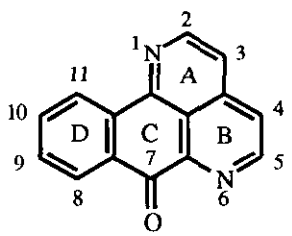
CHEMISTRY OF SAMPANGINES §

Jordan K. Zjawiony[1,2]*, Anita R. Srivastava[1], Charles D. Hufford[1,2], and Alice M. Clark[1,2]

1. Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677, U.S.A.
2. Research Institute of Pharmaceutical Sciences, University, MS 38677, U.S.A.

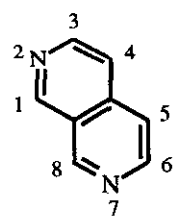
Abstract - The reactivity of sampangines in electrophilic and nucleophilic substitution reactions, nucleophilic addition reactions and the total synthesis of some derivatives are described. These reactions provide access to many analogs substituted in rings A-, B, C-, and D.

Sampangines are relatively recently discovered alkaloids with significant antifungal activity.[1,2] Chemically they are heterocyclic compounds with four totally conjugated six-membered rings, representing a naphtho[1,2,3-*ij*][2,7]naphthyridine ring system. They can be classified as azaoxoaporphine alkaloids, however, the presence of the 2,7-naphthyridine moiety, commonly known as copyrine, suggests the simpler name, copyrine alkaloids.



Sampangine (1)

7*H*-Naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one



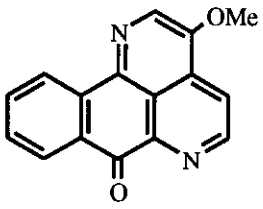
Copyrine

2,7-Naphthyridine

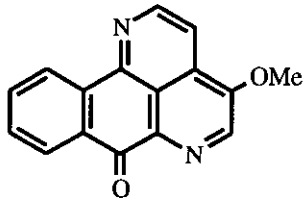
The parent compound of the class, sampangine (**1**), was first isolated in 1986 from the African tree Cananga odorata,[3] and synthesized three years later by Bracher.[4] In 1990 in our laboratories, the first natural sampangine derivative, 3-methoxysampangine (**2**), was isolated by bioassay-directed fractionation from the bark of the West African tree, Cleistopholis patens,[5] and found to be very active in vitro against several AIDS-

§ Dedicated to Dr. Arnold Brossi on the occasion of his 70th birthday.

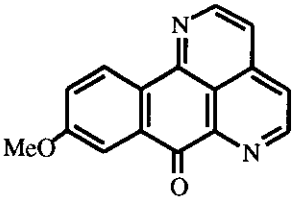
related opportunistic pathogens such as Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, and Mycobacterium intracellulare.[5,6] One year later, other natural sampangines, namely 4-methoxysampangine (**3**), 9-methoxysampangine (**4**), and 4,9-dimethoxysampangine (**5**) were isolated by Carroll and Taylor[7] from the Australian trees Eupomatia bennettii, and Eupomatia laurina, and later synthesized by Kitahara and Kubo.[8]



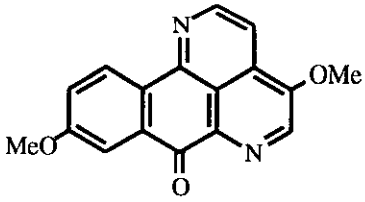
3-MeO-SAM (2)



4-MeO-SAM (3)



9-MeO-SAM (4)



4,9-diMeO-SAM (5)

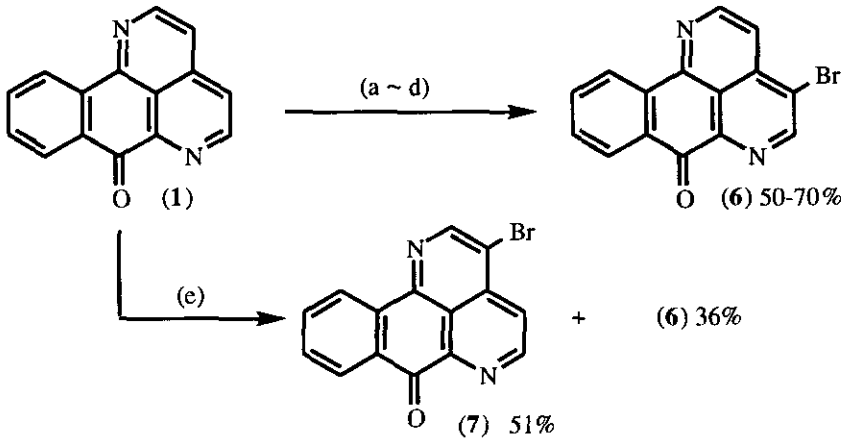
Our interest in the development of natural products as prototype antifungal antibiotics prompted us to examine more closely this interesting group of compounds. This paper deals with the chemistry of sampangines, including the syntheses of various analogs and the reactivity of sampangine in electrophilic and nucleophilic substitution reactions. For the reader's convenience, the results of our studies are presented below in order of the sampangine ring system.

A- and B-ring analogs.

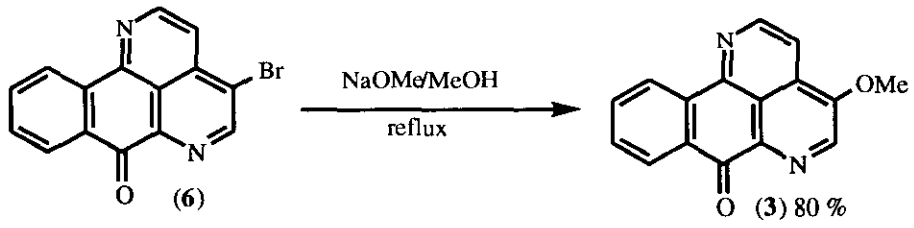
In order to obtain larger quantities of 3-methoxysampangine (**2**) for biological evaluation, a study of the bromination of sampangine and subsequent methoxylation was undertaken. Several methods commonly used in the aromatic bromination of heterocyclic compounds of the pyridine[9] and naphthyridine[10] type were examined, including:

a) bromine in carbon tetrachloride with pyridine (Eisch bromination)[11-13]
b) pyridinium bromide perbromide in chloroform or pyridine[14]
c) bromine with aluminum chloride (swamping catalyst method) [15,16]
d) bromine in methylene chloride and trifluoroacetic acid[17]
e) bromine in nitrobenzene[18-20]

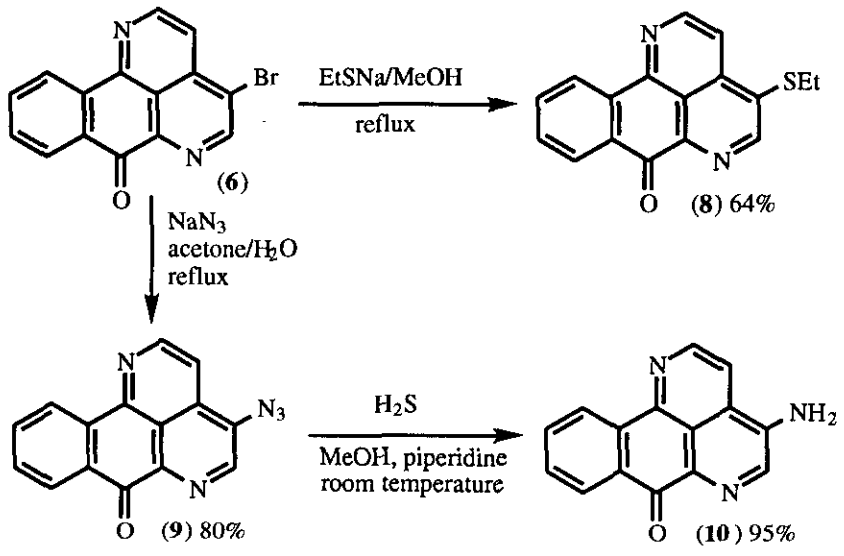
In all cases except the last one, the only product of bromination was 4-bromosampangine (**6**), obtained in yields ranging from 50-70%. Utilizing method (e) of bromination it was possible to obtain a mixture of 4-bromosampangine (**6**) and 3-bromosampangine (**7**) in yields of 36% and 51%, respectively. The two bromides were easily separated by column chromatography and their structures were unambiguously assigned using 2D-nmr spectroscopy, including COSY and long-range HETCOR experiments.



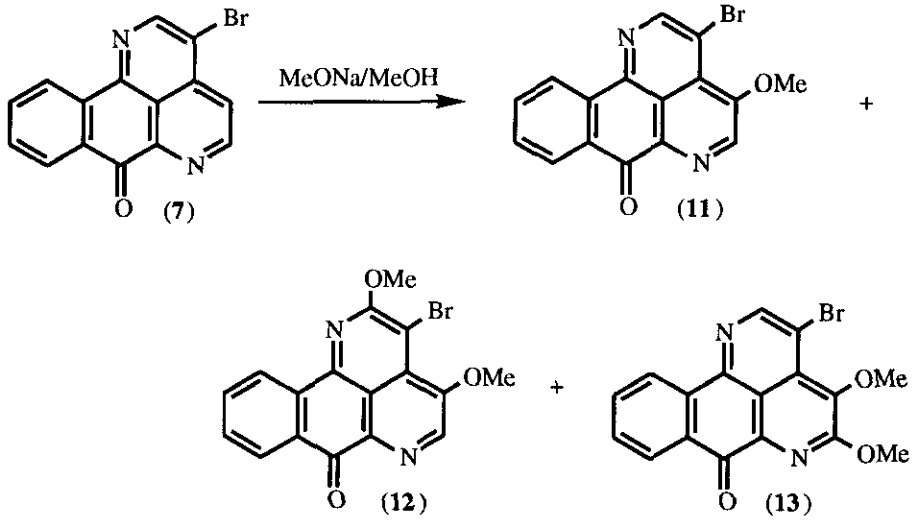
The aromatic nucleophilic substitution reaction of 4-bromosampangine (**6**) with sodium methoxide in methanol gave the expected 4-methoxysampangine (**3**) in 80% yield.[6]



Full 2D nmr spectroscopic analysis and comparison of nmr spectral data of synthetic (**3**) with that of Taylor's[7] natural product, as well as that of 4-methoxysampangine synthesized by Kitahara and Kubo,[8] proves the correct assignment of the structure. Following the observed ease of nucleophilic substitution of the bromine atom in compound (**6**), several other sampangine analogs were prepared, including the ethylsulfide (**8**), the 4-azido (**9**)[6] and the highly fluorescent 4-amino (**10**).[6]



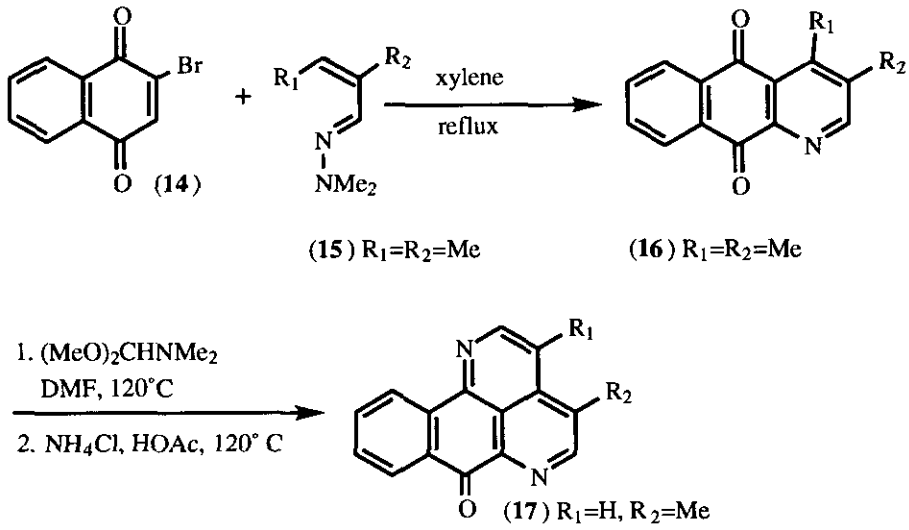
Attempts to substitute the bromine atom in 3-bromosampangine (**7**) by methoxyl ion in the same manner as accomplished for the 4-bromosampangine were unsuccessful. Instead of the desired 3-methoxysampangine, a mixture of at least three compounds was obtained (**11-13**).



