.71.

1-(7,8-Dimethoxy-2-naphthalenyl)-2-nitroethene (**9**).

To a solution of 11.75 g. of the aldehyde **8c** in 240 ml. of nitromethane was added 3.5 g. of ammonium acetate under nitrogen. The mixture was stirred 1 hour at room temperature, heated at 120° for 3.5 hours, then poured over crushed ice. It was diluted with 1.5 l. of water containing 4 g. of ammonium chloride. The precipitated product was extracted with benzene (3 x 250 ml.). The benzene extract was dried over anhydrous sodium sulfate and evaporated to yield a yellow residue, which was triturated with methanol, filtered, and washed with a small amount of cold methanol to give 8.9 g. (63% yield) of **9**, m.p. 124-126°. An analytical sample was prepared by recrystallization from methanol, m.p. 130-131°; uv λ max (ethanol): 234.5 (log ε 4.64), 290 (4.34) and 330 nm (4.41).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.81; H, 5.06; N, 5.40. Found: C, 65.10; H, 5.33; N, 5.49.

6,7-Dimethoxy-3,4-dihydrobenz[*g*]isoquinoline (**11**).

A solution of 5.0 g. (0.02 mole) of the nitro compound **9** in 140 ml. of dry tetrahydrofuran was added, under nitrogen, to a stirred suspension of aluminum hydride [prepared by dropwise addition of 2.6 ml. of concentrated sulfuric acid to a chilled (0°) suspension of 4.0 g. (0.1 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran] at 0°. The mixture was then stirred for 16 hours as it gradually came to room temperature. It was cooled and decomposed with 20 ml. of ice-cooled water followed by 15 ml. of 15% sodium hydroxide. The resulting mixture was filtered and the filtrate dried over anhydrous potassium carbonate. Evaporation of the solution gave 4.5 g. (quantitative yield) of the amine **10a** as an oil.

Three g. of **10a** was added, under nitrogen, to 75 ml. of acetic-formic anhydride at 0-5°. The resulting orange solution was stirred at 0° for 2 hours then stirred at room temperature overnight. It was heated at 80° for 2 hours and cooled. To this was added 50 ml. of cold methanol and the mixture was evaporated *in vacuo*. The residue was made basic with 20 ml. of 10% sodium carbonate and the product extracted with chloroform (3 x 20 ml.). The chloroform extract was dried over anhydrous sodium sulfate and evaporated to give 3 g. (92% yield) of the amide **10b** as a dark orange oil.

A solution of 1.0 g. (0.004 mole) of **10b** in 10 ml. of dry chloroform was added, under nitrogen, to a stirred suspension of 2.1 g. (0.01 mole) of phosphorus pentachloride in 20 ml. of dry chloroform at -10°. An orange color developed within 20 minutes. It was stirred under nitrogen for 48 hours. The mixture was then allowed to slowly come to the room temperature. To this, with cooling, was added 200 ml. of anhydrous ether. The resulting precipitated hydrochloride was collected by filtration, redissolved in 100 ml. of water, made basic with aqueous ammonia, and extracted with chloroform (3 x 30 ml.) to give 0.6 g. (63% yield) of **11** as an oil. This was reconverted to the hydrochloride with ethanolic hydrogen chloride and isolated by addition of ether. An analytical sample was prepared by recrystallization from chloroform-ether to give the hydrochloride of **11** as yellow needles, m.p. 194-195° dec.; uv λ max (ethanol): 272 (log ε 4.23), 362 (3.70), and 415 nm (3.94).

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HCl$: C, 64.86; H, 5.81; N, 5.04. Found: C, 64.59; H, 5.90; N, 4.78.

6,7-Dimethoxybenz[*g*]isoquinoline (**1**).

A mixture of 9.0 g. (0.037 mole) of the free base **11**, 4.5 g. of 10% palladium-on-charcoal, and 130 ml. of *p*-cymene was refluxed under nitrogen with stirring for 6 hours, cooled to 80° and filtered. The solid catalyst was washed with 20 ml. of hot *p*-cymene and the combined filtrate was concentrated under reduced pressure. The resulting residue was washed with hexane to give 5.2 g. (60% yield) of **1**, which was converted to its hydrochloride salt. An analytical sample was obtained by recrystallization from chloroform-ether, m.p. 204-205°; uv λ max (ethanol): 244 (log ε 4.66), 285 (3.88), 304 (3.96), 356 (3.74), and 382 nm (3.86). The hydrochloride salt of **1** had the following nmr (deuteriotrifluoroacetic acid): δ 11.17 (s, 1H, H_1), 8.87 (d, 1H, J = 7 cps, H_3), 8.59 (s, 1H, H_{10}), 8.47 (d, 1H, J = 7 cps, H_4), 8.16 (d, 1H, J = 9 cps, H_9), 8.02 (s, 1H, H_5), 7.86 (d, 1H, J = 9 cps, H_8), 4.26 and 4.23 (d, 6H, OCH_3); m/e: 239 (M^+-HCl-H_2O, 100%).

Anal. Calcd. for $C_{15}H_{13}NO_2 \cdot HCl \cdot H_2O$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.78; H, 5.28; N, 4.73.

6,7-Dimethoxy-2-methylbenz[*g*]isoquinolinium Iodide.

A solution of 2.0 g. of the free base **1** in 40 ml. of chloroform was mixed with 2 ml. of methyl iodide in a pressure bottle. It was allowed to stand at room temperature for 1 hour whereupon a precipitate gradually appeared. After overnight standing, the crystalline solid was collected by filtration, washed with ether, and dried to give 2.2 g. (70% yield) of the methiodide. An analytical sample was prepared by recrystallization from chloroform, m.p. 259-260° dec.; uv λ max (ethanol): 247.5 (log ε 4.65), 271 (4.20), 306 (3.96), and 385 nm (4.00).

