Routes to Mitomycins. Application of Iminium Salts to the Synthesis of Naphthoquinone Mitosene Analogues

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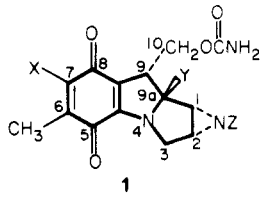
Studies directed toward the synthesis of the mitomycin-type antibiotics are described by using a model system based on 1,4-naphthoquinone. These studies resulted in the synthesis of a benzo-substituted mitosene (3), beginning with 1,4-naphthoquinone and proline. A new route to the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoloquinone skeleton was developed, the key step being an active methylene–iminium salt cyclization. Alternatively, the same ring system was obtained via diazo ketone ring-contraction. Essential to the success of these routes was the development of new methods for the preparation and selective reactions of 2-amino-1,4-naphthoquinones.

The mitomycins (1) have received intense study since their discovery and structure elucidation in 1962.[1] They



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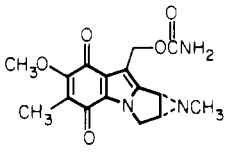


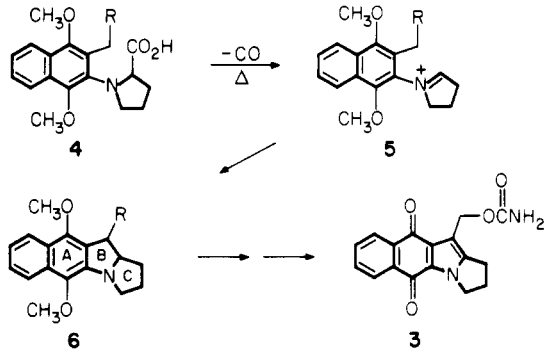
2

	X	Y	Z
Mitomycin A	CH_3O	CH_3O	H
Mitomycin C	NH_2	CH_3O	H
Porfiromycin	NH_2	CH_3O	CH_3

have been shown to possess potent antitumor and antibiotic activity,[2] and many analogues and derivatives have been synthesized in order to better define the structural requirements for both antibiotic and antitumor activity.[2-4] The mitosene analogues are particularly attractive goals for synthesis due to their modified structure and high activity. Aziridinomitosene, 2, obtained from mitomycin B or *N*-methylmitomycin A, retains much of the strong antibiotic and antitumor activity of the parent compounds.[2,5]

Most previous synthetic approaches to the mitomycin tricyclic pyrrolo[1,2-*a*]indole skeleton have been directed toward the mitosenes, and recently the total syntheses of mitomycin A and C and porfiromycin have been reported.[6] The limitations of many of the reported synthetic approaches are their nonconvergent nature and a low-yield oxidation late in the sequence to generate the *p*-quinone. To avoid this oxidation problem, we adopted a synthetic route in which the quinone (or masked quinone) is introduced early. By introducing the quinone functionality early or by using a quinone as educt, one also can exploit quinone reactivity. The convergent routes we chose were ones in which the A ring (as a quinone) and the C ring (as an amine) are first joined and then cyclized to form the B ring. Some published approaches also use this general plan.[7-9] The methods explored for B-ring formation were via an active methylene–iminium salt cyclization and by ring contraction of a diazo ketone. To focus on the key steps of ring construction, we pursued the model system based upon 1,4-naphthoquinone. As a final objective, the unknown mitosene 3 was chosen.

Iminium Salt Route. Iminium salts are versatile, reactive intermediates which are now readily available from α-tertiary amino acids.[10,11] Reaction of a nucleophile with the iminium ion thus generated results in a covalent bond between the α-carbon and the nucleophile. Our iminium salt cyclization approach to the mitosene 3 requires an α-amino acid, 4, where R is an activating group (such as



4 5 6 3

aldehyde, ester, nitrile, etc.). The electrophilic iminium salt 5 could then cyclize with the adjacent activated methylene to give tetracyclic amine 6. The dimethyl ether protected hydroquinone was chosen as the masked quinone since facile oxidative demethylation would return the quinone oxidation state.

The first approach considered for preparing the necessary intermediates corresponding to 4 was one in which

(1) (a) D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam, and N. Bohonos, *J. Am. Chem. Soc.*, **84**, 3184 (1962); J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *ibid.*, **84**, 3185, 3187 (1962); A. Tulinsky, *ibid.*, **84**, 3188 (1962). (b) For the structure and stereochemistry of mitomycin B, see R. Yahashi and I. Matsubara, *J. Antiobiot.*, **29**, 104 (1976). (c) Reviewed by W. A. Remers, "The Chemistry of Antitumor Antiobiotics", Vol. 1, Wiley, New York, 1979, pp 221–76.

(2) S. Kinoshita, K. Uzu, K. Nakano, M. Shimizu, T. Takahashi, and M. Matsui, *J. Med. Chem.*, **14**, 103 (1971); S. Kinoshita, K. Uzu, K. Nakano, and T. Takahashi, *ibid.*, **14**, 109 (1971).

(3) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877, 3878 (1964); W. A. Remers and C. S. Schepman, *J. Med. Chem.*, **17**, 729 (1974); W. G. Taylor, G. Leadbetter, D. L. Fost, and W. A. Remers, *ibid.*, **20**, 138 (1977); M. J. Weiss, G. S. Redin, G. R. Allen, Jr., A. C. Dornbush, H. L. Lindsay, J. F. Poletto, W. A. Remers, R. H. Roth, and A. E. Sloboda, *ibid.*, **11**, 742 (1968), and references therein.

(4) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **30**, 2897 (1965).

(5) J. P. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *J. Am. Chem. Soc.*, **86**, 1889 (1964).

(6) F. Nakatsubo, A. J. Cocuzza, D. E. Keeley, and Y. Kishi, *J. Am. Chem. Soc.*, **99**, 4835 (1977); F. Nakatsubo, T. Fukuyama, A. J. Cocuzza, and Y. Kishi, *ibid.*, **99**, 8115 (1977); T. Fukuyama, F. Nakatsubo, A. J. Cocuzza, and Y. Kishi, *Tetrahedron Lett.*, 4295 (1977).

(7) T. Kametani, K. Takahashi, M. Ihara, and K. Fukumoto, *J. Chem. Soc.*, 389 (1976); *Heterocycles*, **3**, 691 (1975); R. W. Franck, K. Miyano, and J. F. Blount, *ibid.*, **9**, 807 (1978).

(8) L. Mandell and E. C. Roberts, *J. Heterocycl. Chem.*, **2**, 479 (1965).

(9) M. Akiba, Y. Kosugi, M. Okuyama, and T. Takada, *J. Org. Chem.*, **43**, 181 (1978); M. Akiba, S. Ikuta, and T. Takada, *Heterocycles*, **9**, 813 (1978).

(10) R. T. Dean, H. C. Padgett, and H. Rapoport, *J. Am. Chem. Soc.*, **98**, 7448 (1976).

(11) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115, 4183 (1978); H. A. Bates and H. Rapoport, *J. Am. Chem. Soc.*, **101**, 1259 (1979); I. G. Csendes, Y. Y. Lee, H. C. Padgett, and H. Rapoport, *J. Org. Chem.*, in press.

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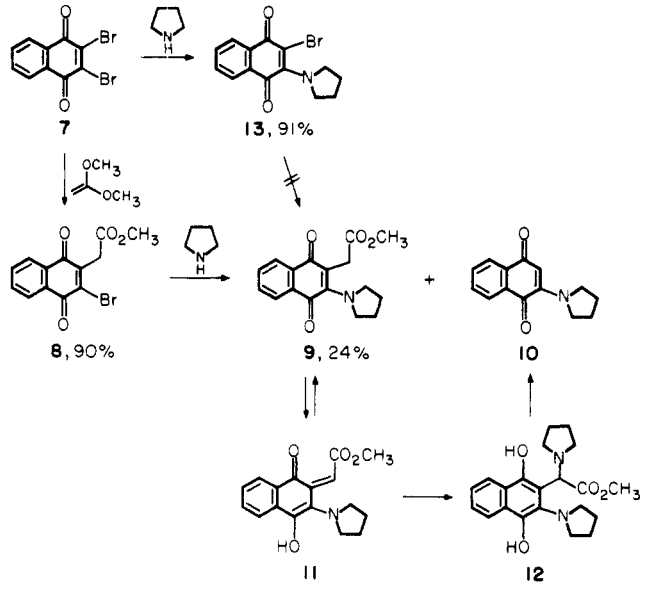
a proline ester is added to a 2-substituted 1,4-naphthoquinone. Thus the bromoquinone 8 was prepared from 2,3-dibromo-1,4-naphthoquinone (7) and ketene dimethyl acetal. Quinone–amine addition was then studied with pyrrolidine and found to be complicated by the appearance of the side product 10 under conditions which consumed the starting quinone 8. Variations in solvent, temperature, and amine stoichiometry (with or without added $NaHCO_3$ as acid scavenger) failed to improve this reaction.

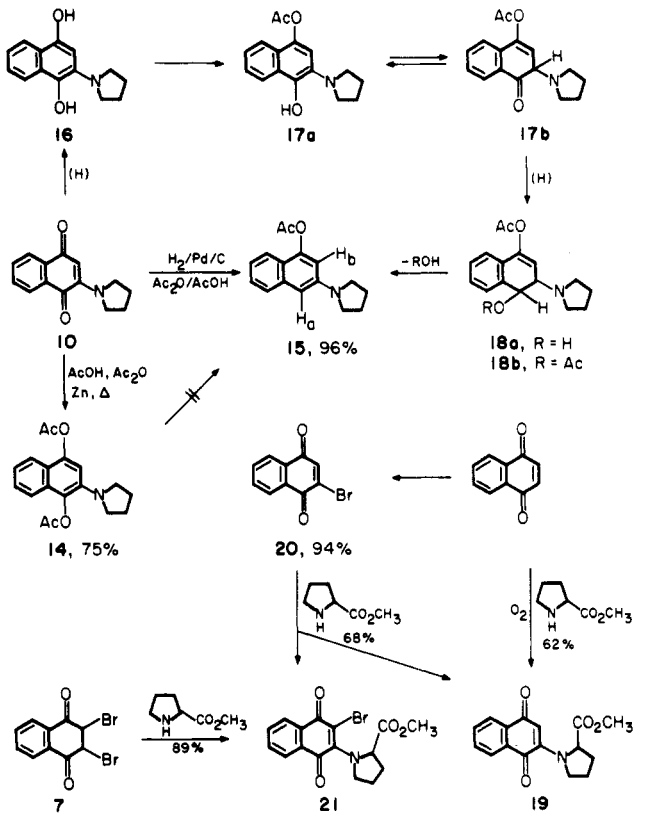
The loss of a methyl group from quinones during amine addition has been observed previously[12] and results from a second amine addition to the initial aminoquinone via the enol tautomer (in this case, 11). Reverse Mannich reaction of diamine 12 then gives dealkylated quinone 10, an authentic sample of which was prepared by the reaction of 1,4-naphthoquinone with pyrrolidine. The low yield of the desired aminoquinone 9 discouraged further attempts to add amines to 2-substituted quinones.[13]

Introduction of the active methylene side chain after amine addition was explored next. The first and most direct approach was suggested by the high-yield conversion of 2,3-dibromo-1,4-naphthoquinone (7) to bromoquinone 8. Thus the aminoquinone 13 was easily prepared in high

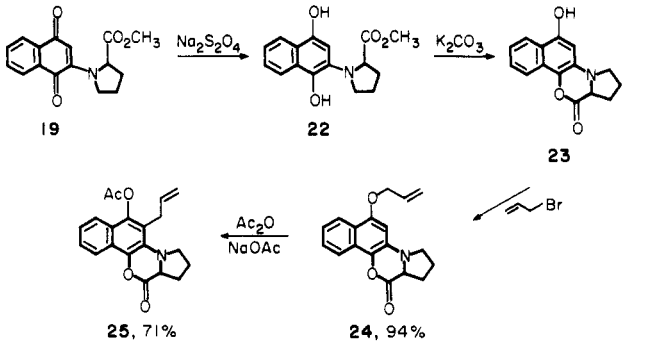


yield by reaction of pyrrolidine with 7. Quinone 13 was sensitive to light, decomposing in solution with loss of its bromine atom. When treated with excess ketene dimethyl acetal in the dark, 13 was unchanged. Likewise, 10 did not react with ketene acetal. This nonreactivity is most reasonably explained by the deactivated "vinylogous amide" nature of aminoquinones as seen in the resonance forms. Other attempts have been reported to add various nucleophiles to the 3-position of 2-amino-1,4-quinones.[8,14] Almost without exception[15] this has been unsuccessful due to the deactivating effect of the amino substituent.