In the major product (**11**), the methoxylation occurred at position 4, with the 3-bromo still present in the molecule. Two other minor products that are difficult to separate were tentatively identified as the dimethoxylated 3-bromo analogs (**12** and **13**). This observed retention of bromine at 3-position, and substitution at C-4 suggest an exceptionally high susceptibility of carbon 4 to nucleophilic attack. Such cases of nucleophilic substitution in heterocyclic systems are rather rare [21] and resemble vicarious nucleophilic

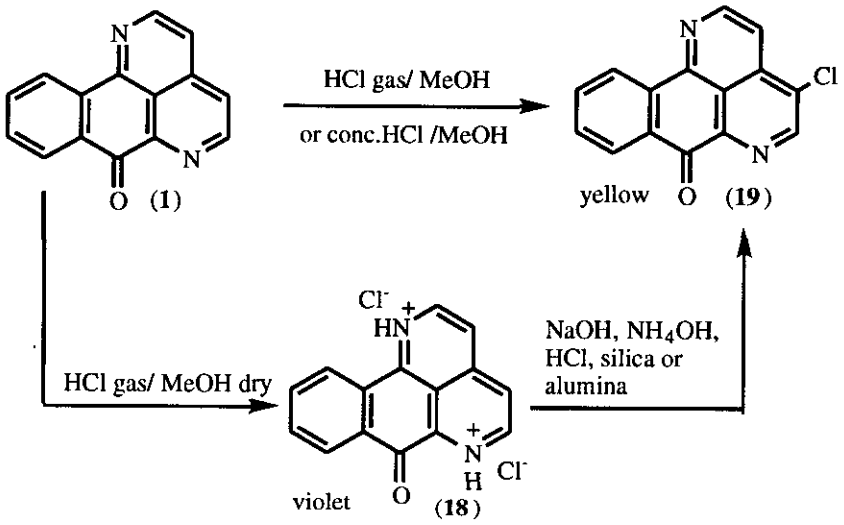
substitution effects observed by Makosza in the substitution of hydrogen by α-halocarbanions.[22] The significantly different reactivity of 3-bromosampangine (**7**) and 4-bromosampangine (**6**) in the reaction with sodium methoxide in methanol is most probably due to differences in stability of intermediate anionic σ-adducts.[23]

In order to prepare 4-alkyl substituted sampangines, such as 4-methylsampangine (**17**), the Bracher[4] strategy for construction of the sampangine ring system was followed, in a manner similar to that which we used to prepare 3-methylsampangine.[6]

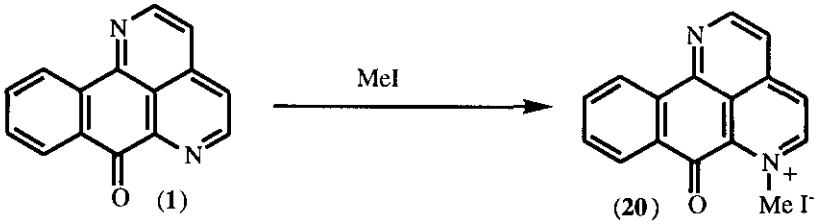


The reactivities of the heterocyclic nitrogen atoms in sampangine (**1**) were also examined by the reactions with a) hydrogen chloride; b) methyl iodide; and c) hydrogen peroxide. The reaction of sampangine (**1**) with hydrogen chloride shows that this particular system is extremely sensitive to traces of moisture when the solvent is not sufficiently dry. Under such conditions, 4-chlorosampangine (**19**) is formed, apparently as a result of nucleophilic substitution of hydride ion by Cl^-. This was further proved by the reaction of sampangine (**1**) with hydrochloric acid. A methanolic solution of sampangine refluxed for 48 hours with concentrated HCl was converted to 4-chlorosampangine (**19**). The product obtained was identified by comparison of its melting point and spectral data with that of 4-chlorosampangine prepared by chlorination of sampangine with *N*-chlorosuccinimide.[6]

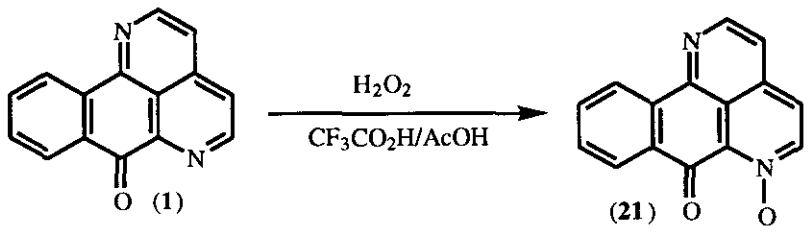
When the reaction of sampangine with HCl is carried out in absolutely dry conditions (dry HCl gas, dry methanol), it is possible to obtain sampangine dihydrochloride (**18**), the structure of which was confirmed by nmr spectroscopy and elemental analysis.



Sampangine dihydrochoride (**18**) can be converted to 4-chlorosampangine (**19**) with aqueous sodium hydroxide solution, ammonium hydroxide, hydrochloric acid, and even on silica or alumina tlc plates. The reaction of sampangine with methyl iodide (MeI) is very slow and requires the use of a relatively large excess of MeI (with or without solvent) and a long time (7-14 days at room temperature). With oxoaporphines (which have a similar ring system except there is no nitrogen atom at position 1) the quaternization with MeI usually takes 24 hours at room temperature. [24] Quaternization of sampangine with MeI afforded a dark green compound, identified by 2D nmr spectroscopy as the 6N-monomethiodide (**20**).

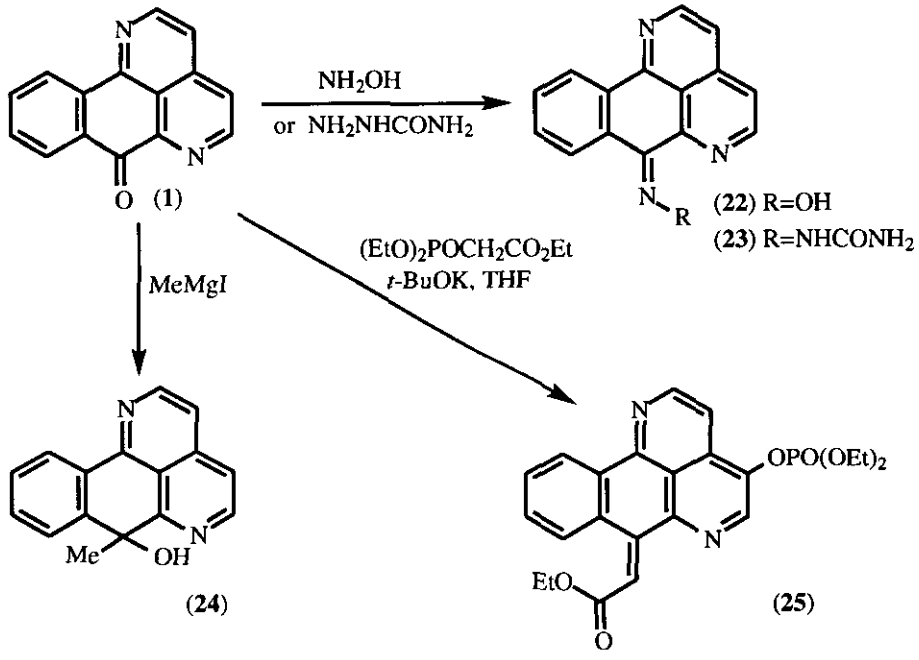


This is consistent with previous literature, in which it has been noted that reactions of naphthyridines with MeI usually provide *N*-monomethiodides, whereas diquaternary salts have been prepared using dimethyl sulfate or methyl fluorosulfonate.[25] The observed regioselectivity is most probably due to a difference in the basicity of the nitrogen atoms of this particular naphthyridine system.[26] Similarly, reaction of sampangine with hydrogen peroxide afforded only the N_6-monooxide. The structure of the *N*-oxide (**21**) was proposed based on nmr spectroscopy.



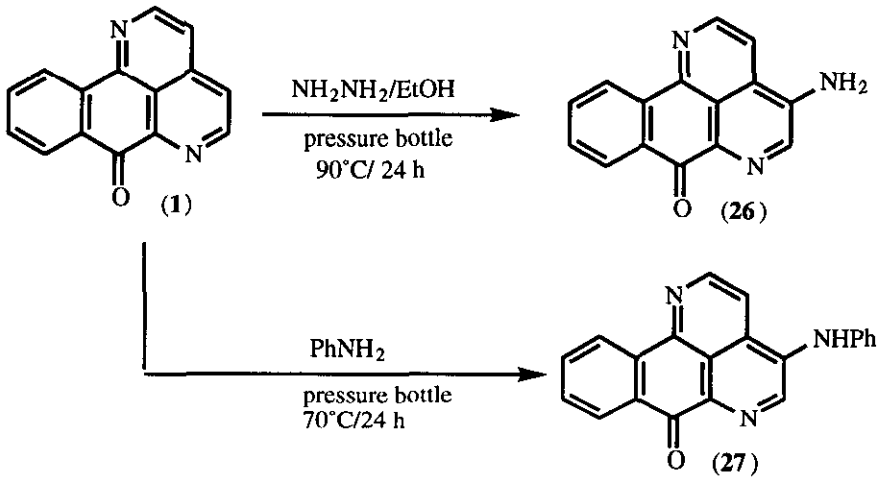
C-ring analogs.

Studies on the reactivity of the carbonyl group at position 7 were carried out by examining nucleophilic addition reactions of sampangine with: a) hydroxylamine; b) hydrazine; c) semicarbazide; d) aniline; e) methylmagnesium iodide; and f) triethyl phosphonoacetate. In cases (a), (c) and (e), the expected products of addition of nucleophilic reagents to the carbonyl group, i.e., the oxime (**22**), semicarbazone (**23**) and tertiary alcohol (**24**) were obtained. *However, the Horner-Emmons reaction of sampangine* with triethyl phosphonoacetate gave the Wittig-type product (**25**) of condensation with the carbonyl group but also with the phosphonic acid residue substituted at the position 4.



