# A Review of the Chemistry of the Antitumor Benzo[*c*]phenanthridine Alkaloids Nitidine and Fagaronine and of the Related Antitumor Alkaloid Coralyne



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## Introduction.

The benzophenanthridine alkaloids, more properly referred to as benzo[*c*]phenanthridines, are an important class of alkaloids in the isoquinoline alkaloid family; approximately thirty naturally occurring benzophenanthridines have been isolated from plant sources (1-3). The most important of these are shown in Figure 1, *viz.*, (+)-chelidonine (**1**), corynoline (**2**), corynoloxine (**3**), corynolamine (**4**), 5-hydroxycorynoline (**5**), 6-epicorynoline (**6**), (+)-14-epicorynoline (**7**), acetylcorynoline (**8**), (+)-acetylisocorynoline (**9**), dihydrosanguinarine (**10**), oxysanguinarine (**11**), 8-methoxydihydronitidine (**12**), bocconoline (**13**), sanguinarine (**14**), chelerythrine (**15**), avicine (**16**), chelirubin (**17**), macarpine (**18**), bucconine (**19**), nitidine (**20**), fagaronine (**21**), 1,3-bis(8-hydrochelerythrinyl)acetone (**22**) and *meso*- and (+)-1,3-bis(8-hydrosanguinarinyl)-acetone (**23**) (1,2).

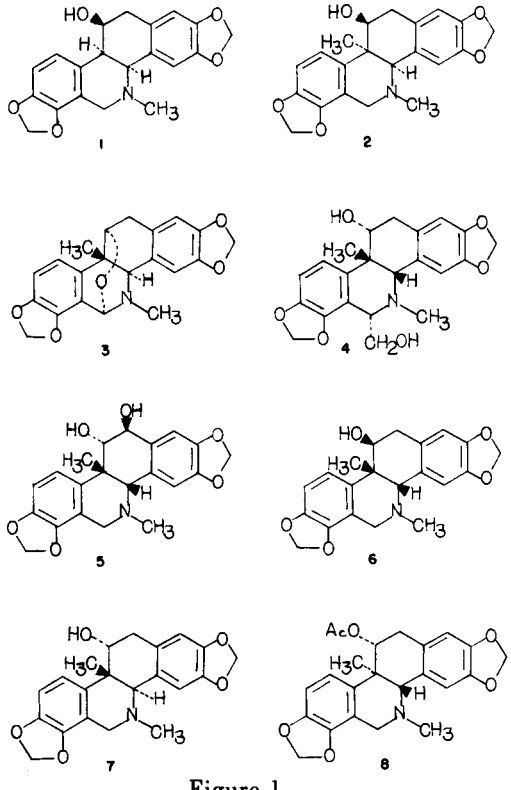
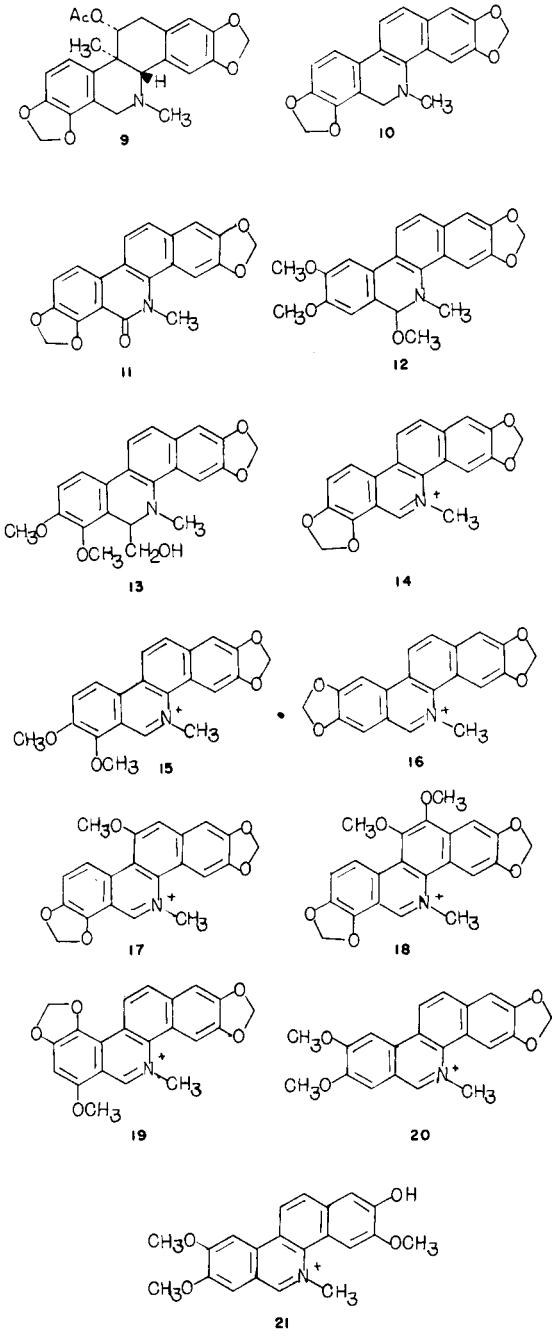


Figure 1



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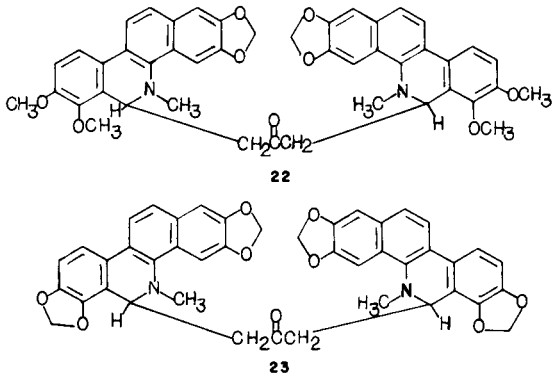

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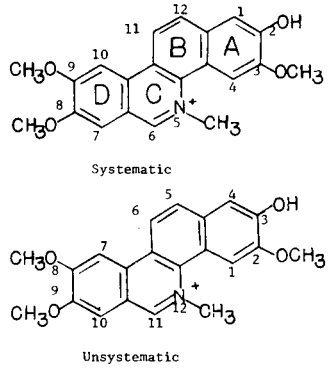



Figure 2

The systematic numbering for the benzo[*c*]phenanthridines and the accepted lettering for each individual ring in the tetracyclic compounds are shown in Figure 2 (4), with fagaronine serving as an example. The unsystematic and less often used numbering system proposed by Shamma (1) is also shown.

