in the same constant-temperature bath which maintained the cell compartment temperature.

The initial reaction mixture of 3.0 ml of 0.1 *M* phosphate buffer at pH 7.50 containing the appropriate model compound was placed in a stoppered, quartz 1.00-cm Beckman cell. A solution of benzylpenicillenic acid in absolute EtOH (0.01 ml) was injected into the reaction cell, producing a concentration of reactant of 3.0×10^{-5} *M*. Optical density measurements were then recorded as a function of time. Spectrophotometric determination of the disappearance of benzylpenicillenic acid was followed at 322 mμ.

Since the concentration of model compound used was greater than the concentration of benzylpenicillenic acid by a factor of 1000, pseudo-first-order rate constants could be obtained. The infinity point was determined in all runs. One obtained, therefore, upon plotting the logarithm of the difference between the optical density at infinity and the optical density at the time in question against time, a straight line directly proportional to the pseudo-first-order rate constant for the reaction. Each run was repeated several times.

Nmr Studies.—Nmr spectra (Me_2CO-d_6–D_2O) were obtained on a Varian HA-100 internal lock nuclear magnetic resonance spectrometer and were used to characterize the methylated products of the reaction of benzylpenicillenic acid and EtSH. The spectrometer was in the frequency sweep mode, and signals were measured relative to TMS as internal standard. Sample concentrations were less than 5% w/v. Signals were read to ±0.03 ppm.

Mass Spectrometry.—A CEC-110B high-resolution mass spectrometer was used to determine the molecular weight of the methylated products of the reaction of benzylpenicillenic acid and EtSH.

Acknowledgments.—We gratefully acknowledge the many helpful discussions with Dr. R. A. Archer, the help of Dr. H. E. Boaz with nmr interpretation and Mr. J. L. Occolowitz with mass spectral interpretation, and the excellent technical assistance of Mr. W. R. Brown.

Centrally Acting Emetics. III. Derivatives of β-Naphthylamine[1a,b]

WILLIAM K. SPRENGER, JOSEPH G. CANNON,[1c] B. K. BARMAN,

Division of Medicinal Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52240

AND ALLAN M. BURKMAN

Division of Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

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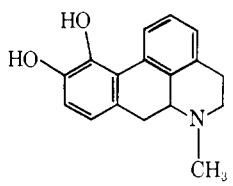
The synthesis of a series of β-naphthylamine derivatives closely corresponding to a portion of the apomorphine molecule was undertaken to investigate structure–activity relationships of this centrally active emetic. Employing independent synthetic routes, derivatives of 2-amino-5,6-naphthalenediol and of 2-amino-1,2,3,4-tetrahydronaphthalene-5,6-diol have been prepared. Biological test data are presented.

Relatively few systematic attempts have been made to elucidate the emetic pharmacophore of apomorphine (**1**), or of other emetic aporphine derivatives. Eddy, in an extensive series of papers,[2] presented data on a series of phenanthrenediols **2** and derivatives which can be viewed as fragments or analogs of fragments of the apomorphine molecule. Some of the compounds pos-



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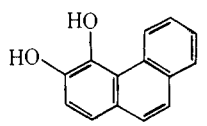

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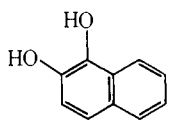

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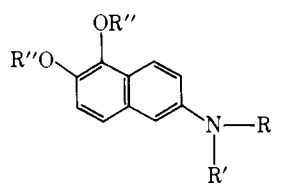
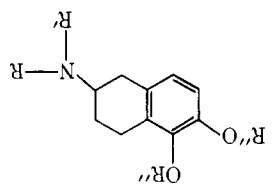
sessed emetic activity in cats, albeit of a lower order than apomorphine. Eddy did not report test data on naphthalenediols **3**, nor on any diols of types **2** and **3** which also possessed an amino function. Thrift[3] prepared 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (an isomer of compound **11** below) as an analog of adrenergic amines, but possible emetic effects were not mentioned. A search of the literature revealed no other reports of simple amino derivatives of **2** or **3**.