Scheme I



Scheme II



These observations indicated that introduction of the side chain required a different approach. The route chosen was to reduce the aminoquinone to hydroquinone and selectively monoblock the 1-hydroxyl. The remaining phenolic hydroxyl should then steer in the side chain, e.g., via Claisen rearrangement of the allyl ether. The double bond of the allyl group could eventually be oxidatively cleaved to provide the desired functionalized side chain.

The first attempt at hydroquinone monoblocking was acetylation/monodeacetylation[16] (Scheme I). When applied to pyrrolidinylnaphthoquinone 10, acetylation easily gave the hydroquinone diacetate 14. However, monodeblocking failed, and only the starting quinone 10 was isolated. Although this particular approach to monoblocking was not pursued further, an unexpected reaction was discovered in exploring methods for preparing the diacetate. When aminoquinone 10 was catalytically reduced in acetic acid/acetic anhydride, the monoacetate 15 was produced in high yield. Its structure was established by

(12) D. W. Cameron, P. M. Scott, and A. Todd, *J. Chem. Soc.*, 42 (1964); D. W. Cameron and P. M. Scott, *ibid.*, 5569 (1964); D. W. Cameron, R. G. F. Giles, and R. B. Titman, *J. Chem. Soc. C*, 1245 (1969).

(13) The successful use of 3-chloro-2-[bis(ethoxycarbonyl)methyl]-1,4-naphthoquinones in amine addition reactions has been recently reported[9] with no mention of side-chain amination or loss. Enolization of the initial amine adduct may be difficult due to severe crowding of the bulky side chain. Use of the bis(ethoxycarbonyl)methyl side chain was not pursued as it is not amenable to our future synthesis plans.

(14) G. Cajipe, D. Rutolo, and H. W. Moore, *Tetrahedron Lett.*, 4695 (1973).

(15) 2,3-Dichloro-1,4-naphthoquinone with excess piperidine at 110 °C has been reported to give 2,3-bis(1-piperidinyl)-1,4-naphthoquinone: E. P. Fokin, A. I. Ryulina, and K. I. Matoshina, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 127 (1963); *Chem. Abstr.*, **60**, 13220*h* (1964).

(16) B. R. Baker, T. H. Davis, L. McElroy, and G. H. Carlson, *J. Am. Chem. Soc.*, **64**, 1096 (1942); C. D. Snyder and H. Rapoport, *ibid.*, **96**, 8046 (1974).

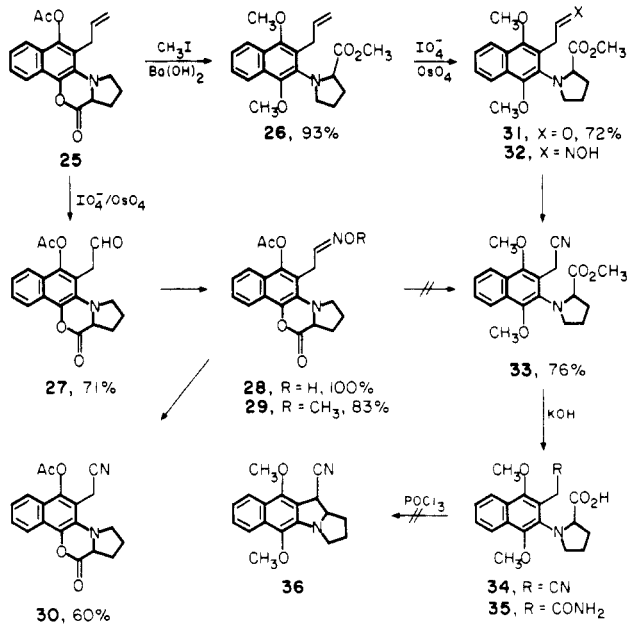
elemental analysis and the 2-Hz coupling constant of protons H_a and H_b which proves the meta orientation of the remaining acetoxy and amine. Diacetate **14**, when subjected to the same conditions, was unchanged. Therefore, **15** does not result from a hydrogenolysis of **14**. The path to **15** probably begins with acetylation of the less hindered hydroxyl of hydroquinone **16** to give intermediate **17a**. Keto–enol tautomerization[17] of this α-naphthalenol then provides keto form **17b** which upon hydrogenation gives alcohol **18a** or after acetylation the diacetate **18b**. Elimination of water or acetic acid gives the observed acetoxy amine **15**.

The problem of monoblocking was solved by the use of lactone intermediates (Scheme II). The required aminoquinone **19** was prepared from proline methyl ester and either 1,4-naphthoquinone (addition–oxidation) or 2-bromo-1,4-naphthoquinone (**20**, addition–elimination). Although the overall yield of **19** beginning with 1,4-naphthoquinone is nearly the same for the two methods, the two-step procedure via **20** is preferred due to the much cleaner amine addition step. However, also formed in this reaction was the bromoaminoquinone **21**, an authentic sample of which was prepared by the reaction of dibromoquinone **7** with proline methyl ester.

Lactonization of aminohydroquinone **22** proved to be an excellent way of selectively blocking the 1-hydroxyl. Quinone **19** in 3-pentanone was reduced with aqueous sodium hydrosulfite under an inert atmosphere,[18] and the aqueous layer was removed by pipet, avoiding exposure to air of the very easily oxidized hydroquinone **22**. The solution was then dried by azeotropic removal of water, and lactonization was effected by removal of methanol after the addition of K_2CO_3. Lactone phenol **23** was directly treated with allyl bromide, consistently giving the crystalline lactone allyl ether **24** in yields of 90% from **19**. Allyl ether **24** then was boiled in acetic anhydride/sodium acetate to give the Claisen-rearranged product **25** as stable crystalline material. Acetic anhydride was used as the solvent since it reacts with the intermediate phenol to give the stable acetate.[19]

The next phase of the synthesis was to transform lactone acetate **25** into a suitable intermediate for an iminium salt cyclization, and the nitrile amino acid **34** was the initial choice. Its synthesis was approached by two related routes, differing in the order of their steps (Scheme III). Hydroquinone dimethyl ether methyl ester **26** was conveniently prepared from lactone acetate **25** by combined hydrolysis–methylation.[20] Ozonolysis of either **25** or **26** gave only extensive oxidation. Finally the desired aldehyde **27** was obtained by using the sodium metaperiodate/catalytic osmium tetraoxide procedure. Its oxime, **28**, was easily

Scheme III



prepared and, without isolation, was dehydrated with 1,1′-carbonyldiimidazole to give lactone nitrile **30**. When the hydrolysis–methylation procedure was applied to **30**, a mixture of several products was obtained. Attempts to improve this reaction were unsuccessful, and alternative routes via oxime **28** directly and *O*-methyloxime **29** also gave a complex mixture of products including nitrile ester **33**.

These difficulties led to a reexamination of the osmium tetraoxide catalyzed periodate cleavage of **26** which had proceeded erratically under standard conditions. We found that when the reaction was conducted at pH 6.5 instead of pH 4–5 as is normally the case, the yield was greatly improved. This change required the use of lithium periodate since sodium periodate is poorly soluble under these conditions. Thus the pure aldehyde **31** was obtained reproducibly in 72% yield. The elusive nitrile **33** was then simply prepared by oximation followed by dehydration.

Hydrolysis of nitrile ester **33** was achieved by brief refluxing with ethanolic potassium hydroxide, but the product appeared to be a mixture of nitrile acid **34** and amide acid **35**. The mass spectrum, however, gave only the molecular ion for nitrile **34**; the molecular ion of amide **35** was not observed nor were its expected fragments. Iminium salt formation was then undertaken on the assumption that even if the product were a mixture of nitrile and amide, it should still be satisfactory since the amide functionality of **35** would be converted by the hot $POCl_3$ treatment into nitrile. However, reaction of crude nitrile amino acid **34** with hot $POCl_3$ followed by the usual isolation procedure gave only polar polymeric material.

The cause of failure of this key cyclization is uncertain. The pK_a of the arylacetonitrile's methylene hydrogens may be too high to observe cyclization at the pH used (6.5), and the lack of an enol form may prevent reaction at low pH's. Cyclization cannot be conducted at higher pH's since the iminium salt would deprotonate to enamine. This approach employing the nitrile activating group was therefore set aside in favor of better precedented activating groups, namely, the acetal or enol ether.[21]

(17) A. Rieche and H. Seeboth, *Justus Liebigs Ann. Chem.*, **638**, 43 (1960); M. S. Pearson, B. J. Jensky, F. X. Greer, J. P. Hagstrom, and N. M. Wells, *J. Org. Chem.*, **43**, 4617 (1978); R. H. Thomson, *Q. Rev., Chem. Soc.*, **10**, 27 (1956).

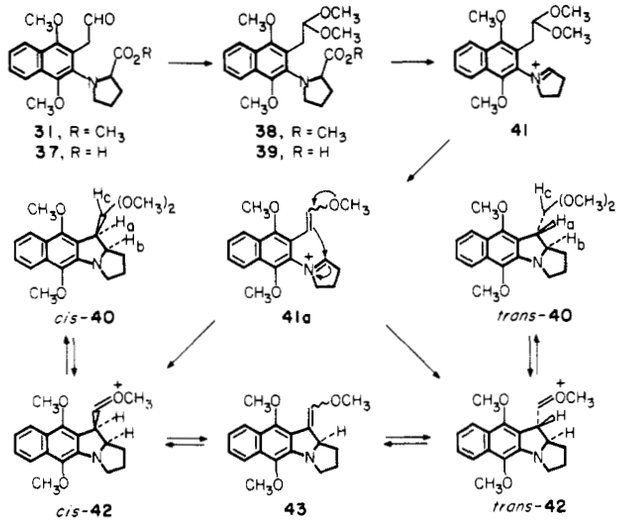
(18) 3-Pentanone (bp 102 °C) was chosen since it is immiscible with water, is a good medium for ether synthesis, and forms an azeotrope with both water and methanol.