This result indicates again the relatively high susceptibility of C-4 for nucleophilic attack, as was also observed during attempts to methoxylate 3-bromosampangine (**7**), and in the formation of 4-chlorosampangine (**19**) from sampangine dihydrochloride (**18**). The reaction of sampangine (**1**) with hydrazine (b) or with aniline (d) surprisingly did not produce any condensation products. To react,

sampangine had to be heated with these reagents in a pressure bottle for 24 h. In both cases once again substitution on C-4 was observed (compounds **26** and **27**).

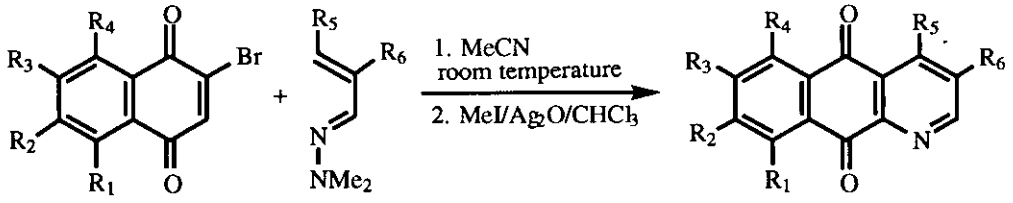


D-ring analogs.

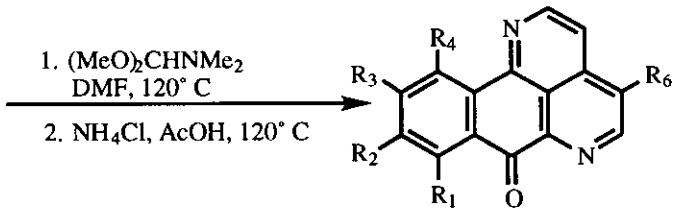
Studies on D-ring analogs have focused thus far on the synthesis of methoxy and methyl derivatives. The synthesis of methoxysampangines substituted in ring D can be achieved from the corresponding bromoquinones following Bracher's method of the construction of the sampangine ring system.[4]

The hydroxybromoquinones such as **28** are obtained from corresponding dihydroxynaphthalenes following the known procedure.[27] 2-Bromo-5-hydroxynaphthoquinone (**28**) reacts with crotonaldehyde *N,N*-dimethylhydrazone (**29**) in acetonitrile at the room temperature,[28] followed by methylation[29] with methyl iodide to provide 9-methoxycleistopholine (**30**), which is in turn converted to 8-methoxysampangine (**32**). In the same way, 8-methoxy-4-methylsampangine (**33**) was obtained from the corresponding hydrazone (**15**).

The Bracher method cannot be utilized, however, for the synthesis of methylsampangine analogs substituted in ring D because of the unavailability of corresponding methylnaphthols. In order to solve this problem, Bracher's synthesis of the cleistopholine skeleton was "reversed" (DC+B to BC+D). 4-Methylquinoline-5,8-dione(**35**),[31] which represents the BC moiety of the sampangine ring system, is obtained from 5,8-dimethoxylepidine (**34**),[30] ring D is then constructed by the Diels-Alder reaction with the correspondingly substituted butadienes.[32] Thus, utilizing a large variety of available butadienes, various sampangine analogs substituted in ring D can be obtained.

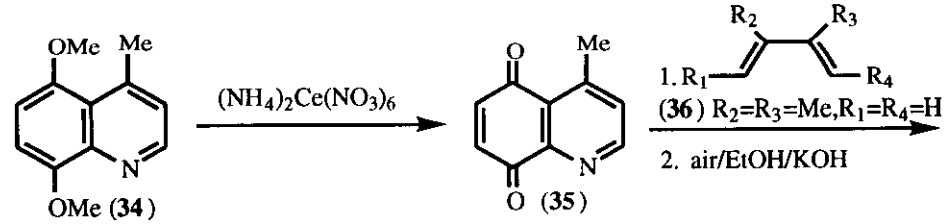


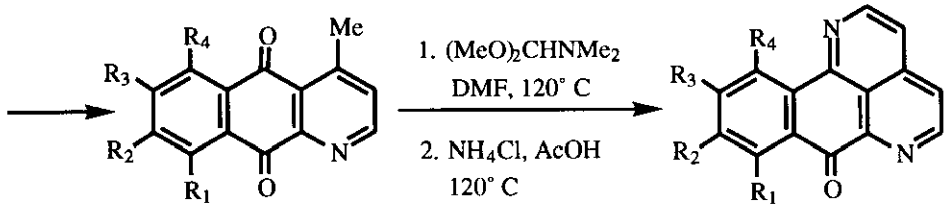
(**28**) R_1=OH (**29**) R_5=Me, R_6=H (**30**) R_1=OMe,R_5=Me,R_2=R_3=R_4=R_6=H
(**15**) R_5=R_6=Me (**31**) R_1=OMe,R_5=R_6=Me,R_2=R_3=R_4=H



(**32**) R_1=OMe,R_2=R_3=R_4=R_6=H
(**33**) R_1=OMe,R_6=Me,R_2=R_3=R_4=H

Reaction of 4-methylquinoline-5,8-dione (**35**) with commercially available 2,3-dimethylbutadiene (**36**) provides 7,8-dimethylcleistopholine (**37**) and, after annulation of the fourth ring, 9,10-dimethylsampangine (**38**) is obtained. In the same manner, other D-ring methylsampangines as well as methoxy, acetoxy, carboxy and other derivatives, can be obtained from correspondingly substituted butadienes. [32]





(**37**) R_2=R_3=Me,R_1=R_4=H (**38**) R_2=R_3=Me,R_1=R_4=H

EXPERIMENTAL

General

Anhydrous solvents such as tetrahydrofuran (THF), methanol, acetonitrile and dimethylformamide (DMF) were purchased from Aldrich Chemical Co in Sure/Seal™ bottles and used under nitrogen. 2-Bromo-1,4-naphthoquinone (**14**),[27] 5-hydroxy-2-bromo-1,4-naphthoquinone (**28**),[27] (E)-2-butenal *N,N*-dimethylhydrazone (**29**),[33] 5,8-dimethoxylepidine (**34**),[30] and sampangine (**1**) [4,6] were prepared by published methods. (E)-2-Methyl-2-butenal *N,N*-dimethoxylhydrazone (**15**) was prepared by analogy to other unsaturated hydrazones. [33,34] Other reagents and solvents were purchased from Aldrich Chemical Co. and Fisher Scientific and were used as received.

Melting points (uncorrected) were determined in open capillary tubes with a Thomas-Hoover capillary melting point apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer 281B spectrophotometer. The nmr spectra were obtained on a Varian VXR-300 FT spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C nmr. Chemical shifts are reported as ppm downfield relative to tetramethylsilane. The numbers in parentheses for the ^{13}C nmr data refer to the number of attached protons on that carbon atom as determined by the attached-proton test (APT). Two-dimensional nmr spectra were obtained using standard Varian pulse sequences for COSY and HETCOR. The long-range HETCOR experiments were optimized for $^{3}J_{C-H}$=10 Hz and $^{3}J_{C-H}$=5 Hz. High resolution mass spectra were obtained at the Mass Spectrometry Laboratory, Department of Chemistry, Univeristy of Kansas, Lawrence, Kansas. Elemental analyses were obtained from Chemical Analysis Group of Oneida Research Services Inc. in Whitesboro, New York and from Elemental Microanalysis of Organic Compounds Laboratory of Atlantic Microlab Inc. in Norcross, Georgia.

Analytical thin-layer chromatography (tlc) was performed on Merck silica gel F-254 glass plates. Visualization was achieved with shortwave ultraviolet light and/or Dragendorff reagent spray. Column chromatography was performed on Merck 230-400 mesh silica gel.

Bromination of Sampangine (1)

a) bromine in carbon tetrachloride with pyridine (Eisch bromination)

To an efficiently stirred suspension of sampangine (**1**) (0.232 g, 1 mmol) in 10 ml of carbon tetrachloride the solution of bromine (0.192 g, 0.062 ml, 1.2 mmol) in 1 ml of carbon tetrachloride was added and the mixture refluxed for 1 h. The solution of pyridine (0.079 g, 0.08 ml, 1 mmol) in 1 ml of carbon tetrachloride was added slowly to the refluxing solution, and the mixture was heated for an additional 12 h. After cooling, the mixture was washed with saturated aqueous sodium bicarbonate solution (3 x 10 ml). The organic layer was dried over anhydrous potassium carbonate and concentrated to dryness. The residual solids were subjected to flash silica gel chromatography while eluting with chloroform to give pure **4-bromosampangine** (**6**) (0.180 g, 58%), mp 244-246°C; ir (KBr) ν 1670, 1590, 1400, 1320 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.72 (ddd, 1H, *J*=7.9, 7.9, 1.4 Hz, H-9), 7.86 (ddd, 1H, *J*=7.9, 7.9, 1.4 Hz, H-10), 7.96 (d, 1H, *J*=5.9 Hz, H-3), 8.46 (dd, 1H, *J*=7.9, 1.4

Hz, H-8), 8.85 (dd, 1H, *J*=7.9, 1.4 Hz, H-11), 8.99 (d, 1H, *J*=5.9 Hz, H-2), 9.28 (s, 1H, H-5); ^{13}C nmr ($CDCl_3$) 118.3 (1), 120.5 (0), 123.7 (0), 125.8 (1), 128.7 (1), 131.8 (1), 132.3 (0), 135.0 (1), 135.1 (0), 138.6 (0), 146.7 (0), 148.6 (1), 150.2 (1), 151.7 (0), 181.6 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{15}H_7N_2OBr$ m/z 309.9742, found 309.9741. Anal. Calcd for $C_{15}H_7N_2OBr$: C 57.90, H 2.27, N 9.00. Found: C 57.70, H 2.27, N 9.26.

b) pyridinium bromide perbromide in chloroform

This method of bromination of sampangine (**1**) was described previously.[6] 4-Bromosampangine (**6**) was obtained in 64% yield. The mp, ir, and ^1H and ^{13}C nmr data reported are consistent with those obtained for other bromination products from experiments (a), (c), (d).[9]

c) bromine with aluminum chloride (swamping catalyst method)

To an ampule containing the suspension of sampangine (**1**) (0.116 g, 0.5 mmol) in 5 ml of methylene chloride was added anhydrous aluminum chloride (0.167 g, 1.25 mmol) followed by bromine solution (0.08 g, 0.026 ml, 0.5 mmol) in 2.5 ml of methylene chloride. The ampule was sealed and heated at 100°C for 48 h. After cooling, ice-water (5 ml) was added to the mixture, made alkaline with 2N KOH and extracted with chloroform (3 x 20 ml). The chloroform extract was dried over anhydrous potassium carbonate and concentrated to dryness. The residue was chromatographed on silica gel column using chloroform as an eluting solvent to provide pure 4-bromosampangine (**6**) (0.078 g, 50 %), mp 244-246°C.

d) bromine in methylene chloride and trifluoroacetic acid

Sampangine (**1**) (0.232 g, 1 mmol) was suspended in methylene chloride (10 ml) and trifluoroacetic acid (2.45 ml) was added. After cooling the solution to 0°C, the solution of bromine (0.160 g, 0.05 ml, 1 mmol) in methylene chloride (5 ml) was added dropwise. The mixture was kept at 0°C for 2 h, followed by stirring at room temperature for 72 h. The mixture was then neutralized with 2N KOH and extracted with chloroform (3 x 25 ml). The chloroform extract was dried over anhydrous potassium carbonate, evaporated to dryness and the residue was chromatographed on silica gel column using chloroform as eluant to give 4-bromosampangine (**6**) (0.218 g, 70%), mp 244-246°C.