The present work was based on the assumption that the apomorphine molecule is more complex than is necessary for maximal emetic activity, and on the premise that significant pharmacophoric groups in apomorphine are the 1,2-diphenolic moiety and the amino function. The simplest fragment of the apomorphine molecule which could be visualized to possess emetic activity was a 2-aminonaphthalene-5,6-diol system. Accordingly, structures **4**–**12** were chosen for study.





4, R = R′ = H; R″ = CH_3
5, R = R′ = R″ = H
6, R = H; R′ = R″ = CH_3
7, R = R″ = H; R′ = CH_3
8, R = R′ = R″ = CH_3
9, R = R′ = CH_3; R″ = H
10, R = R′ = H; R″ = CH_3
11, R = H; R′ = R″ = CH_3
12, R = R′ = R″ = CH_3

Dreiding models indicated that distances between the phenolic groups and the nitrogen atom are almost the same in these naphthalene derivatives as in apomorphine. Since the ring system of apomorphine is rigid and almost planar, evaluation of the emetic activity of **4**–**9** is of

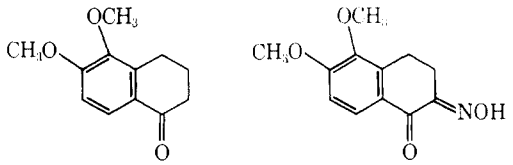
(1) (a) Part II: M. V. Koch, J. G. Cannon, and A. M. Burkman, *J. Med. Chem.*, **11**, 977 (1968). (b) This investigation was supported in part by Grant NB-04349, National Institute of Neurological Diseases and Blindness, and in part by National Institutes of Health predoctoral fellowship GM-19445 (W. K. S.). Abstracted in part from a thesis submitted by W. K. S. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1965. (c) To whom all correspondence should be addressed.

(2) This work was summarized and discussed by L. F. Small, N. B. Eddy, E. Mosettig, and C. K. Himmelsbach, *Public Health Rept. (U. S.), Suppl.*, **138**, 1 (1938).

(3) R. I. Thrift, *J. Chem. Soc., C*, 288 (1967).

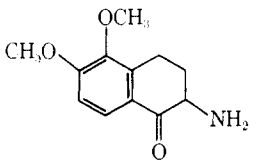
some interest. The tetrahydro series **10–12** has a partially reduced ring system bearing an amino function, which more closely approximates the apomorphine system. It was speculated that the series of compounds might permit further evaluation of the requirement of free, unetherified phenolic groups for maximum emetic activity, as was suggested by Bergell and Pschorr.[4] In addition, it was hoped that these derivatives might permit further evaluation of the role of the nitrogen atom in the emetic action of apomorphine: whether it is mandatory that the nitrogen be a part of a ring system, and whether the degree of substitution on the nitrogen can alter emetic activity.

Compound **4** was prepared from 5,6-dimethoxy-2-naphthol by means of a Bucherer reaction; **6** and **8** were prepared from **4** by alkylation procedures. Compounds **5**, **7**, and **9** were prepared from the corresponding dimethyl ethers by use of boron tribromide, which provided a facile ether cleavage under relatively mild conditions and with a minimum of oxidative decomposition of the resulting 1,2-diol systems. In studies leading to preparation of **10**, it was proposed that 3,4-dihydro-2-amino-5,6-dimethoxy-1(2H)-naphthalenone (**15**) could be obtained by a synthetic sequence beginning with a nitrosation of **13** to form **14**. Treatment of **13**[5]



13

14



15

with a variety of nitrite esters under either acidic or basic conditions gave erratic results and generally unsatisfactory yields of the oximino ketone **14**. Compound **15** was prepared from the oxime tosylate of **13** by a Neber rearrangement;[6] the ketonic group of **15** was removed by hydrogenolysis to form **10**, and the nitrogen of **10** was alkylated by conventional procedures to yield **11** and **12**. Attempts to cleave the dimethyl ether links of **10–12**, using a variety of reagents and procedures, failed.