(19) (a) The first use of acetic anhydride (as an acetic anhydride/*N*,*N*-diethylaniline mixture) in the Claisen rearrangement to protect the phenolic product was by the following: L. F. Fieser and W. C. Lothrop, *J. Am. Chem. Soc.*, **58**, 749 (1936); L. F. Fieser, W. P. Campbell, and E. M. Fry, *ibid.*, **61**, 2206 (1939). However, *N*,*N*-diethylaniline, the traditional Claisen rearrangement solvent, is unsuitable for use in the reaction of allyl ether **24** since the product is also an aniline, thus making the separation of product and solvent difficult. (b) The use of acetic anhydride/sodium acetate has been recently reported in a sealed-tube reaction of D. S. Karanewsky and Y. Kishi, *J. Org. Chem.*, **41**, 3026 (1976).

(20) R. Kuhn and H. Trushman, *Chem. Ber.*, **94**, 2258 (1961); W. E. Bondinell, S. J. DiMari, B. Frydman, K. Matsumoto, and H. Rapoport, *J. Org. Chem.*, **33**, 4351 (1968).

(21) E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Am. Chem. Soc.*, **90**, 6177 (1968); E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *ibid.*, **95**, 8427 (1973).

Scheme IV



Aldehyde **31** was easily converted to the dimethyl acetal **38** and without isolation hydrolyzed to acetal amino acid **39** in 90% yield from **31**. This amino acid was unsuitable for long-term storage, and samples of **39** developed small amounts of the esters **31** and **38** and acid **37**. The mixture of products could be reconverted into ester acetal **38** by retreatment before use. The acetal amino acid **39** upon decarbonylation with $POCl_3$ and addition of water and methanol gave the cyclized acetal **40** in 57% yield.[22]

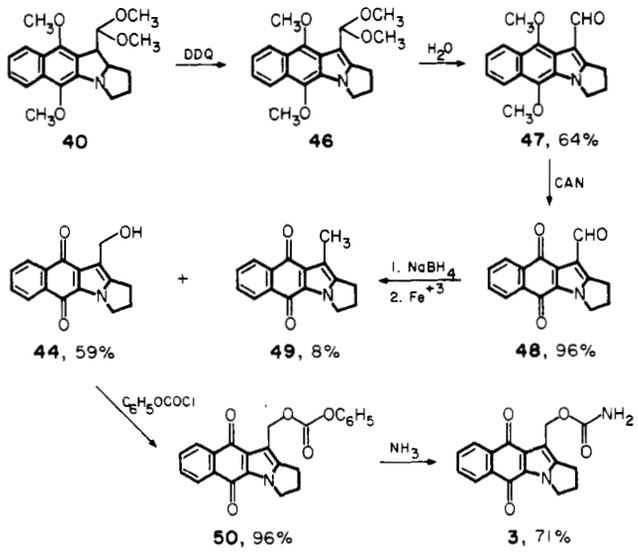
Although the stereochemistry of cyclized acetal **40** cannot be determined from the available data, the presence of a single diastereomer is strongly indicated. The product is crystalline and homogeneous by high-pressure LC. The 90- and 270-MHz ^1H NMR and the 25-MHz ^{13}C NMR spectra show no indications of a diastereomeric mixture. Models of the transition states leading to intermediates *cis*-**42** and *trans*-**42** suggest a less crowded conformation in the latter, and the highly acidic reaction conditions (methanolic HCl and H_3PO_4) would provide a path for isomer interconversion via the enol ether **43** (Scheme IV).

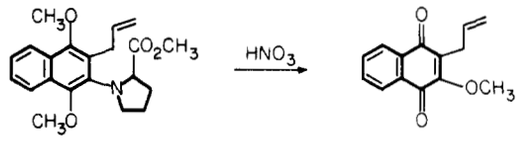
The coupling constants of ring protons H_a and H_b in principle can reveal stereochemical information, although the four *O*-methyl groups make assignments difficult in the 3–4-ppm range. However, from decoupling experiments, proton H_a can be assigned to the triplet at δ 3.73 (J = 3 Hz). This triplet must be the result of a doublet of doublets where $J_{ab} = J_{ac} = 3$ Hz. Unfortunately, models do not clearly reveal which isomer would result in a J_{ab} of 3 Hz.

Having accomplished the construction of the basic mitomycin skeleton by an iminium salt route, we pursued the final mitosene **3**. This required preparation of the (hydroxymethyl)indoloquinone **44** from acetal **40**. Conversion of the alcohol to carbamate should readily follow literature precedent.[4] The transformations required are aromatization of the B ring, oxidative demethylation of the hydroquinone dimethyl ether to quinone, and reduction of aldehyde to hydroxymethyl. The sequence of steps is strictly dictated by the necessity to keep the nitrogen lone pair delocalized.

Experience indicated that the first step could not be oxidative demethylation to quinone. When such procedures had been applied to **26**, the only product was deaminated quinone **45**. It is necessary with these procedures to protect a basic nitrogen even when it is not directly bonded to the aromatic ring.[23] Reduction of the aldehyde group was also not seriously considered as the first step. The acetal group was found to be stable to mild hydrolyzing conditions, and sodium cyanoborohydride in pH 3 water/methanol at room temperature gave no reaction.

Scheme V





26 45

The remaining option was aromatization of the B ring. This step was best accomplished by the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methylene chloride/acetone and gave the indole aldehyde **47** directly in 60–69% yield. The indole acetal intermediate **46** was never isolated from this reaction (Scheme V). In the indole aldehyde **47**, the nitrogen lone pair is delocalized and, thus oxidative demethylation had a good chance for success. If the aldehyde group were reduced before quinone formation, part of this protection would be lost. Also, the product of such a reduction, a β-(hydroxymethyl)-indole, would be quite unstable.[24]

When indole aldehyde **47** was treated with argentic oxide[25] or ceric ammonium nitrate (CAN),[26] the desired indoloquinone aldehyde **48** was obtained in high yield. Subsequent reactions utilized the final steps of the synthesis of 7-methoxymitosene.[4] Aldehyde **48** was reduced with excess sodium borohydride in methanol, and the intermediate hydroquinone was reoxidized with ferric chloride, excluding oxygen to avoid its reaction with indolohydroquinone intermediates. The desired, stable crystalline (hydroxymethyl)indoloquinone **44** was produced in 59% yield. Chromatography of the mother liquor gave the overreduction side product **49** in 8% yield. Alcohol **44** was

(22) This successful cyclization (and similar cyclizations in ref 11) is contrary to some recently promulgated rules for ring closure: J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976); J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *ibid.*, 736 (1976); J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

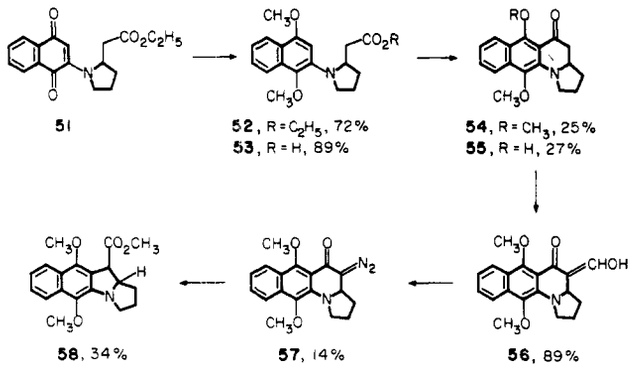
(23) R. G. F. Giles and G. H. P. Roos, *J. Chem. Soc., Chem. Commun.*, 260 (1975).

(24) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959); W. A. Remers, R. H. Roth, and M. J. Weiss, *ibid.*, **86**, 4612 (1964).

(25) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 227 (1972).

(26) P. Jacob, III, P. S. Callery, A. T. Shulgin, and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976).

Scheme VI



converted to its phenyl carbonate **50** by reaction with phenyl chloroformate. The desired carbamate, mitosene analogue **3**, then was obtained by treatment of **50** with ammonia in methylene chloride.

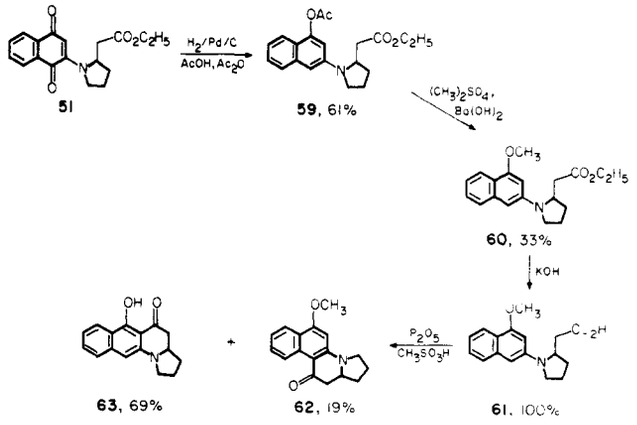
Ring Contraction Route. In pursuing new methods for constructing the basic mitomycin skeleton, we investigated a second approach emanating from aminoquinone chemistry. The plan for this second approach involved the contraction of a six-membered B ring to the needed five-membered ring and is detailed in Scheme VI. Specifically, ester **58** appeared obtainable from α-diazo ketone **57** by Wolff rearrangement.[27] Intramolecular acylation with acid **53** in turn should give the six-membered-ring ketone **54** from which α-diazo ketone **57** would derive.

The synthesis began with homoproline ethyl ester.[8] This was prepared by first treating pyrrole with ethyl diazoacetate in the presence of a copper catalyst, giving the desired ethyl 2-pyrroleacetate plus the previously unreported ethyl 3-pyrroleacetate in a ratio of 91:9. Fractional distillation separated the isomers, giving the lower boiling, internally hydrogen-bonded, 2-substituted isomer in >99% purity. Recently,[28] similar mixtures of 2- and 3-substituted products were reported from *N*-methylpyrrole. The 2-pyrroleacetate was hydrogenated to the homoproline ester which, on reaction with 1,4-naphthoquinone, gave the crystalline aminoquinone **51** in 64% yield. Aminoquinone **51** was converted into the hydroquinone dimethyl ether **52** by catalytic hydrogenation in the presence of dimethyl sulfate/$Ba(OH)_2 \cdot 8H_2O$, and hydrolysis of **52** gave the acid **53** for use in the cyclization.

A large number of cyclizations of related β-anilinopropionic acids have been reported[29] with polyphosphoric acid; however, when β amino acid **53** was exposed to these conditions, none of the desired dihydroquinolone could be isolated. Variations in time and temperature gave either no reaction, demethylated starting material, or polymers. Turning to the 10% phosphorus pentoxide in methanesulfonic acid reagent,[30] we found that at room temperature, acid **53** gave the dihydroquinolones **54** and **55** in yields of 25 and 27%, respectively. Phenol **55** can be remethylated to give the desired dimethyl ether **54** which was thus available in about 50% yield.