Biosynthetically, the benzo[*c*]phenanthridines are related to the protoberberines and are formed by cleavage of the 6,7-bond of protoberberines followed by joining of C-6 to C-13. Battersby, *et al.* (5-9), have elucidated the biogenesis of sanguinarine and (+)-chelidonine in *Chelidonium majus L. (Papaverceae)* by tracer experiments. The biogenetic scheme for both of these alkaloids proceeds *via* the common intermediate (+)-reticuline, which itself originates from the amino acid tyrosine, and is shown in Figure 3. Thus, the biosynthesis of sanguinarine and (+)-chelidonine can serve as an example for the general biosynthetic scheme of the benzo[*c*]-phenanthridines.

Members of the benzo[*c*]phenanthridine alkaloids possess a wide range of biological activity, including depression of the central nervous system, narcosis, antifungal activity and antibacterial activity (1). However, the most significant biological activity exhibited by certain of these alkaloids is antitumor activity. Sanguinarine (14), chelerythrine (15), (+)-1,3-bis(8-hydrosanguinarinyl)-acetone (23), nitidine (20) and fagaronine (21) are all reported to have a certain amount of antitumor activity (10). Nitidine and fagaronine, however, are the only two which possess significant antitumor activity both *in vivo* and *in vitro* (10).

Although a certain amount of the chemistry and biochemistry of nitidine and fagaronine has been reviewed in the literature (1-3, 10-12), a comprehensive review of these important alkaloids is lacking. Therefore, this review will present a comprehensive survey of the chemistry, biochemistry and pharmacology of nitidine and fagaronine, and covers the literature through volume **92** of *Chemical Abstracts.* A comprehensive review of the related antitumor protoberbinium alkaloid coralyne is also included.

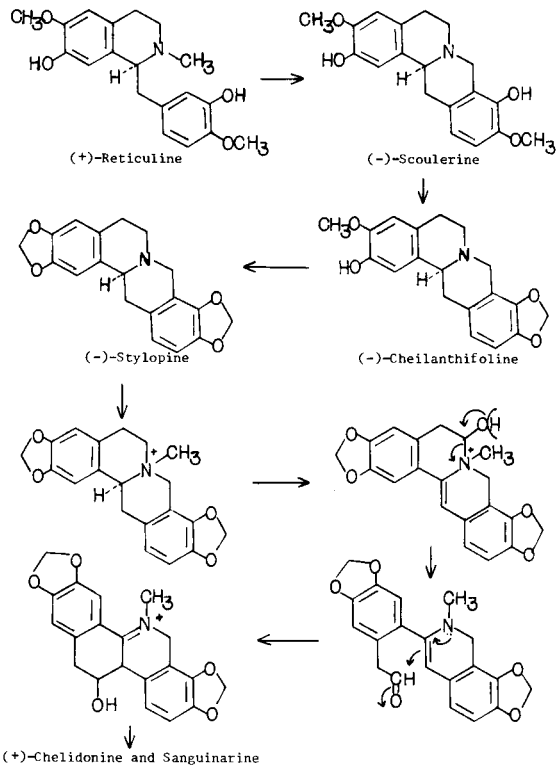



Figure 3

Nitidine.

Isolation.

Nitidine was first isolated as its hydroxide salt in 1958 by Arthur, *et al.* (13,14), from *Zanthoxylum nitidum,* and was later isolated from a wide variety of additional *Zanthoxylum (Xanthoxylum)* and (*Fagara*) species, including *Z. hamiltonianum* (15), *Z. avicennae* (16), *Z. dinklagei* (17), *Z. dipetalum* (18), *Z. Perfoliolum* (19), *Z. myriacanthum* (20), *Z. flavum* (21), *Z. clava-herculis* (22), *Z. boustense* (23), *Z. amaricanum* (24), *X. inerme* (25), *X. cuspidatum* (26), *F. lepieurii* (27), *F. viridis* (28), *F. vitiensis* (29), *F. rubescens* (30), *F. tessmanii* (31), and *F. chalybea* (32).

Although it attracted relatively little attention following its first isolation in 1958, the discovery of the antitumor properties of nitidine in 1971 (33) initiated an intensive research effort dealing with this important alkaloid.

Physical Properties.

Nitidine has been isolated and synthesized as a variety of salts, the most common being the chloride salt. Nitidine chloride can be obtained as yellow needles from methanol and is reported to melt as low as 275° dec. (25), and as high as 284-286° dec. (34). Nitidine chloride is reported to exhibit the following ultraviolet (35), mass spectral and proton nmr (34) data: uv (methanol: λ max (log ε) 234 (4.39), 270 (4.67), 290 (4.62), 299 (4.61), 327 (4.60) and 380 nm (4.07); ms: m/e (relative intensity) 333 ($M^+$ - $CH_3Cl$ -$2H_2O$, 100), 52 (18), 50 ($CH_3Cl$, 60); nmr (DMSO-$d_6$): δ 9.86 (s, 1H), 8.95 (d, 1H, J = 8 Hz), 8.40 (s, 1H), 8.32 (s, 1H), 8.30 (d, 1H, J = 8 Hz), 7.92 (s, 1H), 6.36 (s, 2H), 4.90 (s, 3H), 4.24 (s, 3H) and 4.05 (s, 3H).