Pharmacology. Preparations.—Hydrochloride salts of all compounds were dissolved in appropriate volumes of sterile physiological saline. Solutions were prepared immediately before use.

Acute Toxicity in Mice.—Graded doses of each compound were administered intraperitoneally to groups of mice[7] and the animals were observed for a period of 24 hr following injection. Except for compounds **4**, **6**, and **8**, death usually occurred within 15 min following injection of high doses of the drugs and in all such instances the animals that failed to succumb to the lethal effects within 1 hr survived thereafter. Compounds **4**, **6**, and **8** were characterized by a long latent period, lethal effects rarely appearing before 5 hr had elapsed. Most deaths occurred between 6 and 12 hr, with a few animals succumbing after an 18-hr delay (see Table I). Compounds **4**–**9** failed to exhibit prominent convulsant activity at any dose, but rather produced evidence of drug-induced "depression" which expressed itself mainly in terms of decreased locomotor activity. There was no loss of righting reflex at sublethal doses.

TABLE I

TOXICITY OF β-NAPHTHYLAMINE DERIVATIVES IN ALBINO MICE

No.	CD_{50} ± SE[a] μmoles/kg	RP[b]	LD_{50} ± SE[c] μmoles/kg	RP[b]
1	355 ± 29	1.00	528 ± 21	1.00
5			78 ± 9	6.77
7			84 ± 9	6.28
9			79 ± 6	6.68
4			2380 ± 125	0.22
6			2544 ± 169	0.21
8			3065 ± 157	0.17
10	480 ± 32	0.74	533 ± 28	0.99
11	349 ± 8	1.02	392 ± 15	1.35
12	199 ± 11	1.78	383 ± 29	1.38

[a] Median convulsive dose ± standard error. All doses are expressed in terms of micromoles of base. [b] Potency relative to apomorphine. [c] 10-hr median lethal dose ± standard error.

The naphthalenediols **5**, **7**, and **9** were extremely irritating following intraperitoneal injection, as evidenced by abdominal retraction, "writhing" gait,[8] and, following autopsy, extensive peritoneal congestion. The tetrahydro derivatives **10–12** produced tonic-clonic convulsions of brief duration and **11** appeared to be as potent as apomorphine in terms of doses required to provoke seizures. The *intensity* of convulsions produced by **12** were greater than the corresponding intensities of **10** and **11**, and were comparable to that of apomorphine-induced seizures. Although low, subconvulsive doses of **10–12** usually increased spontaneous locomotor activity, higher subconvulsive doses markedly diminished activity.

Compulsive Gnawing in Mice and Pecking in Pigeons. These stereotyped behavioral responses characteristically generated by low doses of apomorphine were not evoked by any of the new substances.

Emesis in Pigeons and Dogs.—Compounds **4**–**9** produced only an occasional retching episode when administered intramuscularly to pigeons, and only at comparatively high doses. These same substances administered intramuscularly to female mongrel dogs also failed to produce vomiting with doses equivalent to 100 times the threshold dose (TED) for apomorphine. The protocol for screening compounds for emetic activity in dogs has been described.[1a] Compound **10** provoked emesis in pigeons only at doses in excess of 80 μmoles/kg, while **11** and **12** produced violent and sustained vomiting in birds at doses of 20 μmoles/kg. *The last two substances were far more emetic in pigeons than was apomorphine.*

Although relatively high doses of **10–12** provoked vomiting in pigeons, they were devoid of such action in dogs when administered intramuscularly in doses up to 37 μmoles/kg (100TED).

(4) P. Bergell and R. Pschorr, *Therap. Gegenwart*, **45**, 247 (1904).
(5) N. F. Elmore and T. J. King, *J. Chem. Soc.*, 4425 (1961).
(6) C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).
(7) Female Harlan ICR albino mice, 18–22 g (Harlan Industries, Cumberland, Ind.).
(8) R. A. Turner, "Screening Methods in Pharmacology," Academic Press, New York, N. Y., 1965, p 114.