Accompanying the two quinolones **54** and **55** was a small but significant side product in which an entire methoxyl group was missing. This was immediately reminiscent of the previously observed loss of a 1-phenolic hydroxyl group (**5**, Scheme I). This suggested that the reductive-methylation step, **51** to **52**, was responsible due to the similar substrate and hydrogenation conditions. Thus a small amount of material from which the 1-hydroxyl had been lost, carried through the synthesis, could account for this side product.

Scheme VII



To establish this proposed origin of this side product and to prove its structure unambiguously, we undertook its synthesis (Scheme VII). Using the earlier hydrogenation and methylation conditions, we prepared meta acetoxy amine **59** and converted it to methyl ester **60**. Hydrolysis of **60** gave acid **61** which in 10% P_2O_5/CH_3SO_3H gave a 19% yield of ketone **62**, identical with the previously isolated side product. Also isolated was the β-cyclization product, phenol **63**, in 69% yield. These results are in contrast to most naphthalenic Friedel–Crafts cycloacylations which predominantly favor the α-product.[31] When α-product **62** was resubjected to the conditions of cyclization, no change was observed. Phenol **63**, not observed in the previous cyclization, was undoubtedly eliminated when the major phenolic product **55** was recrystallized.

These deoxygenated side products are interesting in that they suggest new heterocyclic ring systems available via aminoquinone chemistry. They undoubtedly could be avoided by the use of different reductive-methylation conditions not involving catalytic hydrogenation. Such improvements were not pursued since the desired product, ketone **54**, was obtained in moderate yield and free of impurities.

We next turned to the preparation of diazo ketone **57** and first explored diazo transfer.[32] Since the reaction fails if the α-hydrogens of the ketone are not sufficiently acidic, initial activation of the methylene with a formyl group[33] was necessary. Thus dihydroquinolone **54** was treated with ethyl formate/sodium hydride to give the α-formyl ketone **56** from which the formyl group was easily lost via reverse Claisen reaction if the reaction was not kept strictly anhydrous. This difficulty in obtaining stable, pure α-formyl ketone **56** encouraged us to try the α-oxalyl group which one report claims to be superior.[34] However, the desired

(27) Recently reviewed by H. Meier and K.-P. Zeller, *Angew. Chem., Int. Ed. Engl.*, **14**, 32 (1975).
(28) B. E. Maryanoff, *J. Heterocycl. Chem.*, **14**, 177 (1977).
(29) M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearin, and R. W. Morris, *J. Med. Chem.*, **8**, 566 (1965); J. Koo, *J. Org. Chem.*, **28**, 1134 (1963); G. Bradley, J. Clark, and W. Kernick, *J. Chem. Soc.*, 2019 (1972); W. N. Speckamp, J. A. von Velthuysen, U. K. Pandit, and H. O. Huisman, *Tetrahedron*, **24**, 5881 (1968).
(30) P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).
(31) R. D. Haworth and F. M. Bolam, *J. Chem. Soc.*, 2248 (1932); R. D. Haworth, *ibid.*, 1125 (1932).
(32) M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967); M. Regitz, *Synthesis*, 367 (1972).
(33) M. Rosenberger and P. Yates, *Tetrahedron Lett.*, 2285 (1964); M. Regitz, J. Rutter, and A. Liedhegener, "Organic Syntheses", Collect. Vol. 51, Wiley, New York, 1971, p 86.
(34) R. E. Harmon, V. K. Sood, and S. K. Gupta, *Synthesis*, 577 (1974).

α-oxalyl derivative of **54** could not be prepared although exhaustive attempts were made. α-Formyl ketone **56** was treated with tosyl azide and triethylamine to give a mixture of α-diazo ketone **57** and several side products; chromatography on alumina gave a pure sample of orange diazo ketone **57**.

The ring contraction was performed photochemically by irradiating diazo ketone **57** in methanol through Pyrex for 10 min. Two major products were isolated in 34% yield and shown to be a mixture of cis and trans isomers of ring-contracted ester **58**. They were separated by column chromatography, but their ^1H NMR spectra show only minor differences, thus preventing stereochemical assignments.

This route was not pursued further due to the success of the iminium salt approach. Important, however, is the demonstration that diazo ketone ring contraction can occur in this system. Both approaches also have the potential of beginning with naturally occurring, optically active amino acids. This potential for asymmetric induction in the iminium salt route as well as its application to the natural benzoquinone mitosenes is under investigation.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on either a Perkin-Elmer 137 or 377 spectrophotometer. UV spectra were obtained in methanol by using a Cary 219 spectrophotometer. Optical rotations were taken on a Perkin-Elmer 241 polarimeter. ^1H NMR (internal Me_4Si) spectra were taken in $CDCl_3$ on Varian T-60 or Varian EM-390 instruments, and the ^{13}C NMR spectrum (internal Me_4Si) was taken on a TT-23. Mass spectra were obtained from AEI MS12 and CEC 21-110 mass spectrometers. TLC was done on EM Laboratories silica gel 60. Column chromatography was done on SiO_2 (EM Laboratories, Inc., silica gel 60, 0.063–0.200 mm), neutral Al_2O_3 (M. Woelm), acidic Al_2O_3 (BioRad, 100–200 mesh), and Florisil (MCB, 60–200 mesh). Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. Final-product organic solutions were washed successively with water, saturated Na_2CO_3, and saturated NaCl, dried over $MgSO_4$, and evaporated on a Berkeley rotary evaporator.

2-Bromo-3-[(methoxycarbonyl)methyl]-1,4-naphthoquinone (8). To 200 mL of benzene was added 12.8 g (40.4 mmol) of 2,3-dibromo-1,4-naphthoquinone (**7**),[35] 50 mL of solvent was distilled off, and 11.1 g (126 mmol) of ketene dimethyl acetal[36] was added to the cooled solution. Refluxing for 44 h and evaporating and crystallizing the residue from $MeOH/H_2O$ gave 11.2 g (89.6%) of **8**: mp 127–128 °C; NMR δ 3.80 (s, OCH_3), 4.00 (s, CH_2COOCH_3), 7.8, 8.2 (2 m, 2 H each, ArH). Anal. Calcd for $C_{13}H_9BrO_4$: C, 50.5; H, 2.9. Found: C, 50.4; H, 2.8.

2-[(Methoxycarbonyl)methyl]-3-(1-pyrrolidinyl)-1,4-naphthoquinone (9). Bromoquinone **8** (1.85 g, 5.99 mmol) was dissolved in a toluene/MeOH mixture (70 mL/40 mL), cooled to −10 to −5 °C, and stirred as sodium bicarbonate (1.5 g, 18 mmol) was added. Over 1 h, 0.5 mL (6 mmol) of pyrrolidine in 10 mL of toluene was added, and this solution was stirred at −12 °C for 18 h at which time 0.5 mL more of pyrrolidine was added. After 50 h the reaction mixture was added to water/benzene, and the organic layer was washed, dried, and evaporated to give 0.94 g of a mixture of **9** and quinone **8**. Chromatography (70 g of silica, CH_2Cl_2 and then 4% acetone in CH_2Cl_2) gave 0.43 g (24%) of **9** on crystallization from methanol: mp 136–139 °C; NMR δ 1.90 (m, NCH_2CH_2), 3.6–4.0 (OCH_3, NCH_2, CH_2COOCH_3), 7.4–8.2 (m, ArH). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7. Found: C, 68.1; H, 5.7; N, 4.7.

From the mother liquors could be isolated 2-(1-pyrrolidinyl)-1,4-naphthoquinone (**10**), identical with the sample prepared below.

2-(1-Pyrrolidinyl)-1,4-naphthoquinone (10).[37] A solution of 1.72 g (10.9 mmol) of 1,4-naphthoquinone in 100 mL of MeOH was stirred under an oxygen atmosphere while 1.2 mL (1.4 mmol) of pyrrolidine was added over 10 min. After 17 h the solution was evaporated, the residue was dissolved in 50 mL of CH_2Cl_2 and washed with 25 mL of 0.5 M HCl, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed, concentrated to 50 mL, filtered through 10 g of Florisil, eluting with 1% acetone in CH_2Cl_2, and evaporated to give 1.28 g (51.9%) of **10**: 1.02 g (41.5%) of **10**, mp 158–160 °C (from MeOH); NMR δ 2.0 (m, NCH_2CH_2), 3.7 (m, NCH_2), 5.73 (s, 3-ArH), 7.5–8.2 (m, ArH). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8; N, 6.2. Found: C, 73.7; H, 6.0; N, 6.0.

2-Bromo-3-(1-pyrrolidinyl)-1,4-naphthoquinone (13). To 2.80 g (8.87 mmol) of dibromoquinone **7**, 60 mL of benzene, and 10 mL of absolute ethanol was added with stirring 1.6 mL (19 mmol) of pyrrolidine in 5 mL of benzene. Stirring of the solution was continued in the dark for 30 min. The reaction mixture was then evaporated, and the residue was recrystallized from 95% ethanol to give 2.47 g (91.0%) of **13**: mp 97–100 °C dec; NMR δ 1.94 (m, NCH_2CH_2), 3.95 (m, NCH_2), 7.4–8.2 (m, ArH). Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.9; H, 3.9; N, 4.6. Found: C, 54.9; H, 3.9; N, 4.6.

2-(1-Pyrrolidinyl)-1,4-naphthohydroquinone Diacetate (14). A mixture of 1.13 g (4.98 mmol) of aminoquinone **10**, 8.0 mL (85 mmol) of acetic anhydride, 2.1 mL (15 mmol) of triethylamine, and 0.68 g (10.4 mmol) of zinc powder was heated to boiling, and the hot solution was filtered. Cooling the solution and adding it to 200 mL of water gave a gummy solid which was dissolved in CH_2Cl_2 and washed, dried, and evaporated to 1.58 g of residue which was recrystallized from ethyl acetate to give 1.17 g (75%) of diacetate **14**: mp 153–154 °C; NMR δ 1.9 (m, NCH_2CH_2), 2.38, 2.41 (2 s, CH_3CO), 3.41 (m, NCH_2), 6.90 (s, 3-ArH), 7.0–7.8 (m, ArH); IR (CH_2Cl_2) 1760 cm^{-1} (C=O). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 68.7; H, 6.1; N, 4.5.

1-Acetoxy-3-(1-pyrrolidinyl)naphthalene (15). Hydrogenation of 1.01 g (4.46 mmol) of aminoquinone **10** in 4.0 mL (42 mmol) of acetic anhydride and 20 mL of glacial acetic acid proceeded over 0.10 g of 10% palladium on carbon at 45 psi of hydrogen for 7 h. After filtration and addition of ether and water, the aqueous layer was separated and extracted twice with ether. The combined ether solution was washed, dried, and evaporated, and the residue was chromatographed on 70 g of silica. Eluting with CH_2Cl_2 gave 1.09 g (95.6%) of pure **15**: mp 73–74 °C (from $MeOH/H_2O$); NMR (CCl_4) δ 1.68 (m, NCH_2CH_2), 2.22 (s, CH_3CO), 3.05 (m, NCH_2), 6.01 (d, J = 2 Hz, 2- or 4-ArH), 6.64 (d, J = 2 Hz, 4- or 2-ArH), 6.9–7.6 (m, ArH); mass spectrum, m/e (relative intensity) 256 (M + 1, 9.2), 255 (M^+, 42.8), 213 (100). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5. Found: C, 75.0; H, 6.7; N, 5.4.