Synthesis.

The first syntheses of nitidine were reported in the literature simultaneously and independently by two research groups in 1973, *viz.*, Kametani, *et al.* (36) (Figure 4), and Cheng and Cheng (35,37,38) (Figure 5). Both of these syntheses are based on the intermediate 3,4-dihydro-6,7-methylenedioxy-1-(2*H*)naphthalenone (**24**). However, the synthesis of this intermediate and the ensuing reaction sequence used to prepare nitidine are different. The scheme used by Cheng and Cheng shown in Figure 5 is based on previous work dealing with the synthesis of

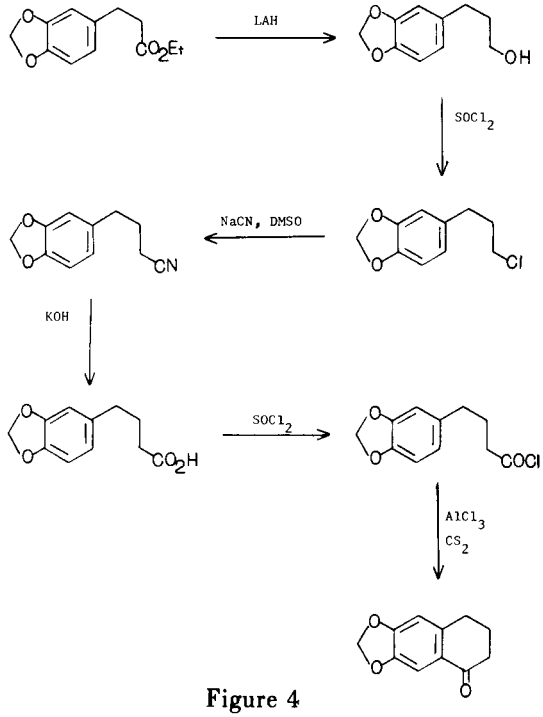



Figure 4

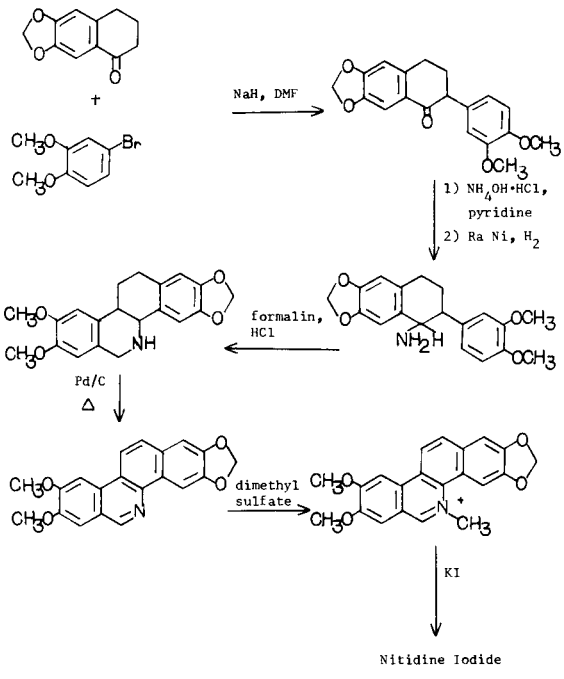



Figure 4 (Continued)

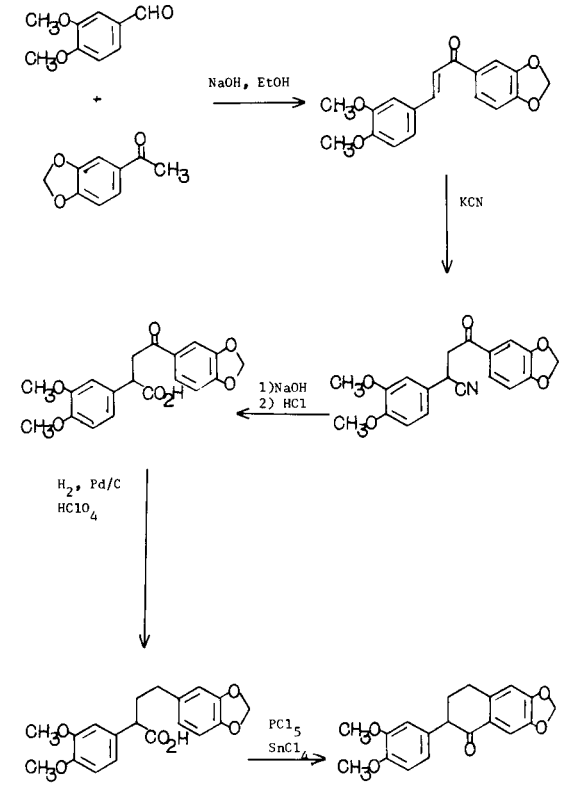



Figure 5

dihydronitidine (39) and involves the Leuckart reaction (40) on **24** followed by ring closure with phosphorus oxychloride and catalytic dehydrogenation to give 8,9-dimethoxy-2,3-methylenedioxybenzo[c]phenanthridine

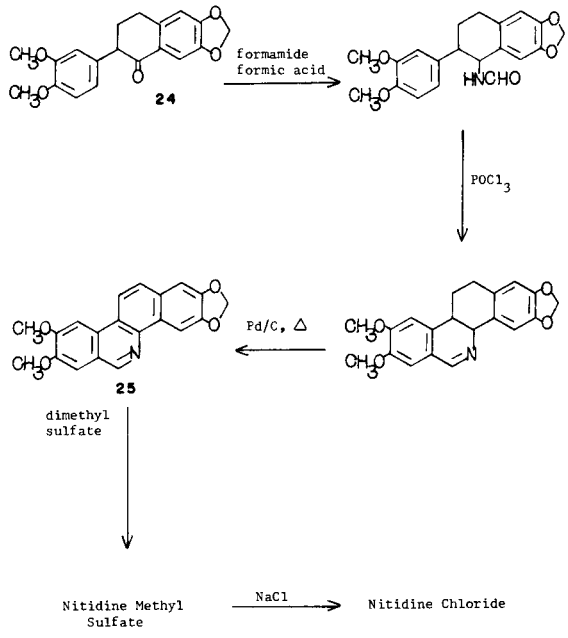



Figure 5 (Continued)