Experimental Section[9]

2-Amino-5,6-dimethoxynaphthalene (4).—A bomb containing 30.0 g (0.147 mole) of 5,6-dimethoxy-2-naphthol[10] and 25 g of SO_2 in 100 ml of concentrated NH_4OH was agitated vigorously and heated at 150–160° for 36 hr. The bomb was cooled with agitation, and the contents were removed with a small amount of H_2O. The aqueous portion was decanted from a yellow granular solid and was extracted with Et_2O (two 150-ml portions). The granular solid was dissolved in 2.5 l. of Et_2O to which were added the ethereal extracts. The combined Et_2O solution was extracted with 5% HCl, (four 500-ml portions), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 7.7 g (26%) of unreacted 5,6-dimethoxy-2-naphthol. The combined acidic extracts were made strongly alkaline with 20% NaOH. The light tan solid which separated was collected on a filter and dried, giving 20.9 g (94%, allowing for recovered starting material) of **4**, mp 147–149°. Two recrystallizations from EtOH gave colorless prisms, mp 148.5–149.5°. *Anal.* ($C_{12}H_{13}NO_2$) C, H, N. The HCl salt was recrystallized from EtOH–Et_2O; mp 243–244° dec. *Anal.* ($C_{12}H_{14}ClNO_2$) C, H, Cl, N.

A picrate salt crystallized from EtOH; mp 194–195° dec. *Anal.* ($C_{18}H_{16}N_4O_9$) C, H, N.

2-Formamido-5,6-dimethoxynaphthalene (16).—A mixture of 15.0 g (0.074 mole) of **4** and 18 g (0.35 mole) of 90% formic acid in 500 ml of 1:1 C_6H_6–toluene was refluxed, using a Dean–Stark trap to collect H_2O. After 24 hr an additional 18.0 g of 90% formic acid was added; refluxing was continued for 96 hr. The solvent was removed under reduced pressure, leaving a light yellow-gray solid which was dissolved in 4 l. of Et_2O and washed with 1% HCl (two 250-ml portions). The Et_2O solution was dried ($MgSO_4$) and evaporated under reduced pressure to yield 16.8 g (98%) of a light pink solid, 132–135°. Two recrystallizations from EtOH–H_2O gave colorless microcrystalline needles, mp 137.5–139°. *Anal.* ($C_{13}H_{13}NO_3$) C, H, N.

2-Methylamino-5,6-dimethoxynaphthalene (6).—Compound **16** (5.0 g, 0.022 mole) in 150 ml of purified[11] THF was added dropwise to a stirred suspension of 3.8 g (0.10 mole) of $LiAlH_4$ in 100 ml of purified THF. After addition was complete, the reaction mixture was refluxed 12 hr, then 15 ml of H_2O was added dropwise. The mixture was filtered, the solid on the filter was washed with several portions of THF, and the combined THF solutions were dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave a light brown semisolid which was mixed with a small amount of cold 2-PrOH and collected, giving 4.1 g (87%) of light tan prisms. Recrystallization from 2-PrOH–H_2O gave colorless needles, mp 64.5–65.5°. *Anal.* ($C_{13}H_{15}NO_2$) C, H, N. The HCl salt was recrystallized from EtOH–Et_2O; mp 201–202° dec. *Anal.* ($C_{13}H_{16}ClNO_2$) C, H, Cl, N.

A picrate salt was recrystallized from EtOH as orange needles, mp 149–150° dec. *Anal.* ($C_{19}H_{18}N_4O_9$) C, H, N.