2-[2-(Methoxycarbonyl)-1-pyrrolidinyl]-1,4-naphthoquinone (19). A. From 1,4-Naphthoquinone. To 20.2 g (0.128 mol) of 1,4-naphthoquinone and 300 mL of MeOH was added 22 g (0.17 mol) of proline methyl ester in 100 mL of MeOH, and the resulting red solution was stirred under an oxygen atmosphere for 66 h in the dark. The solution was then evaporated, ethyl acetate and 0.5 M H_2SO_4 were added, the mixture was filtered, the layers were separated, and the organic layer was washed with 0.5 M H_2SO_4, extracting the combined aqueous solution with ethyl

(35) S. M. McElvain and E. L. Engelhardt, *J. Am. Chem. Soc.*, **66**, 1077 (1944). The procedure for the preparation of the monobromoquinone **20** was modified by including an aqueous wash. Thus the reaction mixture was concentrated, aqueous Na_2CO_3 was added, and the mixture was extracted with CH_2Cl_2. Washing with saturated Na_2CO_3, drying, and evaporating followed by subliming once gave a 94% yield of **20** of satisfactory purity (see ref 38).

(36) Several methods exist for the preparations of ketene dimethyl acetal. We found it most convenient to prepare it from bromoacetaldehyde dimethyl acetal and the potassium salt of 3-methyl-3-pentanol in an excess of this alcohol. For related procedures, see: S. M. McElvain and G. R. McKay, Jr., *J. Am. Chem. Soc.*, **77**, 5601 (1955); S. M. McElvain and H. F. McShane, Jr., *ibid.*, **74**, 2662 (1952); E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *ibid.*, **86**, 5570 (1964).

(37) This compound has been reported previously but without experimental or analytical data: M. Akiba, M. Okuyama, Y. Kosugi, and T. Takada, *Heterocycles*, **6**, 1773 (1977); K. Maruyama, T. Kozuka, and N. Otsuki, *Bull. Chem. Soc. Jpn.*, **50**, 2170 (1977).

acetate. The combined organic phase was washed, dried, and concentrated to 250 mL. This warm solution was filtered through a bed of silica (100 g) which was washed with ethyl acetate, the filtrate was evaporated, and the residue was crystallized from MeOH to give 22.6 g (62.1%) of **19**: mp 146–147 °C; NMR δ 2.13 (m, $NCH_2CH_2CH_2$), 3.53 (m, NCH_2), 3.79 (s, OCH_3), 5.00 (br t, NCH), 5.77 (s, 3-ArH), 7.4–8.1 (m, ArH); IR (Nujol) 1740 cm^{-1} (ester C=O); $[\alpha]^{22}_D$ −236° (*c* 0.72, MeOH); UV λ_{max} 236 nm (ε 17 200), 243 (15 200), 268 (22 600), 274 (25 600), 299 (8060), 327 (3000). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3; N, 4.9. Found: C, 67.4; H, 5.4; N, 4.9.

B. From 2-Bromo-1,4-naphthoquinone. 2-Bromo-1,4-naphthoquinone (**20**; 28.0 g, 118 mmol)[35] was dissolved in 300 mL of benzene, 39.6 g (307 mmol) of proline methyl ester in 50 mL of benzene was added, and the mixture was stirred for 20 h. After the addition of 150 mL of ethyl acetate and 125 mL of 1 M HCl, the mixture was filtered, the layers were separated, and the organic layer was washed, dried, and evaporated to give 22.8 g (67.9%) of aminoquinone **19**[38] from MeOH.

2-Bromo-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]-1,4-naphthoquinone (21). Proline methyl ester (0.48 g, 3.7 mmol) was dissolved in 10 mL of benzene and then added in the dark to 0.505 g (1.60 mmol) of 2,3-dibromo-1,4-naphthoquinone (**7**) in benzene/methanol (15 mL/5 mL) over about 5 min. After 3 days in the dark, another 0.14 g (1.1 mmol) of proline methyl ester was added. After 1 more day, the mixture was evaporated, the residue was dissolved in ether, the ether was washed, dried, and evaporated, and the residue was chromatographed (70 g of silica, CH_2Cl_2) in the dark; 0.52 g (89.1%) of **21** resulted: mp 88–92 °C (from EtOAc/hexane); NMR δ 2.0 (m, $NCH_2CH_2CH_2$), 3.77 (s, OCH_3), 4.0 (m, NCH_2), 5.30 (br t, NCH), 7.5–8.2 (m, ArH); UV λ_{max} 478 nm (ε 4750), 283 (22 400), 236 (14 700). Anal. Calcd for $C_{16}H_{14}BrNO_4$: C, 52.8; H, 3.9; N, 3.8. Found: C, 52.6; H, 4.0; N, 3.7.

10-(Allyloxy)-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]-naphtho[1,2-*e*][1,4]oxazin-4-one (24). A mixture of 9.0 g (31.6 mmol) of aminoquinone **19** in 380 mL of 3-pentanone and 100 mL of a 1 M aqueous solution of $Na_2S_2O_4$ (pH adjusted to 7.0 with 2 M NaOH) was vigorously stirred for 90 min, the aqueous layer was removed by pipet, and 100 mg of solid $Na_2S_2O_4$ was added. The solution was refluxed for 90 min through a Soxhlet cup containing 4A sieves to remove the remaining water, 8.75 g (63.4 mmol) of powdered, anhydrous K_2CO_3 was added, and the solution was then refluxed for 1 h to remove methanol. After the oil-bath temperature was lowered to 65 °C, 4.2 mL (49 mmol) of allyl bromide was added, and the mixture was stirred for 16 h at 65 °C. After the mixture was cooled, filtered, and evaporated, a residue was obtained to which was added 100 mL of cold hexane, and the mixture was stirred in a dry ice/acetone bath for 15 min. Filtration gave 8.71 g (94%) of the lactone allyl ether **24**: mp 128–133 °C dec (from hexane/EtOAc); NMR δ 2.1 (m, $NCH_2CH_2CH_2$), 2.9–4.0 (m, $CHNCH_2$), 4.56 (d, OCH_2), 5.4 (m, $CH{=}CH_2$), 6.0 (m, $CH{=}CH_2$), 6.18 (s, 1 H, β-ArH), 7.4, 8.0 (2 m, 2 H each, ArH); UV λ_{max} 254 nm (ε 46 300), 315 (8250), 354 (3300); mass spectrum, *m/e* (relative intensity) 296 (M + 1, 4.7), 295 (M^+, 26), 267 (19), 227 (18), 226 (100). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.0; H, 5.9; N, 4.8.

10-Acetoxy-11-allyl-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]naphtho[1,2-*e*][1,4]oxazin-4-one (25). A mixture of 19.6 g (66.5 mmol) of lactone allyl ether **24**, 450 mL of acetic anhydride, and 8.2 g (100 mmol) of anhydrous sodium acetate was refluxed for 8.5 h with stirring under an argon atmosphere. The solution was concentrated to 150 mL and then slowly added to 600 mL of cold saturated Na_2CO_3 and 200 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 100 mL). The combined organic phase was washed, dried, concentrated to 150 mL, and filtered with EtOAc through a 60-g bed of Florisil. The filtrate was evaporated and the residue crystallized from EtOAc to give, in several crops, 15.8 g (71%) of the lactone acetate **25**: mp 177–179 °C (from hexane/ethyl acetate); NMR δ 1.8–4.0 (several m, $CH_2NCHCH_2CH_2$, $CH_2CH{=}CH_2$), 2.45 (s, $COCH_3$), 5.1 (2 m, $CH{=}CH_2$), 6.0 (m, $CH{=}CH_2$), 7.5, 8.2 (2 m, 3 H, 1 H, ArH); IR (Nujol) 1760, 1630, 1590 cm^{-1}; UV λ_{max} 240 nm (ε 31 200), 255 (21 100), 297 (7300), 330 (2500); $[\alpha]^{21}_D$ −202° (*c* 0.51, EtOAc). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.7; N, 4.1. Found: C, 71.2; H, 5.7; N, 4.0.

10-Acetoxy-11-(formylmethyl)-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]naphtho[1,2-*e*][1,4]oxazin-4-one (27). To a solution of allyl lactone acetate **25** (1.01 g, 3 mmol) in 50 mL of EtOAc under argon was added 80 mg (0.31 mmol) of OsO_4 in 30 mL of water. After the mixture was vigorously stirred for 5 min, 1.68 g (7.85 mmol) of sodium metaperiodate was added over 90 min in six portions. After 15 h the mixture was separated and the aqueous layer extracted with EtOAc. The combined solution was washed, dried, and evaporated to an oil which was chromatographed (100 g of silica; 3/2, hexane/EtOAc) to give 0.715 g (70.7%) of product **27**: mp 185–187 °C (from EtOAc/hexane); NMR (CCl_4) δ 2.0 (m, $NCH_2CH_2CH_2$), 2.38 (s, CH_3CO), 2.2–3.9 (m's, $CHNCH_2$), 3.49 (d, J = 2 Hz, CH_2CHO), 7.4, 8.1 (2 m, 3 H, 1 H, ArH), 9.76 (d, J = 2 Hz, CHO). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.2; H, 5.1; N, 4.1. Found: C, 67.0; H, 5.2; N, 4.1.

10-Acetoxy-11-(aldoximinomethyl)-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]naphtho[1,2-*e*][1,4]oxazin-4-one (28). Lactone aldehyde **27** (0.587 g, 1.73 mmol) in 30 mL of CH_2Cl_2, under nitrogen, 1.21 g (17.4 mmol) of hydroxylamine hydrochloride, and 1.91 g (23.3 mmol) of sodium acetate in 20 mL of water were stirred for 2 h, the layers were separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phase was washed and dried. This solution was filtered through a bed of Florisil (with CH_2Cl_2) and evaporated to give 0.637 g (104%) of oxime **28**: mp 187–190 °C dec (from CH_2Cl_2); NMR ($CDCl_3$–Me_2SO-d_6) δ 2.0 (m, $NCH_2CH_2CH_2$), 2.40 (s, CH_3CO), 2.6–4.1 (m's, $CHNCH_2$, CH_2CHNOH), 6.58 (t, J = 5 Hz, CHNOH), 7.5, 8.1 (2 m, 3 H, 1 H, ArH), 10.27 (s, CHNOH). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.4; H, 5.1; N, 7.9. Found: C, 64.3; H, 5.2; N, 7.8.