(**25**), rather than the oxime formation, Raney nickel reduction, Mannich reaction catalytic dehydrogenation procedure used by Kametani *et al.* (Figure 4), to give the same intermediate **25**. Both procedures involve methylation and quaternization of **25** with methyl sulfate, followed by anion exchange to give either the iodide or the chloride salt of the desired alkaloid.

Two independent groups (41,42) have reported a synthetic route to nitidine which involves a photochemical ring closure of the C ring. As shown in Figure 6, the photochemical cyclization of 2-bromo-4,5-dimethoxy-*N*-(6,7-methylenedioxy-1-naphthyl)benzamide (**27**), or of the *N*-methyl derivative, leads to the formation of **28**, which, in the case of R = H, can be reacted with lithium aluminum hydride followed by dehydrogenation with hydrogen peroxide in the presence of fluoroboric acid to give the tetrafluoroborate salt of nitidine. A major weakness in this procedure from a synthetic point of view is the tedious synthesis of the aminonaphthalene **26** (42,43).

The most recently reported synthesis of nitidine is shown in Figure 7 (34). This synthesis is unique since it involves a final ring closure of the B ring rather than the C ring, as is the case in each of the other synthetic routes to nitidine. This procedure used 4,5-dimethoxyhomophthalic anhydride (**44**) as starting material in an initial reaction with Schiff base 3,4-methylenedioxybenzylidenemethylamine, and gives better yields in fewer steps when compared with the earlier synthetic routes developed for the preparation of nitidine.