2-Dimethylamino-5,6-dimethoxynaphthalene (8).—A modification of the method of Hünig[12] was employed. A mixture of 5.0 g (0.025 mole) of **4**, 10.0 g (0.119 mole) of $NaHCO_3$, 10 ml (13.3 g, 0.106 mole) of purified[13] Me_2SO_4, and 25 ml of H_2O was stirred and warmed gently until evolution of CO_2 began. The reaction mixture was then placed in a cooling bath at 10° for 3 hr with stirring, then warmed to 55° for 0.5 hr. The mixture was allowed to cool and was extracted with $CHCl_3$ (two 200-ml portions). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated under reduced pressure to yield 5.4 g (95%) of a tan solid, mp 91–94°. Two recrystallizations from EtOH gave light tan needles, mp 94–95°. *Anal.* ($C_{14}H_{17}NO_2$) C, H, N. The HCl salt was recrystallized from EtOH–Et_2O; mp 208–209° dec. *Anal.* ($C_{14}H_{18}ClNO_2$) C, H, Cl, N.

A picrate salt recrystallized from EtOH as dark orange needles, mp 141–142° dec. *Anal.* ($C_{20}H_{20}N_4O_9$) C, H, N.

2-Amino-5,6-naphthalenediol Hydrochloride (5).—BBr_3 (10.0 g, 0.04 mole, Matheson Coleman and Bell) in 50 ml of anhydrous C_6H_6 was added to 2.0 g (0.01 mole) of **4** in 200 ml of anhydrous C_6H_6; a gray solid separated at once. After heating and stirring for several minutes, a clear solution resulted. The reaction was refluxed with stirring for 3 hr; it was cooled and stirred into 500 ml of H_2O. After thorough mixing, the two-phase mixture was allowed to separate and the C_6H_6 layer was removed. The acidic aqueous phase was washed with Et_2O (two 150-ml portions), then was treated with a solution of 20 g of Na_2SO_3 in 200 ml of H_2O. The resulting clear yellow, neutral solution was extracted with ten 200-ml portions of Et_2O. The combined Et_2O extracts were stirred with anhydrous $MgSO_4$ for 0.75 hr, then were allowed to stand for 0.25 hr. The Et_2O solution was filtered and the filtrate was treated with ethereal HCl. A creamy white solid separated and was allowed to stand in the cold for several hours; it was then collected and dried, giving 1.6 g (77%) of a gray-white powder. This was recrystallized twice from MeOH–Et_2O to yield a white solid which, when introduced into a melting point bath at 250°, showed mp 275–277° dec. *Anal.* ($C_{10}H_{10}ClNO_2$) C, H, Cl, N.

An oxalate salt was prepared by treating an ethereal solution of the free base of **5** with a saturated solution of anhydrous oxalic acid in Et_2O; a gray solid was obtained which recrystallized from MeOH–Et_2O as a light gray solid which, when introduced into a melting-point bath at 200°, showed mp 235.5–237° dec. *Anal.* ($C_{13}H_{13}NO_6$) C, H, N.

2-Methylamino-5,6-naphthalenediol Hydrochloride (7).—Compound **6** (2.0 g, 0.0092 mole) was treated with 9.0 g (0.036 mole) of BBr_3, and the product of the reaction was isolated as described for **5**. The HCl salt (1.5 g, 72%) was obtained as a light gray solid from MeOH–Et_2O. This material, when introduced into a melting point bath at 200°, showed mp 233.5–235° dec. *Anal.* ($C_{11}H_{12}ClNO_2$) C, H, Cl, N.

An oxalate salt, prepared as described for **5**, was recrystallized from MeOH–Et_2O to give a light gray solid which, when introduced into a melting point bath at 200°, showed mp 215–216° dec. *Anal.* ($C_{15}H_{13}NO_6$) C, H, N.

2-Dimethylamino-5,6-naphthalenediol Hydrochloride (9).—Compound **8** (2.0 g, 0.0087 mole) was treated with 9.0 g (0.036 mole) of BBr_3, and the product of the reaction was isolated as described or **5**. The HCl salt (1.9 g, 92%) was obtained as a white solid from MeOH–Et_2O. This material, when introduced into a melting-point bath at 200°, showed mp 241–242° dec. *Anal.* ($C_{12}H_{14}ClNO_2$) C, H, Cl, N.

An oxalate salt, prepared as for **5**, was recrystallized from MeOH–Et_2O to give a white solid which, when introduced into a melting point bath at 200°, showed mp 239–240.5° dec. *Anal.* ($C_{14}H_{15}NO_6$) C, H, N.