10-Acetoxy-11-(cyanomethyl)-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]naphtho[1,2-*e*][1,4]oxazin-4-one (30). The crude lactone oxime **28** (0.30 g, 0.85 mmol) was dissolved in 50 mL of CH_2Cl_2 and 0.31 g (1.9 mmol) of 1,1′-carbonyldiimidazole added under nitrogen. After 1 h the solution was washed with 3 M HCl and saturated NaCl. Drying and evaporating gave 0.31 g of residue which was chromatographed (30 g of silica; 3/2, hexane/EtOAc) to give 0.170 g (60%) of **30**: mp 161–163 °C dec (from EtOAc/hexane); NMR δ 2.1 (m, $NCH_2CH_2CH_2$), 2.53 (s, CH_3CO), 2.6–4.0 (m's, $CHNCH_2$), 3.78 (s, CH_2CN), 7.5, 8.1 (2 m, 3 H, 1 H, ArH); IR (KBr) 2280 (C≡N), 1740 cm^{-1} (C=O). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.9; H, 4.8; N, 8.3. Found: C, 67.9; H, 4.9; N, 8.1.

10-Acetoxy-11-(*O*-methylaldoximinomethyl)-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*]naphtho[1,2-*e*][1,4]oxazin-4-one (29). Aldehyde **27** (0.834 g, 2.46 mmol) in 25 mL of CH_2Cl_2 was added to 1.02 g (12.2 mmol) of methoxylamine hydrochloride and 1.42 g (17.3 mmol) of sodium acetate in 25 mL of water. After 3.25 h, the mixture was separated and the aqueous layer extracted three times with CH_2Cl_2. The combined organic extracts were washed, dried, and evaporated. The resulting oil was chromatographed on 50 g of silica (1/1, EtOAc/hexane) to give 0.75 g (83%) of an oil which slowly crystallized: mp 145–147 °C dec (from EtOAc/hexane); NMR δ 1.9 (m, $NCH_2CH_2CH_2$), 2.40 (s, CH_3CO), 2.5–4.0 (m's, CH_2NCH, $ArCH_2$), 3.78 (s, OCH_3), 6.53 (t, J = 4.5 Hz, cis CH=N), 7.3, 7.9 (2 m, trans CH=N, ArH). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.2; H, 5.5; N, 7.6. Found: C, 65.2; H, 5.5; N, 7.6.

2-Allyl-1,4-dimethoxy-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]naphthalene (26). To the lactone acetate **25** (7.70 g, 23.0 mmol) in 180 mL of dimethylacetamide under argon were added 12.8 mL (206 mmol) of methyl iodide and 28.7 g (91.1 mmol) of $Ba(OH)_2{\cdot}8H_2O$. The mixture was stirred for 45 h, filtered, and evaporated, and the residue was added to 400 mL of water and extracted with EtOAc (4 × 100 mL). The combined organic

(38) High-pressure LC analysis of the reaction mixture before recrystallization showed the presence of 14% of **21** and 86% of **19**. GC analysis of the starting quinone **20** revealed the following composition: 2% naphthoquinone, 7% dibromoquinone **7**, 91% monobromoquinone **20**. The dibromoquinone **7** contaminating **20** could maximally account for 7% of the 14% of **21** observed. These data indicate that 2-bromo-1,4-naphthoquinone (**20**) and proline methyl ester reacted by the addition–elimination and addition–oxidation mechanisms in a ratio of about 12:1.

solution was washed, dried, and evaporated to give 9.34 g of an oil which was chromatographed on 200 g of silica with CH_2Cl_2 to yield 7.55 g (93%) of the ester **26**: NMR δ 2.1 (m, $NCH_2CH_2CH_2$), 3.50 (s, $COOCH_3$), 3.5–3.9 (m's, NCH_2, $CH_2CH{=}CH_2$), 3.90 (s, $Ar(OCH_3)_2$), 4.55 (m, NCH), 5.0 (2 m, $CH{=}CH_2$), 6.0 (m, $CH{=}CH_2$), 7.35, 7.95 (2 m, 2 H each, ArH). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.1; N, 3.9. Found: C, 70.9; H, 7.1; N, 3.9.

1,4-Dimethoxy-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]-2-naphthylacetaldehyde (31). To educt **26** (7.55 g, 21.27 mmol) in 340 mL of EtOAc were added 16 mL (0.63 mmol) of 1.0% aqueous OsO_4 and 340 mL of a lithium periodate/lithium phosphate buffer, prepared by dissolving 15.5 g (68.0 mmol) of periodic acid (99.5%) in 340 mL of pH 7.0 lithium phosphate buffer (0.2 M from phosphoric acid and lithium hydroxide) and then adjusting the pH to 6.5 with solid $LiOH{\cdot}H_2O$. The reaction mixture was stirred for 24 h, the layers were separated, the aqueous layer was extracted three times with EtOAc, and the combined organic solution was washed, dried, and evaporated to a residue which was chromatographed on 300 g of silica (3/2, hexane/EtOAc) to give 5.47 g (72.1%) of pure aldehyde **31**. When recrystallized from EtOAc/hexane, 4.63 g (61.0%) of **31** was obtained: mp 91–92.5 °C; NMR δ 2.0 (m, $NCH_2CH_2CH_2$), 3.1 (m, NCH_2), 3.53 (s, $COOCH_3$), 3.83, 3.88 (2 s, $Ar(OCH_3)_2$), 4.02 (d, J = 2 Hz, CH_2CHO), 7.4, 8.0 (2 m, 2 H each, ArH), 9.70 (t, J = 2 Hz, CHO); IR (Nujol) 1730 (ester C=O), 1700 cm^{-1} (aldehyde C=O); UV λ_{max} 327 nm (sh, ϵ 1380), 296 (6080), 263 (13 300). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.2; H, 6.5; N, 3.9. Found: C, 67.3; H, 6.5; N, 3.9.

1,4-Dimethoxy-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]-2-naphthylacetonitrile (33). To a solution of 2.37 g (34.1 mmol) of hydroxylamine hydrochloride and 3.56 g (43.4 mmol) of sodium acetate in 30 mL of water was added aldehyde **31** (1.12 g, 3.13 mmol, in 30 mL of CH_2Cl_2). After 2 h of vigorous stirring, the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic solution was washed and dried, 0.96 g (5.9 mmol) of 1,1'-carbonyldiimidazole was added, and the solution was stirred under nitrogen for 90 min. The reaction mixture was washed three times with 3 M HCl, the aqueous solutions were combined and back-extracted with CH_2Cl_2 (three times), and the combined organic solution was washed, dried, and evaporated to give 0.84 g (76%) of nitrile **33** after crystallization from EtOAc/hexane: mp 143–144 °C; NMR δ 2.1 (m, $NCH_2CH_2CH_2$), 3.3 (m, NCH_2), 3.53 (s, $COOCH_3$), 3.92, 4.02 (s, $Ar(OCH_3)_2$), 3.94, 4.50 (2 d, 1 H each, J = 16 Hz, CH_2CN), 4.6 (m, NCH), 7.4, 7.9 (2 m, 2 H each, ArH); IR (Nujol) 2270 (weak, C≡N), 1730 cm^{-1} (C=O). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.8; H, 6.3; N, 7.9.

1,4-Dimethoxy-3-(2-carboxy-1-pyrrolidinyl)-2-naphthylacetonitrile (34). The ester **33** (0.39 g, 1.1 mmol), dissolved in 15 mL of 95% EtOH, was mixed with a solution of KOH (85%, 0.11 g, 1.7 mmol) in 15 mL of water. After 20 min of reflux under nitrogen, the solution was concentrated to an oil, 30 mL of 1 M NaOH was added, and the solution was extracted twice with $CHCl_3$. The pH of the aqueous solution was then taken to 2 with 3 M HCl, and it was extracted with EtOAc (six times). The combined organic solution was dried and evaporated, the residue was filtered through a bed of Florisil with EtOAc, and evaporation gave 0.29 g (77.0%) of **34**: mp 165–175 °C dec (from EtOAc/hexane); NMR δ 2.0 (m, $NCH_2CH_2CH_2$), 3.90, 4.00 (2 s, $Ar(OCH_3)_2$), 4.12 (s, CH_2CN), 4.55 (m, NCH), 7.4, 7.9 (2 m, 2 H each, ArH), 10.8 (br s, COOH); IR (CH_2Cl_2) 2280 (weak, C≡N), 1700 (C=O); mass spectrum, m/e (relative intensity) 341 (M + 1, 2.7), 340 (M^+, 12.8), 296 (12.8), 295 (58.8), 265 (19.4), 70 (16.0), 45 (23.1), 43 (100), 41 (14.9).

1,4-Dimethoxy-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]-2-naphthylacetaldehyde Dimethyl Acetal (38). To 0.30 g (0.84 mmol) of aldehyde **31** were added 20 mL of MeOH, 0.14 mL (1.3 mmol) of trimethyl orthoformate, and 34 mg (0.18 mmol) of *p*-toluenesulfonic acid monohydrate. This mixture was stirred at room temperature for 4 h under nitrogen, poured into saturated Na_2CO_3, and extracted four times with EtOAc. The combined organic solution was dried and evaporated, and the residue was chromatographed (50 g of silica, 1% acetone in CH_2Cl_2) to give 0.251 g (74%) of **38**: NMR δ 2.2 (m, $NCH_2CH_2CH_2$), 3.27, 3.35 (2 s, $CH(OCH_3)_2$), 3.53 (s, $COOCH_3$), 3.90 (s, $Ar(OCH_3)_2$), 4.53 (m, NCH), 4.90 (dd, J = 5 Hz, J' = 6 Hz, $CH_2CH(OCH_3)_2$), 7.3, 7.9 (2 m, 2 H each, ArH); IR (neat) 1740 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.4; H, 7.2; N, 3.5.

1,4-Dimethoxy-3-(2-carboxy-1-pyrrolidinyl)-2-naphthylacetaldehyde Dimethyl Acetal (39). Aldehyde **31** (3.89 g, 10.9 mmol) was treated with trimethyl orthoformate as above. The crude reaction mixture was evaporated to 60 mL, a solution of KOH (85%, 3.51 g, 53 mmol) in 35 mL of water was added, and the mixture was refluxed for 30 min under nitrogen. Evaporation and then dissolution in 50 mL of 1 M NaOH was followed by extraction with Et_2O. The aqueous solution was diluted with 100 mL of pH 7 buffer (29.6 mL of 1.0 M NaOH plus 50 mL of 1.0 M KH_2PO_4 diluted to 100 mL) and the pH adjusted to 7–8 with 3 M HCl. This solution was saturated with NaCl and extracted with EtOAc (4 × 40 mL), and the combined organic solution was dried and evaporated. The residue was chromatographed on 120 g of silica (2/1, hexane/EtOAc) to give 4.10 g (97%) of **39** as an oil. This product should be stored at 0 °C and used within a day or two. Longer storage produces contaminants of the corresponding esters **31** and **38** and acid **37**. A small sample was filtered through Florisil with CH_2Cl_2 and then evaporated to an oil: NMR δ 2.2 (m, $NCH_2CH_2CH_2$), 3.15 (d, J = 6 Hz, $ArCH_2CH(OCH_3)_2$), 3.33, 3.35 (2 s, $CH(OCH_3)_2$), 3.90, 3.95 (2 s, $Ar(OCH_3)_2$), 4.7 (m, NCH), 4.82 (t, J = 6 Hz, $CH_2CH(OCH_3)_2$), 7.4, 7.9 (2 m, 2 H each, ArH), 10.4 (br s, COOH); IR (neat) 1750 cm^{-1} (C=O). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.8; H, 7.0; N, 3.4. Found: C, 64.8; H, 7.1; N, 3.4.