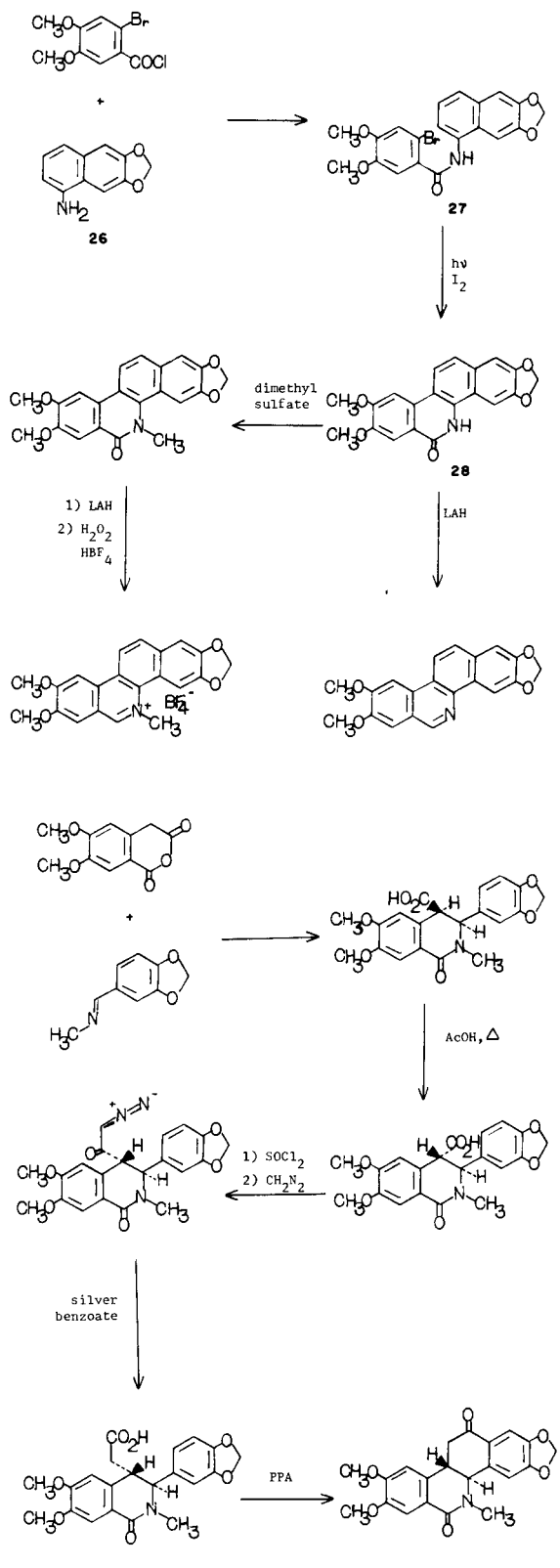



Figure 6

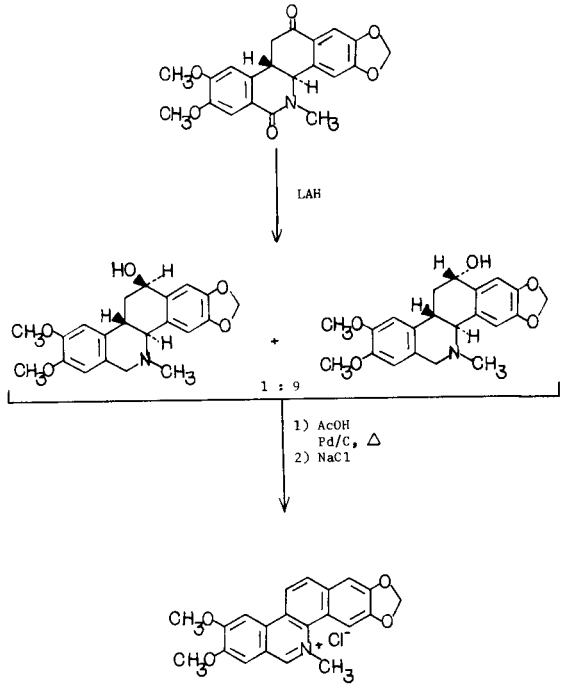



Figure 7

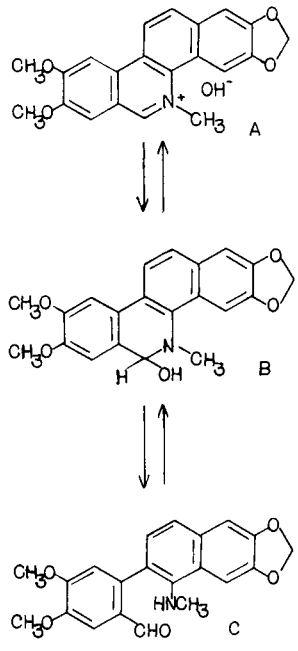



Figure 8

Chemical Properties.

Arthur, *et al.* (13,14), reported that the hydroxide salt of nitidine, which they isolated from natural sources, is extremely unstable. Thus, nitidine was first isolated and characterized as the pseudocyanide (13). Later it was also characterized as the stable acetate, chloride, iodide and periodide salts (14).

In the presence of hydroxide ion, nitidine, as well as other quaternary isoquinolinium salts, may exist in one of three possible tautomeric forms as shown in Figure 8: the iminium (**A**), the carbinol (**B**) and the open amino-aldehyde form (**C**). This tautomeric equilibrium has been shown to depend on: a) the inherent stability of the ring, b) the electronic properties of the substituents on the nitrogen and the carbon atoms of the imine bond, and c) external factors such as temperature and solvent polarity. This tautomeric equilibrium has been studied for nitidine, as well as for other benzo[*c*]phenanthridines and the related protoberbiniums, by two research groups (45-47). They have shown that in alkaline medium, nitidine exists in the carbinol form. This tautomeric equilibrium has been postulated to be of some importance in relation to the biological activity exhibited by nitidine (47).

Concerning the chemical properties of nitidine, it has also been shown that the C ring of nitidine methylsulfate opens easily on oxidation under Baeyer-Villiger like conditions with *m*-chloroperoxybenzoic acid in hexamethylphosphoric triamide to give the *N*-methyl formamide **29** (Figure 9) (48,49). This reaction is believed to proceed

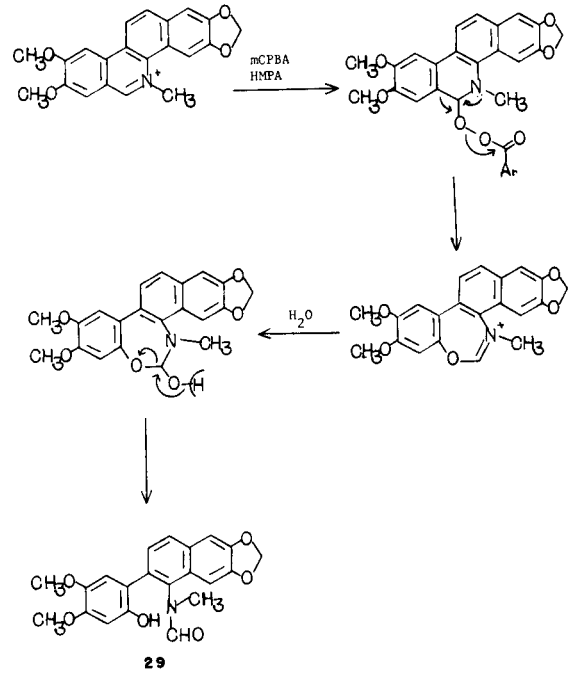



Figure 9

mechanistically as shown in Figure 9 (48). An interesting reaction occurs between the chloride salt of nitidine and *m*-chloroperoxybenzoic acid, which gives the chloro compound **30** (Figure 10) as the major product (33.6%) along with a small amount of **29** (3.8%) (48). The exact position of the chlorine atom on the phenyl group is not known, but it can be removed on hydrogenation of **30** over Raney

nickel (48). Although this chlorine atom appears to originate from the chloride anion of nitidine, the mechanism of chlorination remains unknown.

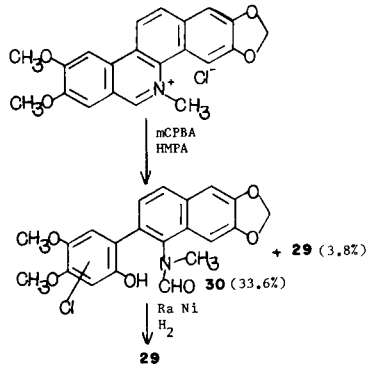



Figure 10

Biological Activity.

Nitidine chloride is reported to have a wide variety of biological activity, including inhibition of yeast respiration (50), cardiovascular activity (51) and antitrypanosomal activity (52). The inhibition of yeast respiration was prevented by divalent cation salts, especially calcium chloride; it is believed that these cations interfere with the transport of nitidine into the yeast cells (50).

The most significant biological activity shown by nitidine is its antitumor activity against L1210 and P388 leukemias, which was first exhibited in mice (33,53). Nitidine is also reported to have curative activity against Lewis lung carcinoma (53). A more recent report has shown that nitidine chloride does not increase the lifespan of mice when infected with sublines of P388 leukemia developed to be resistant to the anthracycline antibiotics adriamycin and daunorubicin (54).