2-Isonitroso-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone (14). Method A was a modification of the method of Hartung and Crossley.[14] Methyl nitrite was generated by adding 4.5 ml of 30% H_2SO_4 dropwise to a solution of 4.0 g (0.058 mole) of $NaNO_2$ in 2.4 ml (0.060 mole) of MeOH and 2.0 ml of H_2O. The methyl nitrite and anhydrous HCl were simultaneously passed into a stirred, cooled solution of 7.2 g (0.035 mole) of **13**[5] in 50 ml of anhydrous Et_2O at such a rate that gentle refluxing occurred. After 0.5 hr, no more methyl nitrite was evolved; the flow of HCl was stopped and stirring and cooling were continued for an additional 0.5 hr. The dark red-brown mixture was extracted with several 50-ml portions of 10% NaOH, then the combined extracts were neutralized with 20% HCl. A yellow-brown, flocculent product separated and was isolated by centrifugation followed by collection on a filter. Recrystallization from H_2O gave a yellow microcrystalline solid (0.035 g, 4%), mp 188–190° dec. *Anal.* ($C_{12}H_{13}NO_4$) N; C: calcd, 61.27; found, 61.76; H: calcd, 5.57; found, 4.83.

Method B.—A modification of the method of Straus and Ekhard[15] was used. Freshly distilled isoamyl nitrite (2.4 g, 0.02 mole) and 4.1 g (0.02 mole) of **13** in 60 ml of anhydrous Et_2O was added dropwise to a cooled, stirred solution of 0.8 g (0.02 g-atom) of K in 5 ml of anhydrous EtOH and 40 ml of anhydrous Et_2O. After addition was complete, the brown mixture was stored overnight in a refrigerator. The chocolate brown solid which separated was collected on a filter, washed with several portions of anhydrous Et_2O, then dissolved in 50 ml of H_2O and the solution was taken to pH 7 with

(9) All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas–Hoover Uni-Melt apparatus and are corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical value. Nuclear magnetic resonance spectra were determined with a Varian A-60 instrument.

(10) M. Gates, *J. Amer. Chem. Soc.*, **72**, 228 (1950).

(11) Purified by shaking with KOH pellets, then distilling from $LiAlH_4$ just prior to use.

(12) S. Hünig, *Chem. Ber.*, **85**, 1056 (1952).

(13) Me_2SO_4 was washed twice with an equal volume of ice water, then with one-half its volume of cold, saturated $NaHCO_3$, and stored over anhydrous K_2CO_3.

(14) W. Hartung and F. Crossley in "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, New York, N. Y., 1943, p 363.

(15) F. Straus and W. Ekhard, *Ann. Chem.*, **444**, 146 (1925).

5% HCl. A yellow solid separated which was collected on a filter. Recrystallization from C_6H_6 gave light yellow microcrystalline needles (1.6 g, 34%), mp 185–186° dec. Further recrystallization from H_2O gave colorless needles, mp 189–190° dec. The ir spectrum of this compound ($CHCl_3$) was identical with that of the product of method A. *Anal.* ($C_{12}H_{13}NO_4$) C, H; N: calcd, 5.96; found, 5.38.

3,4-Dihydro-5,6-dimethoxy-1(2H)-naphthalenone Oxime (17).—Hydroxylamine hydrochloride (17.0 g, 0.245 mole) and anhydrous K_2CO_3 (17.0 g, 0.123 mole) were added to a solution of 30.0 g (0.145 mole) of **13** in 300 ml of MeOH and 30 ml of H_2O. The reaction mixture was stirred and refluxed for 0.75 hr, then was cooled and placed in a refrigerator overnight. The solid material which separated was collected and washed several times with ice water. The dried product (25.8 g, 80%) was obtained as light tan needles, mp 162–164°. Dilution of the methanolic filtrate with H_2O gave an additional 3.3 g of product, mp 158–161°. Recrystallization of the combined products from anhydrous MeOH gave colorless needles, mp 164.5–165.5°. *Anal.* ($C_{12}H_{15}NO_3$) C, H, N.