Anal. Calcd. for $C_{16}H_{16}INO_2$: C, 50.41; H, 4.23; N, 3.67. Found: C, 50.10; H, 4.43; N, 3.79.

N-(7,8-Dimethoxy-2-naphthalenylmethylene)-2,2-diethoxyethylamine (**13**).

A mixture of 12.6 g. (0.058 mole) of 7,8-dimethoxy-2-naphthalenecarboxaldehyde (**8c**), 9.66 g. (0.072 mole) of aminoacetaldehyde diethyl acetal, and 2.1 g. of *p*-toluenesulfonic acid in 340 ml. of toluene was refluxed under nitrogen with stirring for 2 hours using a Dean-Stark apparatus to separate the water formed. The mixture was evaporated to dryness to give 23.5 g. (quantitative yield) of **13** as an oil. An analytical sample was prepared by washing a benzene solution of **13** with 10% sodium bicarbonate, drying over anhydrous sodium sulfate, and distillation, b.p. 180°/0 4 mm.

Anal. Calcd. for $C_{19}H_{25}NO_4 \cdot H_2O$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.60; H, 8.06; N, 3.97.

8,9-Dimethoxybenz[*g*]isoquinoline (**2**).

A solution of 23.5 g. (0.71 mole) of **13** in 150 ml. of methanol was stirred with 5.9 g. of sodium borohydride at 0° for 2 hours. The mixture was then stirred for 2 days while allowing the temperature to slowly come to room temperature. It was then evaporated under reduced pressure and to the solid residue was added 200 ml. of water. The resulting solution was extracted with chloroform (3 x 50 ml.). The chloroform extract was washed with

water, dried over anhydrous sodium sulfate and evaporated to give 20 g. (85% yield) of **14a** as an oil, which possessed a characteristic NH absorption band at 3320 cm^{-1}. This oil was added to 120 ml. of dry benzene and 12 g. of triethylamine and the resulting solution was cooled to 5°. To the solution was added dropwise, with stirring, a solution of 12.5 g. of tosyl chloride in 60 ml. of dry benzene. The mixture was then stirred for 24 hours while allowing to slowly warm to room temperature. It was evaporated under reduced pressure and the residue dissolved in 250 ml. of chloroform. The chloroform solution was washed with water, dried (sodium sulfate), and evaporated again to give 31.2 g. (quantitative yield) of **14b** as a dark yellow viscous oil.

To a solution of 30 g. of **14b** in 600 ml. of *p*-dioxane was added, under nitrogen, 90 ml. of 6*N* hydrochloric acid. The mixture was refluxed with stirring, for 7 hours in the absence of light. It was concentrated under reduced pressure, made basic with 10% sodium carbonate solution, and extracted with chloroform (3 x 50 ml.). The chloroform extract was dried (sodium sulfate) and evaporated to yield 21 g. of residue. This was mixed with potassium *t*-butoxide (prepared from 5 g. of potassium and 200 ml. of *t*-butyl alcohol under dry nitrogen) and refluxed, with stirring, for 30 minutes. The mixture was concentrated and extracted with benzene (3 x 50 ml.). The benzene extract was washed with water and the product was extracted into 150 ml. of 20% hydrochloric acid. The aqueous solution was made basic with 10% sodium carbonate solution and again extracted with chloroform (3 x 50 ml.). After drying and evaporation, it afforded 10 g. (79% yield) of **2** as an oil. Compound **2** (6.2 g.) was dissolved in 30 ml. of 10% ethanolic hydrogen chloride, then poured into 250 ml. of anhydrous ether, and the precipitated hydrochloride salt of **2** was collected by filtration to give 5.8 g. (93% yield) of product, m.p. 209-210°. An analytical sample was prepared by recrystallization from chloroform-ether, m.p. 228-229°; uv λ max (ethanol): 247.5 (log ε 4.01), 251 (4.60), 282 (4.29), 337 (3.57), 350 (3.52), 370 (3.52), and 403 nm (3.44). The hydrochloride salt of **2** gave the following nmr (deuteriotrifluoroacetic acid): δ 10.15 (d, 1H, J = 7 cps, H_3), 9.52 (s, 1H, H_1), 8.80 (d, 1H, J = 7 cps, H_4), 8.27 (s, 1H, H_5 or H_{10}), 8.19 (s, 1H, H_{10} or H_5), 8.06 (d, 1H, J = 9 cps, H_7), 7.88 (d, 1H, J = 9 cps, H_6), and 4.20 (s, 6H, OCH_3); m/e: 239 (M^+-HCl, 100%).

Anal. Calcd. for $C_{15}H_{13}NO_2 \cdot HCl$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.09; H, 5.32; N, 5.04.

8,9-Dimethoxy-2-methylbenz[*g*]isoquinolinium Iodide.

A solution of 3.5 g. of the free base **2** in 50 ml. of chloroform was mixed with 5 ml. of methyl iodide in a pressure bottle. After overnight standing at room temperature, the crystallized product was collected by filtration, washed with ether, and dried to give 5.2 g. (100% yield) of the methiodide, m.p. 245-246°. An analytical sample was prepared by recrystallization from chloroform, m.p. 249-250°; uv λ max (ethanol): 234 (log ε 4.53), 286 (4.49), 332 (3.80), 338 (3.68), and 405 nm (3.58).

Anal. Calcd. for $C_{16}H_{16}INO_2 \cdot \frac{1}{2}H_2O$: C, 49.25; H, 4.39; N, 3.59. Found: C, 49.33; H, 4.14; N, 3.51.

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