5,10-Dimethoxy-2,3,11,11a-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-11-carboxaldehyde Dimethyl Acetal (40). To 1.82 g (4.67 mmol) of amino acid **39** was added 7.4 mL (80 mmol) of $POCl_3$, and the mixture was heated at 98–100 °C while being swirled for a total of 5 min. The flask was then cooled in an ice–water bath, and 4.2 mL of water was added dropwise over 10 min followed by 40 mL of MeOH over 15 min. The bath was removed after 45 min, and the mixture was stirred for 16 h at room temperature and then slowly added to 400 mL of half-saturated Na_2CO_3 at 10–15 °C with vigorous stirring. This mixture was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic phase was washed, dried, evaporated to 50 mL, and filtered through 30 g of Florisil with CH_2Cl_2. After solvent removal, the residue was chromatographed on 175 g of silica (2/1, hexane/EtOAc) to give 0.91 g (57%) of acetal **40** as an oil which crystallized slowly upon seeding and was normally used directly in the next step: mp 105–106 °C (from hexane); ^1H NMR δ 1.4, 1.9 (2 m, 1 H, 3 H, $NCH_2CH_2CH_2$), 3.22, 3.47 (2 s, $CH(OCH_3)_2$), 3.73 (t, J = 3 Hz, $CHCH(OCH_3)_2$), 3.87, 3.93 (2 s, $ArOCH_3$), 4.13 (m, NCH), 4.76 (d, J = 3 Hz, $CH(OCH_3)_2$), 7.3, 7.9 (2 m, 2 H each, ArH); IR (neat) 1610 cm^{-1}; UV (unstable, absorptions decrease with time) λ_{max} 347 nm (ϵ 2200), 304 (5900), 294 (6100), 266 (6300); ^{13}C NMR δ 148.70, 144.42, 135.34, 130.83, 125.74, 122.30, 121.80, 120.43, 106.03, 66.32, 61.12, 58.98, 57.24, 55.44, 51.95, 50.01, 32.33, 26.36 ppm. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.9; H, 7.3; N, 4.1. Found: C, 69.9; H, 7.3; N, 4.0.

5,10-Dimethoxy-1,2-dihydro-3*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-11-carboxaldehyde (47). To acetal **40** (0.542 g, 1.58 mmol) in 15 mL of CH_2Cl_2 and 5 mL of acetone was added 0.438 g (1.93 mmol) of DDQ in 30 mL of CH_2Cl_2 over 30 min. After being stirred another 30 min, the solution was filtered through 50 g of alumina (activity II, neutral) with CH_2Cl_2 and then 2% acetone in CH_2Cl_2. The eluate was evaporated, and the residue was washed with cold hexane to yield the desired indole aldehyde **47**: 0.297 g (64%); mp 220–225 °C dec (from EtOAc/hexane); NMR (Me_2SO-d_6) δ 2.4–3.3 (m's, $NCH_2CH_2CH_2$), 4.04, 4.11 (2 s, $Ar(OCH_3)_2$), 4.51 (t, J = 7 Hz, NCH_2), 7.4, 8.1 (2 m, 2 H each, ArH), 10.5 (s, CHO); IR (KBr) 1620 cm^{-1} (C=O); UV λ_{max} 386 nm (sh, ϵ 10 400), 374 (11 800), 342 (6690), 327 (5500), 311 (8190), 254 (71 200). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.2; H, 5.9; N, 4.6.

2,3-Dihydro-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-5,10-dione-11-carboxaldehyde (48). To aldehyde **47** (0.561 g, 1.90 mmol) in 50 mL of acetonitrile under a nitrogen atmosphere was added with stirring 3.16 g (5.72 mmol) of ceric ammonium nitrate in 30 mL of water over 15 min, followed by stirring for an additional 30 min. The reaction mixture was diluted with 50 mL of water and extracted with EtOAc (100 mL and then 2 × 25 mL), and

the organic solutions were combined, washed, and dried. Evaporation yielded a yellow solid which was dissolved in a small amount of CH_2Cl_2 and filtered through 30 g of Florisil (EtOAc eluent). Evaporation gave quinone **48**: 0.482 g (96%); mp 212–217 °C (from EtOAc/CH_2Cl_2); NMR δ 2.59 (m, $NCH_2CH_2CH_2$), 3.03 (m, $NCH_2CH_2CH_2$), 4.22 (t, J = 7 Hz, NCH_2), 7.6, 7.9 (2 m, 2 H each, ArH), 10.2 (s, CHO); IR (CH_2Cl_2) 1650 cm^{-1} (C=O); UV λ_{max} 399 nm (ϵ 3130), 324 (7520), 282 (sh, 14500), 252 (38700). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.4; H, 4.2; N, 5.3. Found: C, 72.4; H, 4.4; N, 5.2.

2,3-Dihydro-11-(hydroxymethyl)-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-5,10-dione (44). Aldehyde **48** (0.678 g, 2.56 mmol) and 250 mL of methanol were boiled briefly and under an argon atmosphere, with stirring (internal temperature of 45 °C), 1.91 g (50.5 mmol) of $NaBH_4$ was added cautiously, and then the mixture was stirred without external heating for 40 min. Acetone (10 mL) was added, followed by 50 mL of 0.5 M $FeCl_3$ in 0.1 M HCl. Fifteen minutes later, the mixture was diluted with 200 mL of water and extracted with CH_2Cl_2 (100 mL and then 3 × 60 mL). The combined organic phase was washed, dried, and evaporated to a residue which was recrystallized from EtOAc/CH_2Cl_2 to give the alcohol **44**: 0.41 g (59.3%); mp 198–202 °C; NMR δ 2.7 (m, $NCH_2CH_2CH_2$), 4.30 (t, J = 7 Hz, NCH_2), 4.6 (br s, CH_2OH), 7.7, 8.1 (2 m, 2 H each, ArH); IR (KBr) 3710 (OH), 1610 cm^{-1} (C=O); UV λ_{max} 419 nm (ϵ 3620), 335 (5540), 266 (sh, 29400), 262 (29900). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N, 5.2. Found: C, 71.8; H, 4.9; N, 5.2.

The mother liquor from the above crystallization was chromatographed on 15 g of silica (CH_2Cl_2 eluent) to give 0.050 g (7.8%) of **2,3-dihydro-11-methyl-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-5,10-dione (49)**: mp 193–195 °C (from EtOAc/hexane); NMR δ 2.18 (s, $ArCH_3$), 2.6 (m, $NCH_2CH_2CH_2$), 4.17 (t, J = 7 Hz, NCH_2), 7.6, 8.0 (2 m, 2 H each, ArH); IR (KBr) 1640 cm^{-1} (C=O). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.4; H, 5.3; N, 5.6.

2,3-Dihydro-11-(hydroxymethyl)-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-5,10-dione Phenyl Carbonate (50). Alcohol **44** (0.406 g, 1.52 mmol) was dissolved in 20 mL of dry pyridine under nitrogen, and to the cold solution was added 0.80 g (5.1 mmol) of phenyl chloroformate in 5 mL of CH_2Cl_2 over 5 min. After 30 min, the mixture was allowed to come to room temperature, stirred overnight, added to 150 mL of cold 3 M HCl, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed with 3 M HCl (1 × 40 mL) and saturated $NaHCO_3$ (1 × 50 mL). After the solution was dried and concentrated, the residue was filtered through 20 g of silica with CH_2Cl_2 until the yellow color just began to elute. Elution with 5% acetone in CH_2Cl_2 then gave the product fraction which was evaporated, and the resulting solid was recrystallized from EtOAc/hexane to give 0.57 g of phenyl carbonate **50**: 96.1%; mp 180–183 °C; NMR δ 2.55 (pentet, J = 7 Hz, $NCH_2CH_2CH_2$), 2.93 (t, J = 7 Hz, $NCH_2CH_2CH_2$), 4.27 (t, J = 7 Hz, NCH_2), 5.43 (s, CH_2O), 7.2 (m, OPhH), 7.6, 8.0 (2 m, 2 H each, ArH); IR (KBr) 1750 (carbonate C=O), 1640 cm^{-1} (quinone C=O); UV λ_{max} 409 nm (ϵ 3230), 330 (5480), 280 (sh, 15700), 267 (27200), 259 (30600), 244 (sh, 18500). Anal. Calcd for $C_{23}H_{17}NO_5$: C, 71.3; H, 4.4; N, 3.6. Found: C, 71.3; H, 4.5; N, 3.6.

2,3-Dihydro-11-(hydroxymethyl)-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole-5,10-dione Carbamate (3). The phenyl carbonate **50** (0.304 g, 0.786 mmol), dissolved in 40 mL of dry CH_2Cl_2 and cooled in a dry ice/acetone bath, was stirred under a nitrogen atmosphere while ammonia was bubbled into the solution for 30 min. The bath was removed, and after 3 h, the solution was placed in a 30 °C water bath for 30 min. The precipitate was removed and recrystallized (EtOAc/EtOH) to give 0.17 g (71%) of the carbamate **3**: mp 254–258 °C; NMR (Me_2SO-d_6) δ 2.5 (m, $NCH_2CH_2CH_2$), 2.87 (t, J = 7 Hz, $NCH_2CH_2CH_2$), 4.22 (t, J = 7 Hz, NCH_2), 5.10 (s, CH_2O), 6.50 (br s, NH_2), 7.7, 8.0 (2 m, 2 H each, ArH); IR (KBr) 3550 (NH), 1710 (carbamate C=O), 1640 cm^{-1} (quinone C=O); UV (CH_3CN) λ_{max} 412 nm (ϵ 3720), 330 (5740), 279 (sh, 19100), 261 (31600), 241 (sh, 17600). Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.8; H, 4.6; N, 9.0. Found: C, 66.0; H, 4.8; N, 8.8.

Ethyl 2-pyrroleacetate and 3-pyrroleacetate were prepared as directed.[8] The product, after distillation at 0.5 mm removed excess pyrrole, was fractionated at 16 mm, and the following fractions were collected: A, 125–129.5 °C, 55.0 g, 98.4% 2-isomer, 1.6% 3-isomer; B, 129.5–136 °C, 11.0 g, 92.1% 2-isomer, 7.9% 3-isomer; C, 136 °C, 3.12 g, 83.8% 2-isomer, 16.2% 3-isomer; D, 131 °C (9 mm), 4.33 g, 15.7% 2-isomer, 84.3% 3-isomer; E, 100 °C (1 mm), 0.665 g, 3.4% 2-isomer, 96.6% 3-isomer. Assuming equal response factors, the total weights and percentages are as follows: 2-isomer, 68.0 g (91.3%); 3-isomer, 6.54 g (8.7%). Redistillation of fraction A at 155–158 °C (50 mm) gave 99% 2-isomer: NMR δ 1.20 (t, J = 7 Hz, CH_2CH_3), 3.57 (s, CH_2CO), 4.10 (q, J = 7 Hz, CH_2CH_3), 6.04 (m, 2 H, 3- and 4-H), 6.58 (m, 1 H, 5-H), 8.8 (br s, 1 H, NH). 3-Isomer: δ 1.25 (t, J = 7 Hz, CH_2CH_3), 3.51 (s, CH_2CO), 4.18 (q, J = 7 Hz, CH_2CH_3), 6.18 (m, 1 H, 4-H), 6.68 (m, 2 H, 2- and 5-H), 8.6 (br s, 1 H, NH).