e) bromine in nitrobenzene

To a solution of bromine (1.12 g, 0.36 ml, 7 mmol) in nitrobenzene (10 ml), was added sampangine (**1**) (0.232 g, 1 mmol) followed by one crystal of iodine. The mixture was heated at 100 °C for 24 h. After cooling the nitrobenzene was removed by steam distillation and the residue was extracted with chloroform (3 x 20 ml). The chloroform extract was then dried over anhydrous potassium carbonate, evaporated and the residue subjected to flash silica gel column chromatography, eluting products with chloroform and chloroform-ethyl acetate mixture (v/v) 99:1. The main product obtained (0.158 g, 51%) **3-bromosampangine (7)** has mp 266-268 °C. An analytical sample was obtained by crystallization from chloroform: mp 268-269 °C, ir (KBr) ν 1675, 1595, 1400, 1375, 1305 cm^{-1}, ^1H nmr ($CDCl_3$) δ 7.70 (ddd, 1H, *J*=7.8, 7.8, 1.4 Hz, H-9), 7.82 (ddd, 1H, *J*=7.8, 7.8, 1.4 Hz, H-10), 8.17 (d, 1H, *J*=5.7 Hz, H-4), 8.44 (dd, 1H, *J*=7.8, 1.4 Hz, H-8), 8.76 (dd, 1H,

J=7.8, 1.4 Hz, H-11), 9.01 (s, 1H, H-2), 9.22 (d, 1H, J=5.7 Hz, H-5); ^{13}C nmr ($CDCl_3$) 118.4 (0), 120.7 (0), 122.5 (1), 125.5 (1), 128.7 (1), 131.7 (1), 132.0 (0), 134.9 (1), 135.0 (0), 138.3 (0), 148.0 (0), 148.8 (1), 149.5 (1), 150.3 (0), 181.3 (0) ppm. Anal. (exact mass, HRFABms) calcd for $C_{15}H_7N_2OBr$+ H, m/z 310.9820, found 310.9827. Anal. Calcd for $C_{15}H_7N_2OBr$: C 57.91, H 2.27, N 9.00. Found C 57.87, H 2.26, N 9.06. The second product of bromination obtained (0.112 g, 36%) was **4-bromosampangine (6)**, mp 244-246 °C and ir, ^{1}H and ^{13}C nmr consistent with those obtained in separate bromination experiments (a), (b), (c), and (d).

Methoxylation of 4-bromosampangine (6)

A solution of 4-bromosampangine (**6**) (0.311 g, 1 mmol) and sodium methoxide (0.54 g, 10 mmol, freshly prepared from 0.23 g of sodium metal) in dry methanol (30 ml) was heated at 40°C for 48 h. The methanol was then evaporated and the residue dissolved in chloroform (200 ml). The chloroform solution was washed with water (5 x 50 ml), dried over anhydrous potassium carbonate and concentrated. After trituration of the residue with ethyl acetate, pure **4-methoxysampangine (3)** was obtained (0.210 g, 80%). An analytical sample was obtained by crystallization from chloroform: mp 279-280°C (decomp.); ir (KBr) ν 1670, 1595, 1570, 1500, 1405, 1375, 1320 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 4.25 (s, 3H, OCH_3), 7.69 (ddd, 1H, J=7.9, 7.9, 1.2 Hz, H-9) , 7.82 (ddd, 1H, J=7.9, 7.9, 1.2 Hz, H-10), 8.00 (d, 1H, J=5.8 Hz, H-3), 8.49 (dd, 1H, J=7.9, 1.2 Hz, H-8), 8.66 (s, 1H, H-5), 8.85 (dd, 1H, J=7.9, 1.2 Hz, H-11), 8.89 (d, 1H, J=5.8 Hz, H-2); ^{13}C nmr ($CDCl_3$) 56.9 (3), 114.3 (1), 120.0 (0), 125.3 (1), 128.4 (1), 128.9 (1), 130.3 (0), 131.2 (1), 132.8 (0), 134.2 (1), 135.6 (0), 141.0 (0), 146.6 (1), 150.4 (0), 152.7 (0) 181.1 (0) ppm. Anal. (exact mass, HRFABms) calcd for $C_{16}H_{10}N_2O_2$ m/z 262.0742, found 262.0740. Anal. Calcd for $C_{16}H_{10}N_2O_2$: C 73.27, H 3.84, N 10.68. Found: C 73.08, H 3.88, N 10.68.

Methoxylation of 3-bromosampangine (7)

A solution of 3-bromosampangine (**7**) (0.062 g, 0.2 mmol) and sodium methoxide (0.054 g, 1 mmol, freshly prepared from 0.023 g of sodium metal) in dry methanol (30 ml) was heated at 40°C for 48 h. The methanol was then evaporated and the residue dissolved in chloroform (200 ml). The chloroform solution was washed with water (5 x 50 ml), dried over anhydrous potassium carbonate and concentrated. The residue was chromatographed on flash silica gel column eluting with the mixture of chloroform-ethyl acetate (94:6 v/v) to give 24 mg (35%) of **3-bromo-4-methoxysampangine (11)**, as the major product, mp 248-250 °C (decomp.), ir (KBr) ν 1665, 1600, 1545, 1490, 1400 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 4.25 (s, 3H, OCH_3), 7.70 (ddd, 1H, J=7.8, 7.8, 1.4 Hz, H-9) , 7.82 (ddd, 1H, J=7.8, 7.8, 1.4 Hz, H-10), 8.46 (dd, 1H, J=7.8, 1.4 Hz, H-8), 8.73 (br s, 1H, H-5), 8.83 (dd, 1H, J=7.8, 1.4 Hz, H-11), 9.04 (s, 1H, J, H-2); ^{13}C nmr ($CDCl_3$) 56.7 (3), 93.6 (0), 113.6 (0), 121.4 (0), 125.6 (1), 128.3 (1), 130.9 (1), 131.4 (1), 132.1 (0), 134.3 (1), 135.3 (0), 141.0 (0), 149.1 (0), 150.8 (1), 152.7 (0), 181.0 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{16}H_9N_2O_2Br$ + H, m/z 340.9926, found 340.9931. Anal. Calcd for $C_{16}H_9N_2O_2Br \cdot {}^1/_4\ H_2O$: C 55.59, H 2.77, N 8.10. Found: C 55.75 , H 2.85, N 7.88, and the mixture (18 mg) of **3-bromo-2,4-dimethoxysampangine (12)** with **3-bromo-4,5-dimethoxysampangine (13)** in about 3:8 ratio based on the nmr spectrum. All efforts to separate these compounds by column chromatography or crystallization failed.

4-Ethylthio-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (4-Ethylthiosampangine, 8)

To the suspension of 4-bromosampangine (**6**) (0.155 g, 0.5 mmol) in anhydrous methanol (30 ml) was added to the sodium salt of ethanethiol (0.126 g, 1.5 mmol). The reaction mixture was refluxed for 12 h under nitrogen. The methanol was then removed by evaporation, water (20 ml) was added to the residue, and the mixture extracted with ethyl acetate (3x 50 ml). The organic extract was washed with water (2 x 50 ml) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was subjected to flash chromatography using the chloroform-ethyl acetate (80:20 v/v) as eluant to give pure **4-ethylthiosampangine** (**8**) (0.094 g, 64%), mp. 225-226°C; ir (KBr) ν: 1670, 1590, 1400, 1370 cm $^{-1}$; ^{1}H nmr ($CDCl_3/CD_3OD$) δ 1.48 (t, 3H, CH_3), 3.26 (q, 2H, CH_2), 7.66 (ddd, 1H, *J*=7.8, 7.5, 1.2 Hz, H-9), 7.79 (ddd, 1H, *J*=7.8, 7.5, 1.2 Hz, H-10), 7.89 (d, 1H, *J*=5.9 Hz, H-3), 8.40 (dd, 1H, *J*=7.8, 1.2 Hz, H-8), 8.76 (dd, 1H, *J*=7.8, 1.2 Hz, H-11), 8.83 (d, 1H, *J*=5.9 Hz, H-2), 8.83 (s, 1H, H-5); ^{13}C nmr ($CDCl_3/CD_3OD$) 13.5 (3), 26.1 (2), 115.9 (1), 118.6 (0), 125.3 (1), 128.2 (1), 131.3 (1), 132.3 (0), 134.4 (1), 135.1 (0), 136.9 (0), 143.6 (1), 144.1 (0), 146.9 (1), 148.4 (0), 151.3 (0), 181.7 (0) ppm; Anal. Calcd for $C_{17}H_{12}N_2OS \cdot {}^1/_4\ H_2O$: C68.78, H 4.24, N 9.43. Found C 69.01, H 3.80, N 9.46. *Anal. (exact mass, HREIms) calcd for* $C_{17}H_{12}N_2OS$ m/z 292.0670, found 292.0672.

***(E)*-2-Methyl-2-butenal *N,N*-dimethylhydrazone (15)**

N,N-Dimethylhydrazine (13.2 g, 17 ml, 0.22 mol) was added dropwise over 15 min to (*E*)-2-methyl-2-butenal (17 g, 19.5 ml, 0.2 mol) while cooling the mixture in an ice bath. The bath was then removed and the mixture stirred for 2 h at ambient temperature. Calcium chloride (20 g) was added to the reaction mixture and allowed to stand for 20 min, and product was decanted. Distillation (bp 60-65°C/15 mm Hg) of the oil through a 15 cm Vigreaux column provided pure **15** (13.8 g, 48%); ir ($CHCl_3$) ν 1635, 1570, 1460, 1440, 1380 cm^{-1}, ^{1}H nmr ($CDCl_3$) δ 1.75 (d, 3H, *J*=7 Hz, $CH_3C(3)H$-), 1.80 (br s, 3H, CH3C(2)=), 2.76 (s, 6H, $(CH_3)_2N$-), 5.59 (q, 1H, *J*=7 Hz, C(3)H), 7.00 (s, 1H, C(1)H); ^{13}C nmr ($CDCl_3$) 11.1 (3), 13.6 (3), 43.0 (2x3), 127.0 (1), 135.1 (0), 140.3 (1) ppm. Anal. (exact mass, HRFABms) calcd for $C_7H_{14}N_2$ + H m/z 1227.1235, found 127.1233. Anal. Calcd for $C_7H_{14}N_2$: C 66.62, H 11.18, N 22.20. Found C 66.82, H 11.06 , N 22.08.