Nitidine inhibits catechol *O*-methyltransferase and transfer RNA methyltransferase (55). Experimental evidence has shown a higher rate of transfer RNA methyl transferase activity in fetal or malignant tumor tissue than in normal or benign tumor tissue (56-64). Thus, a possible correlation between inhibition of *t*-RNA methyltransferase and antineoplastic activity has been postulated (65).

Nitidine has also been shown to inhibit sodium and potassium dependent ATPase activity in guinea pig brain (66). Further, Cheng, *et al.* (67), have studied the relationship of nitidine with the related carcinogenic benz[*a*]-anthracenes. It has been suggested that the presence of a quaternary nitrogen atom and alkoxy groups could be important in alleviating the mutagenicity of the parent carcinogenic compounds.

Finally, nitidine inhibits oncornavirus nucleic acid polymerase, oncornavirus reverse transcriptase and cellular nucleic acid polymerase (68-70). It has been suggested that the inhibitory activity of nitidine against reverse transcriptase of the RNA tumor viruses avian myeloblastosis virus, Rauscher leukemia virus and simian sarcoma virus, involves interaction with the template primers, particularly at the adenine-thymine base pairs, and not with the enzyme proteins. Nitidine inhibits DNA synthesis at the initiation of the polymerization stage (70). It has been suggested that since nitidine interferes with viral DNA polymerase synthesis *in vitro*, it could be a promising prophylactic agent in cancer chemotherapy (70).

Although nitidine initially showed great promise as a clinically useful antitumor agent, it was dropped after preclinical pharmacologic and toxicologic evaluation (11) due to its erratic toxicity (71).

Fagaronine.

Isolation.

Fagaronine was first isolated in 1972 from the roots of *Fagara zanthoxyloides (Rutaceae)* and was crystallized as bright yellow needles from ethyl acetate-methanol as the chloride salt (72,73). The structure of fagaronine was first proposed based on spectroscopic data (72), and was later confirmed based on the spectroscopic data of *N*-demethylfagaronine (73). The isolation of fagaronine from additional plant species has not been reported in the literature.

Physical Properties.

Fagaronine chloride exhibits unusual melting properties, melting first at 202°, followed by solidification and melting finally at 255° (72). The uv spectrum of fagaronine resembles that of nitidine, showing λ max 233 (log ε 4.29), 272 (4.55), 305 (4.44) (sh) and 328 nm (4.44); however, in 0.1*N* sodium hydroxide, a bathochromic shift to λ max 346 nm (log ε 4.31) was observed, indicating the presence of a phenolic hydroxyl group (72). Fagaronine exhibits the following additional spectroscopic data; ir (potassium bromide): 3500-3200 $cm^{-1}$ (broad); nmr (DMSO-$d_6$): δ 5.11 (s, $^{+}N$-$CH_3$, 3H), 4.24, 4.11 and 4.04 (3 singlets, $OCH_3$, 9H), 9.97 (s, H-6, 1H), 8.86 and 8.16 (2 doublets, H-11 and H-12, J = 9 Hz), 7.66, 7.94, 8.13 and 8.36 ppm (4 singlets, H-1, H-4, H-7, H-10, 4H); ms: m/e 350 ($M^{+}$), 349 (M - 1), 348, 335 (base peak, M-15), 334, 320, 306, 292 (72).

Synthesis.

The first synthesis of fagaronine was reported in 1974 by Stermitz, *et al.* (74), as shown in Figure 11. The starting 5-nitro-2,3-dimethoxynaphthalene (**31**) can be obtained by nitration of 2,3-dimethoxynaphthalene with fuming nitric acid in acetic acid to give all three possible isomeric nitro-2,3-dimethoxynaphthalenes, followed by isolation of the desired **31** by fractional crystallization. Cleavage of the diether **31** *via* either photolysis in basic solution or reaction with hydrobromic acid, gave a 1:1 mixture (50% yield) of **32** and **33**, which were separable on crystallization. Compound **32** was then reacted in the three step sequence as shown to give **34**, which was cyclized under

Kessar conditions (75) to give **35**. Both fagaronine methyl sulfate and fagaronine chloride were then synthesized as shown.

The major weakness in this synthesis, the tedious preparation of **31**, was improved by Stermitz, *et al.* (76), in a procedure involving the nitration of 2,3-dimethanesulfonoxynaphthalene (**36**) as shown in Figure **12**. This nitration gave a 57.8% yield of the desired 5-nitro isomer, which crystallized out of the reaction mixture; the isomeric 6-nitro isomer remains in solution.