3,4-Dihydro-5,6-dimethoxy-1(2H)-naphthalenone O-*p*-Toluenesulfonyloxime (18).—Compound **17** (25.0 g, 0.113 mole) in 100 ml of pyridine was added dropwise with stirring to a cold solution of 44.0 g (0.231 mole) of *p*-$MeC_6H_4SO_2Cl$ in 100 ml of pyridine. The reaction vessel was cooled in an ice bath, and addition was maintained at such a rate that the temperature was kept at 2–4°. After addition was complete, the mixture was stirred for 12 hr in the cold, then it was poured over 3 l. of cracked ice. The product which separated was collected on a filter, triturated in a mortar, washed thoroughly with H_2O, and again collected on a filter. The dried product was a tan powder, mp 116–119°. Repeated crystallization from anhydrous EtOH gave 40.7 g (96%) of colorless needles, mp 124–125°. *Anal.* ($C_{19}H_{21}NO_5S$) C, H, N.

3,4-Dihydro-2-amino-5,6-dimethoxy-1(2H)-naphthalenone Hydrochloride (15).—A suspension of 40.0 g (0.107 mole) of **18** in 130 ml of anhydrous EtOH was added to a stirred, cooled solution of 4.5 g (0.115 g-atom) of K in 70 ml of anhydrous EtOH. The reaction mixture was kept cold for 6 hr, then was allowed to come to room temperature over the next 12 hr. The dark green mixture was filtered and the solid material on the filter was washed twice with anhydrous Et_2O. The washings were added to the filtrate, to which was then added 800 ml of Et_2O; this green solution was poured into 200 ml of 10% HCl in a separatory funnel. After thorough agitation, the two-phase mixture was separated, and the dark red organic layer was extracted with 10% HCl (four 200-ml portions). The combined aqueous extracts were washed once with 250 ml of Et_2O, then the H_2O was removed at 40° under reduced pressure. The residual brown solid was treated with 300 ml of hot anhydrous EtOH; this extract was treated with charcoal and filtered, and the filtrate was diluted with 3 l. of anhydrous Et_2O. A light tan solid (14.7 g, 54%) which separated was collected, mp 205–208° dec. Repeated reprecipitation from EtOH–Et_2O gave material, mp 208.5–210° dec. *Anal.* ($C_{12}H_{16}ClNO_3$) C, H, Cl, N.

1,2,3,4-Tetrahydro-2-amino-5,6-dimethoxynaphthalene (10).—A mixture of 15.0 g (0.058 mole) of **15** and 3.0 g of 10% Pd–C in 300 ml of glacial AcOH was hydrogenated in a Parr shaker apparatus at a maximum pressure of 3.16 kg/cm² and a temperature of 40°. Uptake of H_2 was complete in 36 hr. The reaction vessel was cooled and a solution of 10 ml of 70% $HClO_4$ in 10 ml of glacial AcOH was added to the charge. Hydrogenation was continued, employing a maximum pressure of 2.81 kg/cm² and a temperature of 80–90°. Uptake of H_2 was complete in 8 hr. The reaction mixture was cooled and the catalyst was removed by filtration. The clear yellow filtrate was treated with a solution of 15.0 g of KOAc in 50 ml of glacial AcOH; $KClO_4$ precipitated immediately and was collected on a filter. The filtrate was concentrated under reduced pressure to a semisolid mass; this was taken up in 500 ml of 5% HCl and the solution was extracted with Et_2O (two 200-ml portions) which was discarded. The aqueous phase was made strongly alkaline with 20% KOH, then was extracted with Et_2O (three 250-ml portions). The combined Et_2O extracts were washed once with 5% NaCl then were dried (Na_2SO_4). Filtration and concentration of the filtrate under reduced pressure gave 5.1 g (42%) of a clear yellow-brown liquid which was distilled at 121–123° (0.5 mm) to give a colorless product: $n^{25}D$ 1.5528; nmr (CCl_4), δ 1.17 (s, 2), 1.3–2.2 (m, 2), 2.2–3.2 (m, 5), 3.72 (s, 3), 3.75 (s, 3), and 6.5–7.2 ppm (m, 2). *Anal.* ($C_{12}H_{17}NO_2$) C, H, N.