3,4-Dimethylbenzo[*g*]quinoline-5,10-dione (3-Methylcleistopholine, 16)

(*E*)-2-methyl-2-butenal *N,N*-dimethylhydrazone (**15**) (3.28 g, 26 mmol) in xylene (10 ml) was added rapidly to a xylene solution (40 ml) of 2-bromo-1,4-naphthoquinone (**14**) (4.74 g, 20 mmol), and the mixture was heated at reflux for 3 h under a nitrogen atmosphere. After cooling, the contents of the flask were transferred to a separatory funnel, and solid material was dissolved in ethyl acetate (150 ml). The combined organic solutions were then extracted with 2N sulfuric acid (3 x 100 ml). The acid extracts were combined, chilled in ice, and made basic (pH 10, test paper) with 6N sodium hydroxide solution and extracted with ethyl acetate (4 x 100 ml). The ethyl acetate extracts were dried over potassium carbonate and concentrated to dryness. The crude material was purified by flash silica gel chromatography, eluting with ethyl acetate-petroleum ether (80-20% v/v) to give pure **3-methylcleistopholine (16)** (2.2.g, 46%), mp 191-192 °C; ir (KBr) ν 1680, 1670, 1590, 1550 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.74-7.77 (m, 2H, H-7, H-8), 7.16-7.19 (m, 1H, H-6), 8.27-8.29 (m, 1H, H-9), 8.74 (s, 1H, H-2); ^{13}C nmr ($CDCl_3$) δ 17.4 (3), 17.9 (3),

127.0 (1), 127.1(1), 128.8 (0), 132.4 (0), 133.9 (1), 134.2 (0), 134.3 (1), 138.6 (0), 148.5 (0), 149.5 (0), 154.3 (1), 182.9 (0), 185.3 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{15}H_{11}NO_2$ m/z 237.0790, found 237.0786. Anal. Calcd for $C_{15}H_{11}NO_2 \cdot {}^1/_4\ H_2O$: C 74.52, H 4.69, N 5.79. Found C 74.49, H 4.49, N 5.80.

4-Methyl-7*H*-naphtho[1,2,3-*ij*][2,7]-naphthyridin-7-one (4-Methylsampangine, 17)

Dimethylformamide dimethyl acetal (2.5 g, 2.8 ml, 21 mmol) was added to a solution of 3-methylcleistopholine (20) (1.66 g, 7 mmol) in dimethylformamide (7 ml) and heated at 120°C under nitrogen for 3 h. Ammonium chloride (0.5 g, 9 mmol) and glacial acetic acid (7 ml) were then added and the mixture was heated again at 120°C for an additional 2 h. After cooling, the mixture was poured onto water (100 ml) and extracted with methylene chloride (4 x 50 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml), water (3 x 50 ml), dried over anhydrous potassium carbonate and concentrated to dryness. Flash silica gel column chromatography of the crude product, using chloroform-petroleum ether (50-50% v/v) for elution gave pure **4-methylsampangine (17)** (0.52 g, 30%), mp 243-245 °C; ir (KBr) ν 1670, 1590, 1405, 1375, 1320, 1270, 1230 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.72 (s, 3H, CH_3), 7.64 (ddd, 1H, *J*=7.9, 7.5, 1.2 Hz, H-9), 7.71 (d, 1H, *J*=5.9 Hz, H-3), 7.77 (ddd, 1H, *J*=7.9, 7.5, 1.2 Hz, H-10), 8.40 (dd, 1H, *J*=7.9, 1.2 Hz, H-8), 8.73 (dd, 1H, *J*=7.9, 1.2 Hz, H-11), 8.80 (d, 1H, *J*=5.9 Hz, H-2), 8.89 (s, 1H, H-5); ^{13}C nmr ($CDCl_3$) δ 15.9 (3), 116.0 (1), 118.6 (0), 125.1 (1), 128.0 (1), 131.0 (1), 132.0 (0), 132.3 (0), 134.2 (1), 135.1 (0), 137.6 (0), 145.8 (0), 146.7 (1), 148.1 (1), 150.8 (0), 181.6 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{16}H_{10}N_2O$ m/z 246.0793 found 246.0796. Anal. Calcd for $C_{16}H_{10}N_2O \cdot {}^1/_4\ H_2O$: C 76.63, H 4.12, N 11.17. Found C 76.64, H 4.14, N 11.09.

7*H*-naphtho[1,2,3-*ij*][2,7]-1,6-naphthyridinium-7-one dichloride (Sampangine dihydrochloride, 18)

Dry hydrogen chloride gas was passed through a solution of sampangine (**1**) (0.116 g, 0.5 mmol) in methanol (50 ml) at room temperature for 3 h. Methanol was removed by evaporation in a stream of dry nitrogen to give 0.152 g (100%) of violet *dihydrochloride* (*23*), mp > 300°C, ir (KBr) ν 3100-2800, 1690, 1660, 1630, 1570, 1515, 1410, 1380, 1370 cm^{-1}, ^{1}H nmr (CD_3SOCD_3): δ 6.75 (d, 1H, *J*=6.4 Hz), 7.71 (m, 1H), 7.87 (m, 3H), 8.26 (m, 2H), 8.44 (d, 1H, *J*=6.4 Hz). Anal. Calcd for $C_{15}H_{10}N_2OCl_2$: C 59.04, H 3.30, N 9.18, Cl 23.24. Found C 58.68, H 3.30, N 9.02, Cl 23.09.

In another experiment with sampangine (**1**) (0.116 g, 0.5 mmol), carried out in non-anhydrous conditions (reagent grade methanol, hydrogen chloride gas directly from lecture bottle), instead of sampangine dihydrochloride (23), **4-chlorosampangine (19)** (0.082 g, 62%) was obtained; mp 262-263°C; ir (KBr) ν 1670, 1590, 1410, 1315 cm $^{-1}$; ^{1}H nmr ($CDCl_3$) δ 7.68 (ddd, 1H, *J*=7.6, 7.6, 1.4 Hz, H-9), 7.81 (ddd, 1H, *J*= 7.6, 7. 6, 1.4 Hz, H-10), 7.95 (d, 1H, *J*=5.9 Hz, H-3), 8.41 (dd, 1H, *J*=7.6, 1.4 Hz, H-8), 8.76 (dd, 1H, *J*=7.6, 1.4 Hz, H-11), 8.93 (d, 1H, *J*=5.9 Hz, H-2), 9.09 (s, 1H, H-5); ^{13}C nmr ($CDCl_3$) 115.7 (1), 120.0 (0), 125.6 (1), 128.5 (1), 131.7 (1), 132.0 (0), 132.2 (0), 134.8 (1), 135.0 (0), 136.9 (0), 146.0 (0), 147.2 (1), 148.2 (1), 151.5 (0), 181.2 (0) ppm. Anal (exact mass, HREIms) calcd for $C_{15}H_7N_2OCl$ m/z 266.0247, found 266.0245. Anal. Calcd for $C_{15}H_7N_2OCl$: C 67.56, H 2.65, N 10.50. Found: C 67.63, H 2.52, N 10.54. Mp and all above spectral and analytical data are identical or consistent with authentic sample of 4-chlorosampangine obtained

earlier [6] from an independent method. Heating the sampangine (1) (0.06 g, 0.25 mmol) with concentrated hydrochloric acid (1 ml) in methanol (10 ml) at reflux for 48 h also produces some *4-chlorosampangine* (24) (0.015 g, 22%) accompanied by unreacted starting material.

7*H*-Naphtho[1,2,3-*ij*][2,7]-6-methylnaphthyridinium-7-one iodide (Sampangine 6-methiodide, 20)

A solution of sampangine (1) (0.116 g, 0.5 mmol) in methyl iodide (50 ml) was stirred at room temperature for 7 days. Evaporation of methyl iodide left dark-green *sampangine 6-methiodide* (25) (0.187 g, 100%) mp > 300°C, ir(KBr) ν 1680, 1615, 1585, 1535, 1505, 1495, 1470, 1380, 1370, 1340 cm^{-1}, ^1H nmr (CD_3SOCD_3) δ 4.85 (s, 3H, N-CH_3) 7.79 (m, 1H, H-9), 7.93 (m, 2H, H-10 and H-3), 8.06 (d, 1H, *J*=5.7 Hz, H-4), 8.29 (m, 1H, H-8), 8.78 (m, 2H, H-11 and H-2), 8.95 (d, 1H, *J*=5.7 Hz, H-5). Anal. (exact mass, HREIms) calcd for $C_{16}H_{11}N_2OI$ m/z 373.9918, found . Anal. Calcd for $C_{16}H_{11}N_2OI$: C 67.56, H 2.65, N 10.50. Found: C 67.63, H 2.52, N 10.54.

7*H*-Naphtho[1,2,3-*ij*][2,7]-6-naphthyridinium-7-one oxide (Sampangine 6-N-oxide, 21)

Trifluoroacetic acid (3.0 ml, 40 mmol) and hydrogen peroxide (30%, 4.5 ml, 44 mmol) were added to a stirred solution of sampangine (1) (0.16 g, 0.5 mmol) in glacial acetic acid (3 ml). The reaction mixture was stirred at room temperature for 48 h. Water (50 ml) was added to the mixture and extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with 5% sodium bicarbonate solution (3 x 10 ml), then with brine (3 x 10 ml) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to flash silica gel chromatography, eluting with ethyl acetate to obtain pure **sampangine 6-N-oxide** (**21**, 0.1 g, 85%), mp 186-188°C, ir (KBr) γ: 1665, 1655, 1590, 1415, 1380, 1335, 1305 cm-1, ^1H nmr ($CDCl_3$) : δ 7.72 (*m*, 2H, H-9 and H-4), 7.85 (*m*, 2H, H-10 and H-3), 8.41 (d, 1H, *J*=7.2 Hz, H-2), 8.52 (dd, 1H, *J*=1.3, 7.9 Hz, H-8), 8.89 (d, 1H, *J*=5.4 Hz, H-5), 8.92 (dd, 1H, *J*=1.3, 7.9 Hz, H-11); ^{13}C nmr ($CDCl_3$ + CD_3SOCD_3): 118.2 (1), 119.2 (0), 123.4 (1), 125.2 (1), 126.0 (1), 128.5 (0), 129.3 (1), 131.2 (0), 132.2 (1), 132.7 (0), 133.8 (0), 143.3 (1), 144.1 (0), 144.6 (1), 173.4 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{15}H_8N_2O_2$ m/z 248.0586, found 248.0584.

7*H*-Naphtho[1,2,3-*ij*][2,7]-naphthyridin-7-oxime (Sampangine oxime, 22)

To a stirred suspension of sampangine (1) (0.116 g, 0.5 mmol) in methanol (7 ml), hydroxylamine hydrochloride (0.114 g, 2 mmol) and sodium acetate (0.164 g, 2 mmol) were added. The reaction mixture was refluxed for 48 h. After cooling, the solvent was evaporated, water (50 ml) was added, and the mixture extracted with ethyl acetate (3 x 50 ml). The organic extract was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by flash silica gel column chromatography, eluting with chloroform to give **sampangine oxime (22)** (0.08 g, 65%), mp 218-220°C; ir (KBr) ν 1605, 1570, 1540, 1470, 1400, 1340, 1300 cm^{-1}, ^1H nmr ($CDCl_3$) δ 7.61 (*m*, 3H, H-9, H-10 and H-3), 7.82 (d,1H, *J*=5.8 Hz, H-4), 8.55 (m, 1H, H-8), 8.64 (d, 1H, *J*=5.8 Hz, H-2), 8.82 (m, 1H, H-11), 8.90 (d, 1H, *J*=5.8 Hz, H-5); ^{13}C nmr ($CDCl_3$) 116.7 (0), 117.2 (1), 121.4 (1), 123.7 (1), 125.3 (1), 129.6 (1), 129.8 (0), 131.2 (1), 131.8 (0), 139.4 (0), 141.6 (0), 142.6 (1) , 148.1 (0), 148.7 (10, 152.5 (0) ppm. Anal. (exact mass, HREIms) calcd for

$C_{15}H_9N_3O$ m/z 247.0746, found 247.0748. Anal. Calcd for $C_{15}H_9N_3O \cdot {}^1/_4\ H_2O$: C 71.56, H 3.80, N 16.69. Found: C 71.52 , H 3.79 , N 16.59.