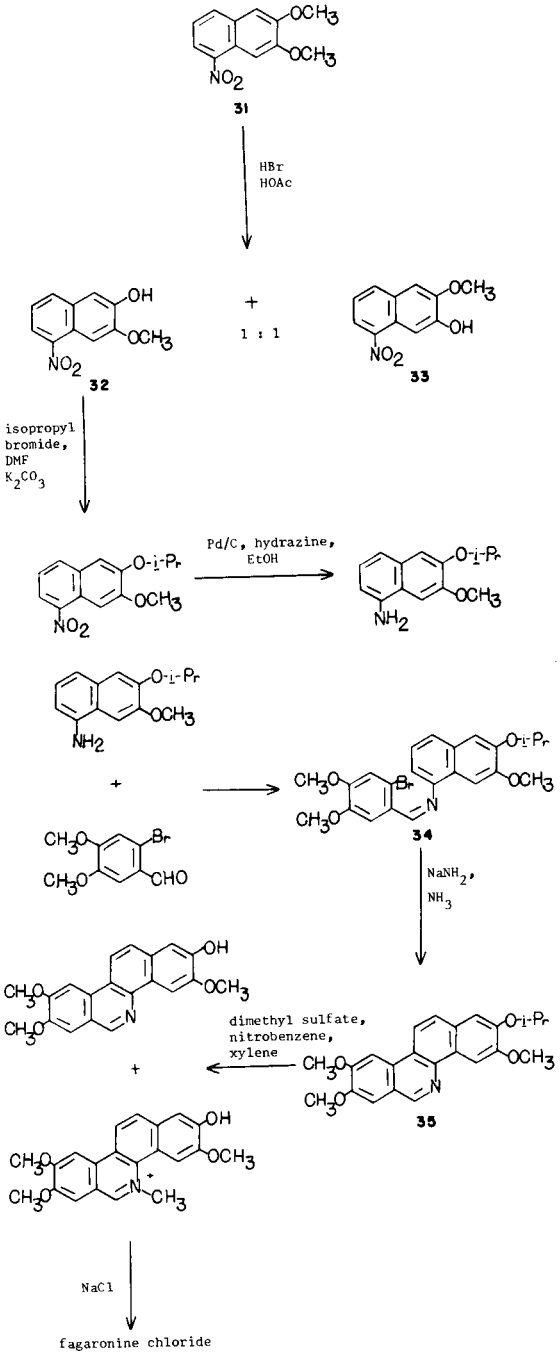



Figure 11

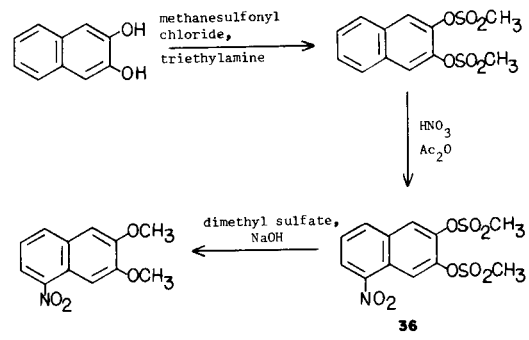



Figure 12

Chemical Properties.

Fagaronine shows similar properties to nitidine in basic solution existing primarily as the carbinol form (**B**) (Figure 8) (47). Fagaronine is also readily demethylated on heating at 270° for five minutes giving *N*-demethylfagaronine (73).

Biological Activity.

Following its initial isolation, the potent antitumor activity of fagaronine was reported, giving prolongations of life on the order of 265, 210 and 190% T/C at doses of 100, 50 and 25 mg./kg., respectively (72), in mice possessing P388 leukemia. Several leukemic mice treated with fagaronine were considered as cures. As with nitidine, fagaronine inhibits reverse transcriptase activity of various RNA tumor viruses (68-70,77). Due to its low toxicity and potent biological activity, fagaronine is currently under development as an antitumor agent (71).

Coralyne.

Introduction.

Coralyne is a protoberbinium alkaloid, another class of the isoquinoline alkaloid family related to the benzo[*c*]-phenanthridines. The structure of coralyne oriented as it usually appears in the literature, along with its systematic numbering is shown in Figure 13. A unique structural feature found in this alkaloid is a quaternized nitrogen atom at a bridgehead position in the tetracyclic fused ring-system.

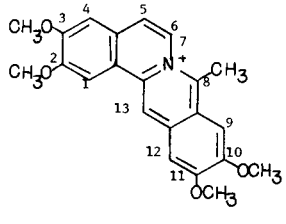


Figure 13

A structural resemblance of coralyne with the benzo[*c*]-phenanthridines is apparent. However, the close relationship of coralyne to nitidine and fagaronine is further substantiated by the related biosynthetic pathways of the

benzophenanthridines and the protoberberines, which has already been discussed, and by the potent antitumor activity which is exhibited by coralyne (10,11).

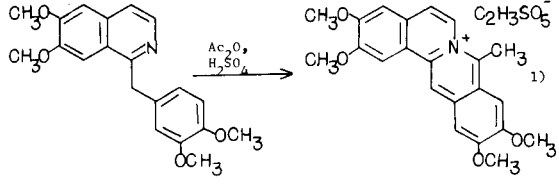
Physical Properties.

Coralyne sulfoacetate is isolated as bright yellow crystals from methanol, m.p. 278-280°; uv (ethanol): λ max 220 (log ε 4.39), 233 (4.37), 243 (4.32), 286 (4.59), 300 (4.74), 310 (4.78), 327 (4.66), 361 (3.94), 405 (4.17) and 425 nm (4.29); ir (potassium bromide): 1735 $cm^{-1}$; nmr (trifluoroacetic acid): δ 1.62 (s, H-1), 2.30 (s, H-4), 2.00 (d, H-5), 1.20 (d, H-6), 6.53 (3 singlets, $CH_3$), 2.14 (s, H-9), 2.40 (s, H-12), 0.63 (s, H-13) and 5.71, 5.80 ($OCH_3$), $J_{5,6}$ = 8 Hz; ms: m/e 363 ($M^+ - C_2H_4SO_5$) (78). Coralyne chloride is obtained as yellow crystals from ethanol, m.p. 250-252°; uv (ethanol): λ max 234 (log ε 4.36), 241 (4.32), 284 (4.46), 300 (4.72), 310 (4.77), 325 (4.66), 360 (3.84), 405 (4.17) and 425 nm (4.28) (78). The fluorescence spectrum of coralyne has also been studied (79).

Synthesis.

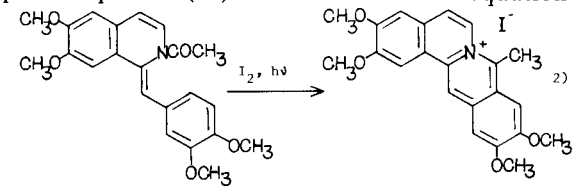
Coralyne distinguishes itself from nitidine and fagaronine in that it has not been isolated from natural sources. Although several naturally occurring protoberbines have been reported in the literature (80,81), coralyne is a purely synthetic member of this class.

The first preparation of coralyne was reported in 1920 by Schneider and Schroeter (82). In a reaction which later became known as the coralyne reaction, they treated papaverine with a solution of sulfuric acid and acetic anhydride and obtained a compound which formed intense yellow needles on recrystallization in ethanol-water, to which they assigned the structure shown in equation 1. They also noted that this product gave intense yellow green fluorescent solutions in organic solvents.