The HCl salt was recrystallized from EtOH–Et_2O: mp 270–272° dec. *Anal.* ($C_{12}H_{18}ClNO_2$) C, H, Cl, N.

1,2,3,4-Tetrahydro-2-formamido-5,6-dimethoxynaphthalene (19).—A mixture of 1.4 g (0.0068 mole) of **10** and 3.0 g (0.06 mole) of 90% formic acid in 50 ml of PhMe was refluxed using a Dean–Stark trap to collect H_2O. After 24 hr, an additional 3.0 g of 90% formic acid was added and refluxing was continued for another 48 hr. The light yellow solution was taken to dryness under reduced pressure and the cream-colored residue was dissolved in 500 ml of Et_2O. The Et_2O solution was washed with 100 ml of 1% HCl, then it was dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave 1.45 g (91%) of a light cream-colored solid, mp 120–126°. Repeated recrystallization from cyclohexane gave small colorless prisms, mp 134–135°. *Anal.* ($C_{13}H_{17}NO_3$) C, H, N.

1,2,3,4-Tetrahydro-2-methylamino-5,6-dimethoxynaphthalene (11).—A solution of 1.2 g (0.0051 mole) of **19** in 250 ml of anhydrous Et_2O was added dropwise to a stirred suspension of 1.9 g (0.05 mole) of $LiAlH_4$ in 250 ml of anhydrous Et_2O. After addition was complete, the stirred mixture was heated under reflux for 10 hr. To the cooled reaction mixture was added 6 ml of H_2O dropwise and the resulting suspension was filtered. The solid on the filter was washed with several portions of Et_2O, and the combined filtrate and washings were dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave 0.95 g (84%) of a faintly yellow liquid which was distilled through a short-path distillation apparatus as a clear, colorless liquid, bp 115–116° (0.3 mm), $n^{24}D$ 1.5448. On exposure to air, this product darkened rapidly. *Anal.* ($C_{13}H_{19}NO_2$) C, H, N.

The HCl salt was recrystallized from EtOH–Et_2O: mp 209–211° dec. *Anal.* ($C_{13}H_{20}ClNO_2$) C, H, Cl, N.

1,2,3,4-Tetrahydro-2-dimethylamino-5,6-dimethoxynaphthalene (12).—A mixture of 1.4 g (0.0068 mole) of **10** and 2.0 g (0.039 mole) of 90% formic acid was prepared in the cold, then was warmed until a clear solution resulted. This was treated with 1.5 g (0.017 mole) of 35% HCHO solution and the resulting mixture was placed in an oil bath at 100°. Evolution of CO_2 began within 5 min and subsided after 1 hr. The reaction mixture was maintained at 100° for 12 hr, then was cooled and removed from the reaction vessel with the aid of 50 ml of 5% HCl. The acid mixture was concentrated under reduced pressure, and the resulting brown semisolid was taken up in 50 ml of H_2O. This solution was made strongly alkaline with 20% NaOH; the resulting suspension was extracted with C_6H_6 (three 50-ml portions). The combined extracts were dried (K_2CO_3) and filtered, and the filtrate was concentrated under reduced pressure to give 1.6 g of a dark liquid which was distilled through a short-path apparatus to give 1.05 g (66%) of a colorless liquid, bp 132–134° (0.4 mm), $n^{26}D$ 1.5409. On exposure to air, the liquid darkened rapidly. *Anal.* ($C_{14}H_{21}NO_2$) C, H, N.

The HCl salt was recrystallized from EtOH–Et_2O: mp 238–240° dec. *Anal.* ($C_{14}H_{22}ClNO_2$) C, H, Cl, N.