7*H*-Naphtho[1,2,3-*ij*][2,7]-naphthyridin-7-semicarbazone (Sampangine semicarbazone, 23)

A mixture of sampangine (1) (0.116 g, 0.5 mmol), semicarbazide hydrochloride (0.223 g, 2 mmol) and anhydrous triethylamine (0.3 ml, 2 mmol) in anhydrous ethanol (5 ml) was heated at reflux for 40 h. Water (10 ml) was added to the cooled mixture, and the resulting solid was filtered. The crude product was purified by flash silica gel column chromatopraphy using chloroform-ethyl acetate (50:50 v/v) as eluant to provide pure **sampangine semicarbazone (23)** (0.08 g, 56%), mp 154-155°C ; ir (KBr) ν 1700, 1680, 1615, 1605, 1580, 1550, 1520 cm^{-1}, ^1H nmr (CD_3SOCD_3) δ 7.61 (m, 2H, H-9 and H-10), 7.85 (d, 1H, *J*=5.6 Hz, H-3), 7.98 (d, 1H, *J*=5.8 Hz, H-4), 8.72 (m, 1H, H-8), 8.78 (m, 1H, H-11), 8.87 (d, 1H, *J*=5.8 Hz, H-2), 8.92 (d, 1H, *J*=5.8 Hz, H-5); ^{13}C nmr (CD_3SOCD_3) 117.2 (0), 117.8 (1), 119.6 (1), 124.2 (1), 124.7 (1), 128.4 (0), 128.5 (1), 129.7 (0), 130.5 (1), 133.1 (0), 138.7 (0), 144.8 (1), 147.6 (1), 148.8 (0), 150.7 (0), 155.9 (0) ppm. Anal.(exact mass, HREIms) calcd for $C_{16}H_{11}N_5O$ m/z 289.0963, found 289.0958.

7-Methyl-7*H*-naphtho[1,2,3-*ij*][2,7]-naphthyridin-7-ol (24)

A suspension of sampangine (1) (0.116 g, 0.5 mmol) in anhydrous tetrahydrofuran (10 ml) was added to a solution of methylmagnesium iodide in tetrahydrofuran (3.5 ml of 3M solution, 10.5 mmol) and the mixture was refluxed under nitrogen for 24 h. After cooling tetrahydrofuran was evapoarted after cooling, water was added (20 ml), and the mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (2 x 50 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was subjected to a short flash silica gel column chromatography, eluting with petroleum ether-ethyl acetate (50:50 v/v) to give pure (**24**) (0.04 g, 32%), mp 138-140°C; ir (KBr) ν 1620, 1580, 1550, 1470, 1450, 1410, 1395 cm^{-1}, ^1H nmr ($CDCl_3$) δ 7.50 (ddd, 1H, *J*=7.8, 7.8, 1.4 Hz, H-9), 7.53 (d, 1H, *J*=5.7 Hz, H-3), 7.57 (d, 1H, *J*=5.7 Hz, H-4), 7.60 (ddd, 1H, *J*=7.8, 7.8, 1.4 Hz, H-10), 8.01 (dd, 1H, *J*=7.8, 1.4 Hz, H-8), 8.68 (dd, 1H, *J*=7.8, 1.4 Hz, H-11), 8.72 (d, 1H, *J*=5.7 Hz, H-2), 8.77 (d,1H, *J*=5.7 Hz, H-5); ^{13}C nmr ($CDCl_3$) 38.9 (3), 73.0 (0), 116.6 (0), 119.2 (1), 119.6 (1), 126.6 (1), 127.7 (1), 129.4 (1), 130.6 (0), 132.7 (1), 140.2 (0), 145.3 (0), 147.8 (1), 149.0 (1), 154.0 (0), 166.1 (0) ppm. Anal.(exact mass, HREIms) calcd for $C_{16}H_{12}N_2O$ m/z 248.0950, found 248.0932.

4-Diethylphosphono-7-carboethoxymethylene-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridine (25)

Triethyl phosphonoacetate (0.224 g, 0.198 ml, 1 mmol) was added to a solution of potassium *t*-butoxide (0.168 g, 1.5 mmol) in anhydrous tetrahydrofuran (10 ml), and the resulting mixture was stirred at room temperature under nitrogen for 1 h. The mixture was then cooled to 0°C and a suspension of sampangine (1) (0.116 g, 0.5 mmol) in anhydrous benzene (10 ml) was added. The contents of the flask were warmed to room temperature, then heated at reflux for 2 h. After cooling, the mixture was concentrated in vacuo and the residue was subjected to flash silica gel column chromatography, using ethyl acetate as eluent to provide pure (**25**) (0.09 g, 40%), mp 146-147°C; ir(KBr) ν 1730,1670,1605, 1595, 1570, 1495, 1485, 1440, 1400, 1380 cm^{-1}, ^1H nmr($CDCl_3$) δ 1.25 (m, 9H, 3 x CH_3), 4.12 (m, 4H, 2 x OCH_2), 4.27 (m, 2H, OCH_2), 4.98 (d, 1H, *J*=25

Hz, =CH), 7.65 (br dd, 1H, *J*=7.8, 7.8 Hz, H-9), 7.79 (br dd, 1H, *J*=7.8, 7.8 Hz, H-10), 7.94 (d, 1H, *J*=6.0 Hz, H-3), 8.40 (br d, 1H, *J*=7.8 Hz, H-8), 8.78 (br d, 1H, *J*=7.8 Hz, H-11), 8.89 (d, 1H, *J*=6.0 Hz, H-2), 9.43 (d, 1H, *J*=2.7 Hz, H-5); ^{13}C nmr ($CDCl_3$) 14.0 (3), 16.3 (3), 16.4 (3), 47.9 (1), 62.7 (2), 63.8 (2), 63.9 (2), 116.2 (1), 119.5 (0), 126.2 (1), 126.3 (0), 128.4 (1), 131.4 (1), 132.3 (0), 134.7 (1), 135.6 (0), 137.9 (0), 147.3 (0), 147.5 (1), 149.7 (1), 151.7 (0), 166.3 (0), 181.1 (0) ppm. ^{31}P nmr ($CDCl_3$ + H_3PO_4) 2092.76 (P=O) + 2075.23 *(P=O) in 5:1 ratio due to the mixture of isomers.* Anal. (exact mass HREIms) calcd for $C_{23}H_{23}N_2O_6P$ m/z 454.1294, found 454.1290. Anal. Calcd for $C_{23}H_{23}N_2O_6P\bullet\ ^3/_4\ H_2O$: C 59.04, H 5.28, N 5.99. Found C 59.05, H 5.04, N 6.08.

4-Amino-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (4-Aminosampangine, 26)

A mixture of sampangine (0.116 g, 0.5 mmol), hydrazine monohydrate, (98%, 1 ml), and absolute ethanol (4 ml), was placed in a pressure bottle and heated at 90°C for 24 h. Shiny red crystals appeared in the mixture at the end of heating period. The mixture was cooled and the product filtered and washed with cold ethanol, followed by petroleum ether to give pure **4-aminosampangine (26)** (0.062 g, 50%), mp >300°C, ir(KBr) ν 3300(br), 1725, 1625, 1585, 1505, 1460, 1385, 1300 cm^{-1}, ^{1}H nmr (CD_3SOCD_3) δ 7.72 (ddd, 1H, *J*=7.5, 7.5, 1.3 Hz, H-9), 7.83 (ddd, 1H, *J*=7.5, 7.5, 1.3 Hz, H-10), 7.95 (br s, 2H, NH_2), 8.21 (d, 1H, *J*=5.9 Hz, H-3), 8.26 (dd, 1H, *J*=7.5, 1.3 Hz, H-8), 8.38 (s, 1H, H-5), 8.75 (dd,1H, *J*=7.5, 1.3 Hz, H-11), 8.81 (d, 1H, *J*=5.9 Hz, H-2); ^{13}C nmr (CD_3SOCD_3) 115.7 (1), 119.8 (0), 124.1(0), 124.7 (1), 127.0(1), 130.9 (1), 132.0 (1), 132.8 (0), 132.9 (0), 133.1 (1), 134.7 (0), 144.3 (1), 145.1(0), 148.5 (0), 178.4 (0) ppm. Anal. (exact mass HREIms), calcd for $C_{15}H_9N_3O$ m/z 247.0746, found 247.0744. Anal. Calcd for $C_{15}H_9N_3O$. H_2O: C 67.92, H 4.18, N 15.84. Found C 68.30, H 3.80, N 15.75. Mp and all above spectral and analytical data are identical or consistent with authentic sample of 4-aminosampangine obtained by us earlier [6] by independent way.

4-Phenylamino-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (4-Anilinosampangine, 27)

A mixture of sampangine (0.116 g, 0.5 mmol) and aniline (2 ml) was placed in the pressure bottle and heated at 70°C for 24 h. The reaction mixture was cooled and the separated solid filtered, and washed with petroleum ether.T he crude product was subjected to flash silica gel column chromatography, using chloroform-ethyl acetate (95:5 v/v) as eluant to give pure **4-anilinosampangine (27)** (0.09 g, 54%), mp 270-272°C, ir (KBr) ν 1660, 1640, 1590, 1560, 1535, 1400, 1380 cm^{-1}, ^{1}H nmr (CD_3SOCD_3) δ 7.27 (m, 1H, Ph), 7.51 (m, 4H, Ph), 7.75 (br dd, 1H, *J*=7.8, 7.8 Hz, H-9), 7.87 (br dd, 1H, *J*=7.8, 7.8 Hz, H-10), 8.27 (br d, 1H, *J*=7.8 Hz, H-8), 8.38 (d, 1H, *J*=5.9 Hz, H-3), 8.67 (s, 1H, H-5), 8.77 (br d,1H, *J*=7.8 Hz, H-11), 8.90 (d, 1H, *J*=5.9 Hz, H-2), 9.71 (s, 1H, NH); ^{13}C nmr (CD_3SOCD_3): 115.3 (1), 119.7 (0), 122.7 (1), 122.8 (1), 124.8 (1), 125.1 (1), 126.9 (0), 127.1 (1), 129.0 (1), 129.7 (1), 131.0 (1), 132.7 (0), 133.5 (1), 134.9 (0), 136.2 (0), 139.0 (1), 139.2 (0), 139.9 (0), 145.1 (1), 148.9 (0), 178.9 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{21}H_{13}N_3O$ m/z 323.1059, found 323.1053. Anal. Calcd for $C_{21}H_{13}N_3O$: C 78.00, H 4.05, N 12.99. Found C 77.81, H 4.11, N 13.11.