Owing to the resemblance of this product which was obtained to the known coralydine, it was given the name coralyne. The chloride, iodide and nitrate salts of coralyne were also all prepared at this time and the structure of coralyne was confirmed one year later in 1921 by additional chemical degradative studies (83). Several researchers have further substantiated this reaction (84-87). Since the total synthesis of papaverine is well known (78), the coralyne reaction completes a sequence for the total synthesis of coralyne (88-91).

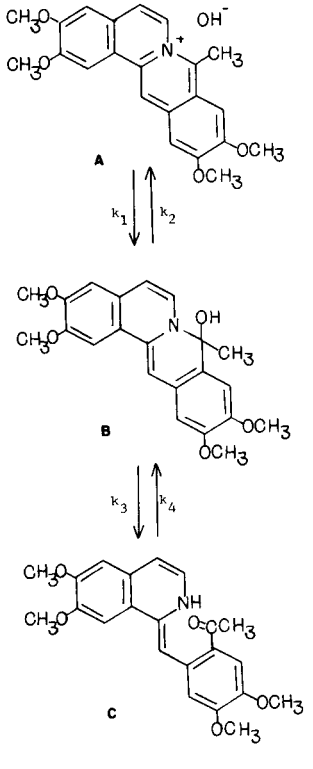
Only one other procedure, in addition to the one already discussed, for the preparation of coralyne appears in the literature. This photolytic procedure is reported in a Japanese patent (92) and is shown in equation 2.




Chemical Properties.

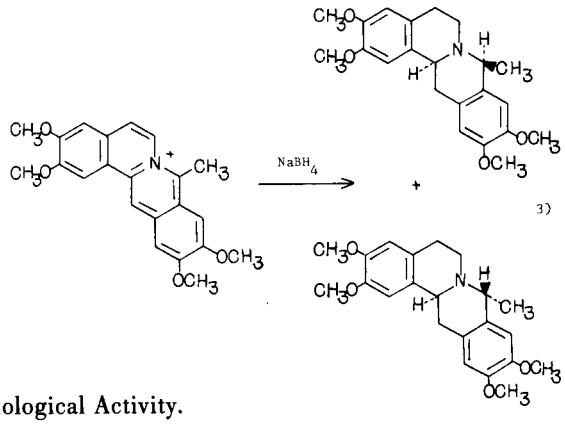
Studies concerning the structure of coralyne in basic solution have revealed that it exists in the carbinol tautomeric form (**B**) as in the case of nitidine and fagaronine (Figure 16) (45,46). Further, it has been shown that the degree of tautomerism of isoquinoline alkaloid salts to the carbinol forms increases with the *p*H of the medium and decreases in the order nitidine > berberines > pseudoberberines (46).

An extensive kinetic study of this tautomeric equilibrium and its relationship to possible liquid dosage forms of coralyne as a drug has been reported by Cheng, *et al.* (93). They have shown that the reaction of coralyne in the imminium form (**A**) to give either the carbinol tautomer (**B**) or the open amino-aldehyde form (**C**) occurs in basic solution, and also that a different reaction can be photochemically induced in aqueous solutions of coralyne exposed to visible light. From this study it was concluded that: a) appreciable amounts of the open amino-aldehyde tautomer (**C**) do not exist in dilute solutions with *p*H values below 10; b) the photochemical reaction, presumably a photodehydration, of coralyne in water can be reversed by heating or by increasing the *p*H of the solution to values



greater than 12; c) the rate of the photochemical reaction of coralyne can be reduced by increasing the concentration of coralyne in solution; and d) since it is possible to prepare more concentrated solutions of coralyne sulfoacetate than coralyne chloride in dilute aqueous sodium hydroxide, more stable basic solutions of the sulfoacetate salt can be prepared.

Reduction of coralyne sulfoacetate with sodium borohydride is reported to give a mixture of products, *viz.*, α-coralydine and *O*-methylcorytenchirine in 27% and 47% yields, respectively, as shown in equation 3 (94).




3)

Biological Activity.

Coralyne exhibits potent activity against leukemias L1210 and P388 in mice (88,95). The antitumor activity of the chloride and the sulfoacetate salts of coralyne has been studied more than the activity of other coralyne salts (88,95). As in the case of nitidine, coralyne chloride does not increase the lifespan of mice infected with sublines of P388 leukemia developed to be resistant to adriamycin and daunorubicin (54). Further, studies concerning combination chemotherapy with coralyne and various other antitumor agents have also been reported in the literature (96).

Based on the electronic absorption spectra and viscometric analysis, it has been reported that coralyne forms an intercalated complex with DNA at low molar ratios of drug to DNA (97-99). This interaction with DNA may account for the antileukemic activity of coralyne as has been demonstrated with other antitumor agents (100). Wilson, *et al.* (98) have further demonstrated that as the molar ratio of drug to DNA increases, coralyne forms a DNA induced molecular aggregate stacked along the deoxyribose phosphate backbone. The electronic absorption spectra for unbound, stacked and intercalated coralyne molecules has been shown to differ significantly.

As in the case of nitidine and fagaronine, coralyne inhibits catechol *O*-methyltransferase (55). Coralyne also inhibits horse liver alcohol dehydrogenase, and prevents ethanol inhibitors competitive with ethanol from binding (101). A charge transfer is postulated to take place during this interaction of coralyne with liver alcohol dehydrogenase. Spectrometric studies have revealed that the site of binding of coralyne is the region of the enzyme designated as the "active site pocket" (91). Finally, studies concerning the disposition of coralyne sulfoacetate in rodents (102), and assays for measuring the biological half-life of coralyne sulfoacetate in dogs and in monkeys have been reported (103).

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