9-Methoxy-4-methylbenzo[*g*]quinoline-5,10-dione (9-Methoxycleistopholine, 30)

(E)-2-butenal-*N,N*-dimethylhydrazone(**29**)[33] (18 g, 0.16 mol) was added to the solution of 2-bromo-5-hydroxy-1,4-naphthoquinone(**28**)[27](25.3 g, 0.1 mol) in anhydrous acetonitrile (300 ml) and the mixture was stirred in the dark at room temperature for 24 h. After evaporation of the solvent the residue was chromatographed on a flash silica gel column using ethyl acetate as eluant to provide 9-hydroxycleistopholine (5 g, 21%), mp 237-238°C (lit.,[28] mp 238°C); ir (KBr) ν 3600-3300, 1690, 1630, 1575, 1455, 1460, 1355 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.95 (s, 3H, CH_3), 7.36 (dd, 1H, *J*=8.4, 1.0 Hz, H-8), 7.55 (d, 1H, *J*=4.8 Hz, H-3), 7.71 (dd, 1H, *J*=8.4, 7.6 Hz, H-7), 7.91 (dd, 1H, *J*=7.6, 1.0 Hz, H-6), 8.94 (d, 1H, *J*=4.8 Hz, H-2), 12.54 (s, 1H, OH); ^{13}C nmr ($CDCl_3$) 22.5 (3), 116.0 (0), 118.7 (1), 124.1 (1), 128.5 (0), 131.2 (1), 132.3 (0), 136.5 (1), 149.5 (0), 150.7 (0), 153.3 (1), 161.3 (0), 180.4 (0), 190.2 (0) ppm. Mp and spectral data are consistent with the same compound published in the literature.[28] Silver oxide (Ag_2O, 11.6 g, 50 mmol), and methyl iodide (114 g, 50 ml, 1 mol) were added to a solution of 9-hydroxycleistopholine (6 g, 25 mmol) in chloroform (250 ml). The mixture was stirred in the dark at room temperature for 12 h. After that time the mixture was filtered and the solid residue was washed with hot chloroform (2 x 100 ml). The combined filtrates were washed with water (2 x 50 ml) and dried over anhydrous sodium sulfate. Evaporation of solvent gave the pure **9-methoxycleistopholine (30)** (4.4 g, 70%), mp 188-189°C; ir (KBr) ν 1660, 1580, 1470, 1450, 1430, 1400, 1370 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.85 (s, 3H, CH_3), 4.03 (s, 3H, CH_3O), 7.35 (dd, 1H, *J*=8.0, 1.0 Hz, H-8), 7.45 (d, 1H, *J*=4.8 Hz, H-3), 7.70 (dd, 1H, *J*=8.0, 8.0 Hz, H-7), 7.96 (dd, 1H, *J*=8.0, 1.0 Hz, H-6), 8.80 (d, 1H, *J*=4.8 Hz, H-2); ^{13}C nmr ($CDCl_3$) 22.7 (3), 56.6(3), 118.2 (1), 119.7 (1), 122.1 (0), 130.7 (0), 131.2 (1), 134.5 (0), 134.8 (1), 148.8 (0), 150.7 (0), 152.7 (1), 159.7 (0), 182.3 (0), 184.2 (0) ppm. Anal. (exact mass HREIms) calcd for $C_{15}H_{11}NO_3$ m/z 253.0739, found 253.0716. Anal. Calcd for $C_{15}H_{11}NO_3$. $^1/_2$ H_2O: C 68.69, H 4.61, N 5.34. Found C 68.95, H 4.36, N 5.47.

8-Methoxy-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (8-Methoxysampangine, 32)

Dimethylformamide dimethyl acetal (3.1 g, 3.5 ml, 26 mmol) was added to a solution of 9-methoxycleistopholine (**30**) (1.5 g, 6 mmol) in dimethylformamide (5 ml) and heated at 120°C under nitrogen for 14 h. Ammonium chloride (3 g) and glacial acetic acid (3 ml) were then added and the mixture was heated again at 120 °C for an additional 2 h. After cooling, the mixture was poured onto water (100 ml) and extracted with methylene chloride (4 x 50 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml), water (3 x 50 ml), dried over anhydrous potassium carbonate and concentrated to dryness. Flash silica gel column chromatography of the crude product, using chloroform-petroleum ether (50-50% v/v) for elution gave pure **8-methoxysampangine (32)** (0.2 g, 20%), mp 168-170°C; ir (KBr) ν 1670, 1610, 1585, 1545, 1530, 1470, 1400, 1370 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 4.08 (s, 3H, CH_3O), 7.41 (dd, 1H, *J*=8.0, 1.2 Hz, H-9), 7.59 (dd, 1H, *J*=8.0, 8.0 Hz, H-10), 7.61 (d, 1H, *J*=5.8 Hz, H-3), 7.89 (d, 1H, *J*=5.8 Hz, H-4), 8.16 (dd, 1H, *J*=8.0, 1.2 Hz, H-11), 8.93 (d, 1H, *J*=5.8 Hz, H-2), 9.07 (d, 1H,*J*=5.8 Hz, H-5); ^{13}C nmr ($CDCl_3$) δ 57.1 (3), 117.8 (1), 119.4 (1), 120.0 (0), 121.7 (1), 123.3 (0), 123.9 (1), 131.8 (1), 134.6 (0), 138.6 (0), 146.9 (0), 147.0 (1), 148.1 (1), 152.2 (0), 159.3 (0), 182.2 (0) ppm. Anal. (exact mass, HRFABms) calcd for $C_{16}H_{10}N_2O_2$ + H m/z 263.0821 found 263.0821.

3,4-Dimethyl-9-methoxybenzo[*g*]quinoline-5,10-dione (3-Methyl-9-methoxycleistopholine, 31)
(E)-2-methyl-2-butenal-*N,N*-dimethylhydrazone(**15**) (15.1 g, 0.12 mol) was added to a solution of 2-bromo-5-hydroxy-1,4-naphthoquinone(**28**)[27] (25.3 g, 0.1 mol) in anhydrous acetonitrile (300 ml) and the mixture was stirred in the dark at room temperature for 24 h. After evaporation of the solvent the residue was chromatographed on flash silica gel column using ethyl acetate as eluant to provide 3-methyl-9-methoxycleistopholine (6.35 g, 25%), mp 140-141°C ; ir (KBr) ν 3200-2900, 1720, 1670, 1585, 1535, 1445, 1360 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.47 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 7.31 (dd, 1H, *J*=8.4, 1.2 Hz, H-8), 7.66 (dd, 1H, *J*=8.4, 7.5 Hz, H-7), 7.86 (dd, *J*=7.5, 1.2 Hz, H-6), 8.78 (s, 1H, H-2), 12.54 (s, 1H, OH); ^{13}C nmr ($CDCl_3$): 17.7 (3), 17.8 (3), 115.9 (0), 119.1 (1), 124.4 (1), 127.7 90), 131.9 (0), 136.0 (1), 138.5 (0), 147.9 90), 149.5 (0), 154.3 91), 161.8 90), 180.4 (0), 190.5 (0) ppm. Anal. (exact mass HREIms) calcd for $C_{15}H_{11}NO_3$ m/z 253.0739, found 253.0741. Anal. Calcd for $C_{15}H_{11}NO_3.{}^1/_2\ H_2O$: C 68.70, H 4.61 , N 5.34. Found C 69.08 , H 4.51, N 5.32.

Silver oxide (Ag_2O, 9.3 g, 40 mmol), and methyl iodide (91.2 g, 40 ml, 0.64 mol) were added to a solution of 3-methyl-9-methoxycleistopholine (5 g, 20 mmol) in chloroform (250 ml). The mixture was stirred in the dark at room temperature for 24 h. After that time the mixture was filtered and the solid residue was washed with hot chloroform (2 x 100 ml). The combined filtrates were washed with water (2 x 50 ml) and dried over anhydrous sodium sulfate. Evaporation of solvent gave crude material which was crystallized from ethyl acetate-petroleum ether (20:80 v/v) to give pure **9-methoxy-3-methylcleistopholine (31)** (4.0 g, 76%), mp 167-169°C; ir (KBr) ν 1675, 1660, 1585, 1550, 1470, 1440, 1380, 1365, 1330 cm^{-1}, ^{1}H nmr ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.99 (s, 3H, CH_3O), 7.28 (dd, 1H, *J*=8.0, 1.0 Hz, H-8), 7.64 (dd, 1H, *J*=8.0, 8.0 Hz, H-7), 7.88 (dd, 1H, *J*=8.0, 1.0 Hz, H-6), 8.67 (s, 1H, H-2); ^{13}C nmr ($CDCl_3$) 17.2 (3), 17.8 (3), 56.5 (3), 118.0 (1), 119.5 (1), 123.0 (0), 131.2 (0), 134.5 (1), 134.6 (0), 138.6 (0), 147.2 (0), 148.3 (0), 153.7 (1), 159.4 (0), 182.6 (0), 185.2 (0) ppm. Anal. (exact mass HREIms) calcd for $C_{16}H_{13}NO_3$ m/z 267.0895, found 267.0891. Anal. Calcd for $C_{16}H_{13}NO_3 \cdot {}^1/_4\ H_2O$: C 70.71, H 5.01, N 5.15. Found C 70.41, H 4.98, N 5.14.

8-Methoxy-4-methyl-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (8-Methoxy-4-methylsampangine, 33)
Dimethylformamide dimethyl acetal (2.5 g, 2.8 ml, 21 mmol) was added to a solution of 9-methoxy-3-methylcleistopholine (**31**) (1.87 g, 7 mmol) in dimethylformamide (4 ml) and heated at 120 °C under nitrogen for 3 h. Ammonium chloride (0.6 g, 11 mmol) and glacial acetic acid (6 ml) were then added and the mixture was heated again at 120 °C for an additional 2 h. After cooling, the mixture was poured onto water (100 ml) and extracted with methylene chloride (4 x 50 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml) , water (3 x 50 ml), dried over anhydrous potassium carbonate and concentrated to dryness. Flash silica gel column chromatography of the crude product using chloroform-methanol (200:1 v/v) for elution, gave pure **8-methoxy-4-methylsampangine (33)** (0.38 g, 20%), mp 163-164 °C; ir (KBr) ν 1670, 1600, 1585, 1470, 1400 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.72 (s, 3H, CH_3), 4.08 (s, 3H, CH_3O), 7.38 (dd, 1H, *J*=8.0, 1.2 Hz, H-9), 7.57 (dd, 1H, *J*=8.0, 8.0 Hz, H-10), 7.67 (d, 1H, *J*=5.9 Hz, H-3), 8.11 (dd, 1H, *J*=8.0, 1.2 Hz, H-11), 8.88 (s, 1H, H-5), 8.93 (d, 1H, *J*=5.9 Hz, H-2); ^{13}C nmr ($CDCl_3$)

δ 16.1 (3), 57.1 (3), 114.8 (1), 119.2 (1), 119.6 (0), 121.5 (1), 122.9 (0), 131.9 (1), 132.7 (0), 134.5 (0), 137.8 (0), 145.2 (0), 146.3 (1), 148.3 (1), 152.1 (0), 159.3 (0), 181.9 (0) ppm. Anal. (exact mass, HREIms) calcd for $C_{17}H_{12}N_2O_2$ m/z 276.0899 found 276.0891. Anal. Calcd for $C_{17}H_{12}N_2O_2 \cdot {}^1/_4H_2O$: C 72.72, H 4.49, N 9.98. Found: C 72.33, H 4.63, N 9.76.

4-Methylquinoline-5,8-dione (35)

To a solution of 5,8-dimethoxylepidine (**34**)[30] (1.5 g, 7.5 mmol) in acetonitrile (50 ml), a cooled (0-5°C) solution of ceric ammonium nitrate (8.22 g, 15 mmol) in water (25 ml) was slowly added with vigorous stirring within 20 min. The reaction mixture was cooled in an ice bath during the addition. After addition was complete the cooling bath was removed and the mixture stirred at room temperature for additional 30 min. After addition of water (50 ml), the mixture was transferred to a separatory funnel and extracted with chloroform (3 x 100 ml). The combined chloroform extracts were washed with water (3 x 50 ml), dried over anhydrous potassium carbonate and evaporated. The crude product was crystallized from chloroform-hexane (90:10 v/v) to give pure **4-methylquinoline-5,8-dione (35)** (1.1 g, 86%), mp 118-119°C; ir(KBr) ν 1680, 1660, 1605, 1580, 1440, 1370, 1300 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.71 (s, 3H, CH_3), 6.91 (ABd, 1H, *J*=10.4 Hz, H-6), 7.01 (ABd, 1H, *J*=10.4 Hz, H-7), 7.39 (d, 1H, *J*=5.0 Hz, H-3), 8.75 (d, 1H, *J*=5.0 Hz, H-2); ^{13}C nmr ($CDCl_3$): 22.0 (3), 127.3 (0), 130.8 (1), 137.0 (1), 139.4 (1), 148.2 (0), 150.4 (0), 152.9 (1), 183.1 (0), 186.4 (0) ppm. Anal. (exact mass, HRFABms) calcd for $C_{10}H_7NO_2$ + H, m/z 174.0555 found 174.0540. Anal. Calcd for $C_{10}H_7NO \cdot {}^1/_8H_2O$: C 68.46, H 4.17, N 7.98. Found: C 68.62, H 4.14, N 7.99.

4,7,8-Trimethylbenzo[*g*]quinoline-5,10-dione (7,8-Dimethylcleistopholine, 37)

4-Methylquinoline-5,8-dione (**36**) (1.0 g, 5.8 mmol) and 2,3-dimethyl-1,3-butadiene (**36**) (0.95 g, 1.3 ml, 11.6 mmol) in absolute ethanol (10 ml) were heated under reflux for 24 h. The solid that separated from the cooled reaction mixture was dissolved in 5% ethanolic potassium hydroxide (25 ml), and air was passed through the mixture for 6 h. The initial green solution turned yellow during that time. After cooling to about -10°C, the separated product was filtered, washed with cold water (10 ml), followed by cold ethanol (5 ml), and finally with cold petroleum ether (10 ml). The crude product was crystallized from methylene chloride-petroleum ether (20:80 v/v) to give pure **7,8-dimethylcleistopholine (37)** (0.84 g, 60%), mp 235-236°C; ir (KBr) ν 1680, 1660, 1600, 1580, 1520, 1440 cm $^{-1}$, ^{1}H nmr ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.40 (d, 1H, *J*=4.8 Hz, H-3), 7.82 (s, 1H, H-6), 7.96 (s, 1H, H-9), 8.79 (d, 1H, *J*=4.8 Hz, H-2); ^{13}C nmr($CDCl_3$) 20.0 (3), 20.2 (3), 22.7 (3), 127.9 (1), 128.0 (1), 128.9 (0), 130.4 (0), 130.9 (1), 131.7 (0), 144.1 (0), 144.5 (0), 150.1 (0), 151.2 (0), 153.0 (0), 181.8 (0), 184.7 (0) ppm. Anal. (exact mass HRFABms) calcd for $C_{16}H_{13}NO_2$ + H m/z 252.1025, found 252.1023. Anal. Calcd for $C_{16}H_{13}NO_2$: C 76.48, H 5.21, N 5.57. Found: C 76.19, H 5.27, N 5.50.

9,10-Dimethyl-7*H*-naphtho[1,2,3-*ij*][2,7]naphthyridin-7-one (9,10-Dimethylsampangine, 38)

Dimethylformamide dimethyl acetal (1.07 g, 1.2 ml, 9 mmol) was added to a solution of 7,8-dimethylcleistopholine (**37**) (0.75 g, 3 mmol) in dimethylformamide (3 ml) and heated at 120 °C under nitrogen for 3 h. Ammonium chloride (0.25 g, 5 mmol) and glacial acetic acid (3 ml) were then added and the

mixture was heated again at 120 °C for an additional 2 h. After cooling, the mixture was poured onto water (100 ml) and extracted with methylene chloride (4 x 50 ml). The combined organic phases were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml), water (3 x 50 ml), dried over anhydrous potassium carbonate and concentrated to dryness. Flash silica gel column chromatography of the crude product, using ethyl acetate for elution, gave pure **9,10-dimethylsampangine (38)** (0.2 g, 25%), mp 230-231 °C; ir (KBr) ν 1670, 1600, 1585, 1470, 1400 cm $^{-1}$, ^{1}H ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.08 (s, 3H, CH_3O), 7.54 (d, 1H, *J*=5.5 Hz, H-3), 7.79 (d,1H, *J*=5.5 Hz, H-4), 8.01 (s, 1H, H-8), 8.25 (s, 1H, H-11), 8.66 (d, 1H, *J*=5.5 Hz, H-2), 8.99 (d, 1H, *J*=5.5 Hz, H-5); ^{13}C nmr ($CDCl_3$) δ 19.7 (3), 20.3 (3), 118.6 (1), 119.4 (0), 123.1 (1), 126.0 (1), 129.1 (1), 130.1 (0), 132.9 (0), 138.4 (0), 140.7 (0), 144.6 (0), 147.0 (1), 147.9 (0), 148.1 (1), 151.3 (0), 181.6 (0) ppm. Anal. (exact mass, HRFABms) calcd for $C_{17}H_{12}N_2O$ + H, m/z 261.1028 found 261.1038. Anal. Calcd for $C_{17}H_{12}N_2O.^1/_4 H_2O$: C 77.11, H 4.76, N 10.58. Found: C 76.96, H 4.92, N 10.33.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS, Grant No. RO1-AI-32485. The laboratory assistance of Mr. Jinhui Dou, Mr. Ashraf Khalil, Mr. Khaled Orabi and Mr. Krushna Sahu is graciously recognized.

REFERENCES

1. A.M. Clark and C.D. Hufford, 'Human Medicinal Agents from Plants:Discovery and Development of Novel Prototype Antibiotics for Opportunistic Infections Related to Acquired Immunodeficiency Syndrome', ACS Symposium Series 534, ed. by E.D. Kinghorn and M.F. Balandrin, American Chemical Soviety, Washington D.C., 1993, pp. 228-241.
2. A.M. Clark and C.D. Hufford, 'The Alkaloids:Antifungal Alkaloids', Vol. 42, ed. by G.A. Cordell, Academic Press, Inc., San Diego, 1992, pp. 117-150.
3. J.U.M. Rao, G.S. Giri, T. Hanumaiah, and K.V.J. Rao, *J. Nat. Prod.*, 1986, **49**, 346.
4. F. Bracher, *Liebiegs Ann. Chem.*, **1989**, 87.
5. S. Liu, B. Oguntimein, C.D. Hufford, and A.M. Clark, *Antimicrob. Agents Chemother.*, 1990, **34**, 529
6. J.R. Peterson, J.K. Zjawiony, S. Liu, C.D. Hufford, A.M. Clark, and R.D. Rogers, *J. Med. Chem.*, 1992, **35**, 4069.
7. A. R. Carroll and W.C. Taylor, *Aust. J. Chem.*, 1991, **44**, 1615.
8. Y. Kitahara and A. Kubo, *Heterocycles*, 1992, **34**, 1089.
9. E.F.V. Scriven in Comprehensive Heterocyclic Chemistry, The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds, Vol. 2, Eds. A.R. Katrizky, C.W. Rees, A.J. Boulton, and A. McKillop, Pergamon Press, New York, 1984, pp. 198-205.

10. P.A. Lowe in Comprehensive Heterocyclic Chemistry, The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds, Vol. 2, Eds. A.R. Katrizky, C.W. Rees, A.J. Boulton, and A. McKillop, Pergamon Press, New York, 1984, pp. 587-589.
11. J.J. Eisch, *J. Org. Chem.*, 1962, **27**, 1318.
12. W.W. Paudler and T.J.Kress, *J. Org. Chem.*, 1968, **33**, 1384.
13. W.W. Paudler and S.J. Cornrich, *J. Heterocycl. Chem.*, 1970, **7**, 419.
14. K. Piers, C. Meimaroglou, R.V. Jardine, and R.K. Brown, *Can. J. Chem.*, 1963, **41**, 2399.
15. D.E. Pearson, W.W. Hargrove, J.K.T. Chow, and B.R. Suthers, *J. Org. Chem.*, 1961, **26**, 789.
16. R.A. Abramovitch and M. Saha, *Can. J. Chem.*, 1966, **44**, 1765.
17. R.W. Weber, S.J. Lee, S. Milosevich, W.B. England, and J.M. Cook, *Can. J. Chem.*, 1982, **60**, 3049.
18. J. King and G.R. Ramage, *J. Chem. Soc.*, **1954**, 936.
19. T.J. Kress and L.L. Moore, *J. Heterocycl. Chem.*, 1973, **10**, 153.
20. H.C. Van der Plas and M. Wozniak, *J. Heterocycl. Chem.*, 1976, **13**, 961.
21. O.N. Chupakhin, V.N. Charushin, and H.C. Van der Plas, *Tetrahedron*, 1988, **44**, 1.
22. M. Makosza, *Synthesis*, **1991**, 103.
23. E. Buncel, M.R. Crampton, M.J. Strauss, and F. Terrier, Electron Deficient Aromatic- and Heteroaromatic-Base Interactions, The Chemistry of Anionic Sigma Complexes, Elsevier, New York, 1984.
24. N.Atanes, L. Castedo, E. Guitian, C. Saa, J.M. Saa, and R. Suau, *J. Org. Chem.*, 1991, **56**, 2984
25. Ref 10, pp 594-595.
26. W.W. Paudler and T.J. Kress, *J. Heterocycl. Chem.*, 1968, **5**, 561.
27. J.R. Grunwell, A. Karipides, C.T. Wigal, S.W. Heinzman, J. Parlow, J.A. Surso, L. Clayton, F.J. Fleitz, M. Daffner, and J.E. Stevens, *J. Org. Chem.*, 1991, **56**, 91.
28. M.Chigr, H.Fillion, and A. Rougny, *Tetrahedron Lett.* 1988, **29**, 5913.
29. J.F. Garden and R.H. Thomson, *J. Chem. Soc.*, **1957**, 2483.
30. C.E. Kaslow and N.B. Sommer, *J. Am. Chem.. Soc.*, 1946, **68**, 644.
31. B.H. Babu and N.V. Subba Rao, *Symp. Syn. Heterocycl. Compounds Physiol. Interest, Hyderbad, India* **1964**, 114(*Chem. Abstr.*, 1968, **69**, 10339f).
32. K.T. Potts, D. Bhattacharjee, and E.B. Walsh, *J. Org. Chem.*, 1986, **51**, 2011.
33. T. Severin, G. Wanninger, and H. Lerche, *Chem. Ber.*, 1984, **117**, 2875.
34. A. Waldner, *Helv. Chim. Acta*, 1988, **71**, 486.

Received, 4th April, 1994