2-[2-[(Ethoxycarbonyl)methyl]-1-pyrrolidinyl]-1,4-naphthoquinone (51). To 20.0 g (0.127 mol) of 1,4-naphthoquinone in 350 mL of 95% ethanol were added 43.6 g (0.201 mol) of homoproline ethyl ester acetate [distilled at 88–90 °C (2 mm)][8] and 150 mL of 95% ethanol. This mixture was stirred at room temperature under an oxygen atmosphere for 48 h after which it was evaporated. The resulting oil was dissolved in EtOAc and washed with half-saturated Na_2CO_3 (six times), the aqueous washes were combined and back-extracted with EtOAc (twice), the combined organic solution was washed with 3 M HCl (six times), and again the combined aqueous solutions were back-extracted twice. The total EtOAc solution was washed, dried, concentrated to 400 mL, and filtered through a bed of Florisil. Evaporation gave 35.7 g (90%) of solid which was recrystallized twice from hexane/EtOAc to give 25.5 g (64%) of pure **51**: mp 91–93 °C; NMR δ 1.31 (t, J = 7 Hz, CH_2CH_3), 1.8–3.1 (m's, $NCH(CH_2COOEt)CH_2CH_2$), 3.58 (br m, NCH_2), 4.17 (q, J = 7 Hz, CH_2CH_3), 4.78 (br m, NCH), 5.72 (s, 3-ArH), 7.4–8.1 (m, ArH). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5. Found: C, 68.9; H, 6.2; N, 4.4.

1,4-Dimethoxy-2-[2-[(ethoxycarbonyl)methyl]-1-pyrrolidinyl]naphthalene (52). Hydrogen was bubbled through a solution of 5.43 g (17.3 mmol) of aminoquinone **51** in 170 mL of DMF to which was added 0.27 g of 10% Pd/C until the solution was colorless (2–3 h). Then 16.0 g (50.9 mmol) of $Ba(OH)_2 \cdot 8H_2O$ and 8.0 mL (85 mmol) of dimethyl sulfate were added and slow hydrogen bubbling was continued. After 24 h, 2 mL (21 mmol) of dimethyl sulfate was added, and after another 24 h, the solution was filtered and evaporated. Water was added to the residue, the mixture was extracted with EtOAc, and the EtOAc solution was washed and dried. Evaporation and chromatography of the residue on 170 g of silica (CH_2Cl_2) gave, after evaporation, 4.31 g (72.4%) of **52**: NMR δ 1.17 (t, J = 7 Hz, CH_2CH_3), 1.6–3.4 (m's, $NCH_2CH_2CH_2$, CH_2COOEt), 3.70 (s, 1-OCH_3), 3.93 (s, 4-OCH_3), 4.03 (q, J = 7 Hz, CH_2CH_3), 4.30 (m, NCH), 6.51 (s, 3-ArH), 7.3, 8.0 (2 m, 2 H each, ArH). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.9; H, 7.3; N, 4.1. Found: C, 69.8; H, 7.3; N, 4.0.

1,4-Dimethoxy-2-[2-(carboxymethyl)-1-pyrrolidinyl]naphthalene (53). To ethyl ester **52** (7.76 g, 22.6 mmol) dissolved in 100 mL of 95% ethanol was added KOH (85%, 3.8 g, 58 mmol, in 10 mL of water). This mixture was refluxed for 15 min and evaporated, water was added, and the solution was extracted twice with $CHCl_3$ after which the aqueous layer was acidified to pH 1–2. This acidic solution was extracted with CH_2Cl_2 (five times), and then the combined organic layers were dried, filtered, and evaporated to a residue which was chromatographed on 200 g of silica (1% MeOH and 1% AcOH in EtOAc as eluent) to give 6.30 g (88.5%) of **53** as an oil which was normally used directly in the cyclization step but crystallized slowly on storage at 0 °C. Recrystallization from EtOAc/hexane gave pure **53**: mp 122–125 °C; NMR δ 1.7–3.4 (m's, $NCH_2CH_2CH_2$, CH_2COOH), 3.75 (s, 1-OCH_3), 3.93 (s, 4-OCH_3), 4.20 (m, NCH), 6.57 (s, 3-ArH), 7.3, 8.0 (2 m, 2 H each, ArH), 11.6 (br s, COOH). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.7; N, 4.4. Found: C, 68.5; H, 6.6; N, 4.3.

6,11-Dimethoxy-2,3,3a,4-tetrahydrobenzo[*g*]pyrrolo[1,2-*a*]quinolin-5(1*H*)-one (54), 6-Hydroxy-11-methoxy-2,3,3a,4-tetrahydrobenzo[*g*]pyrrolo[1,2-*a*]quinolin-5(1*H*)-one (55), and 6-Methoxy-2,3,12,12a-tetrahydrobenzo[*f*]pyrrolo[1,2-*a*]quinolin-11(1*H*)-one (62). To 2.62 g (8.32 mmol) of acid **53** was added 26 g of a solution of 10% P_2O_5 in methanesulfonic acid. The mixture was swirled under nitrogen until homogeneous, left at room temperature for 40 h, poured into ice and aqueous

Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed, dried, and evaporated, and the entire residue of 2.56 g was chromatographed on 150 g of silica (CH_2Cl_2 and then 2% acetone in CH_2Cl_2) to give first the demethylated product **55** (recrystallized from hexane/EtOAc; 0.63 g, 27%) and then a mixture of **54** and **62** (0.78 g). This mixture was chromatographed on 70 g of silica (EtOAc/hexane, 2/3) to give the methyl ether **54** (0.61 g, 25%) and the side product **62** (0.15 g, 7%).

Phenol **55** was recrystallized from hexane/EtOAc: mp 132–133 °C; NMR δ 1.9 (m, $NCH_2CH_2CH_2$), 2.50, 2.65 (d, J = 3 Hz, and s, CH_2CO), 3.67 (s, OCH_3), 3.7 (m, CH_2NCH), 6.9–8.2 (m, ArH), 14.0 (s, OH); UV λ_{max} 450 nm (ϵ 2950), 325 (sh, 10500), 297 (35000), 249 (35900); IR (KBr) 1620, 1600 cm^{-1}. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1; N, 4.9. Found: C, 72.2; H, 6.1; N, 4.9.

Methyl ether **54** was recrystallized from hexane/EtOAc: mp 100–102 °C; NMR δ 2.0 (m, $NCH_2CH_2CH_2$), 2.5 (m's, CH_2CO), 3.75, 4.02 (2 s, OCH_3), 3.7 (m, $CHNCH_2$), 7.0–8.2 (m, ArH); UV λ_{max} 459 nm (ϵ 2000), 314 (sh, 8640), 282 (30800), 243 (27300); IR (KBr) 1660 (C=O), 1610, 1570, 1550 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4; N, 4.7. Found: C, 72.8; H, 6.5; N, 4.6.

Side product **62** was recrystallized from EtOAc and then sublimed [160 °C (0.03 mm)]: mp 214–216 °C; NMR δ 1.8 (m, $NCHCH_2CH_2$), 2.42, 2.58 (d, J = 7 Hz, s, CH_2CO), 3.3 (m, CH_2NCH), 3.90 (s, OCH_3), 5.77 (s, 1 H, ArH), 7.0–7.6 (m, 2 H, ArH), 7.97 (dd, J = 8 Hz, J' = 2 Hz, 1 H, ArH), 9.43 (identical with the 7.97 absorption); IR (KBr) 1630 cm^{-1} (C=O); UV λ_{max} 223 nm (ϵ 24700), 257 (sh, 33400), 264 (sh, 42500), 271 (50400), 305 (7700), 318 (8430), 396 (8590), 413 (8700); mass spectrum, found m/e 267.1265 (M^+), $C_{17}H_{17}NO_2$ requires m/e 267.1259. Anal. Calcd for $C_{17}H_{17}NO_2 \cdot {}^1/_2H_2O$: C, 73.9; H, 6.6; N, 5.1. Found: C, 73.7; H, 6.2; N, 5.0.

Methylation of Dihydroquinolone 55. To 1.36 g (4.82 mmol) of dihydroquinolone **55** and 1.46 g (10.6 mmol) of anhydrous, powdered potassium carbonate were added 70 mL of 2-butanone and 0.80 mL (8.5 mmol) of dimethyl sulfate. After 5 mL of solvent was distilled, the mixture was refluxed for 23 h under argon, filtered, and evaporated, and the resulting oil was dissolved in EtOAc. This solution was washed with saturated Na_2CO_3, the aqueous layer was extracted once with EtOAc, and the combined organic phase was washed and dried. Evaporation gave an oil which solidified on standing and was chromatographed on 70 g of silica with CH_2Cl_2 (eluting 0.048 g, 3.5%, of **55**) and then 2% acetone in CH_2Cl_2 (eluting **54**). Recrystallization from hexane (plus a small amount of EtOAc) gave **54** (1.24 g, 87%) identical with the material isolated above.

1-Acetoxy-3-[2-[(ethoxycarbonyl)methyl]-1-pyrrolidinyl]naphthalene (59). In a hydrogenation bottle were placed 0.94 g (3.0 mmol) of aminoquinone **51**, 95 mg of 10% Pd/C, 20 mL of acetic acid, and 3.0 mL of acetic anhydride, and the mixture was hydrogenated at 45 psi of hydrogen for 24 h. The resulting solution was filtered, diluted with EtOAc, and then stirred vigorously with saturated Na_2CO_3 for 15 min. Separation of the organic layer followed by washing, drying, and evaporating gave a residue which was chromatographed on 70 g of silica (CH_2Cl_2); 0.55 g (61%) of **59** was obtained: NMR δ 1.18 (t, J = 7 Hz, CH_2CH_3), 1.8 (m, $NCH_2CH_2CH_2$), 2.31 (s, CH_3CO), 2.1–3.4 (m's, CH_2COOEt, NCH_2), 4.05 (q, J = 7 Hz, CH_2CH_3), 4.2 (br m, NCH), 6.57, 6.67 (2 d, J = 2 Hz, 2- and 4-ArH), 6.9–7.7 (m, ArH). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.4; H, 6.8; N, 4.1. Found: C, 70.3; H, 6.8; N, 4.1.

1-Methoxy-3-[2-[(ethoxycarbonyl)methyl]-1-pyrrolidinyl]naphthalene (60). To 0.580 g (17 mmol) of acetate **59** were added, under nitrogen, 30 mL of DMF, 0.60 mL (6.3 mmol) of dimethyl sulfate, and 1.57 g (4.98 mmol) of $Ba(OH)_2 \cdot 8H_2O$. This mixture was stirred at room temperature for 2.5 h, evaporated, and diluted with water. After the pH was adjusted to 2–3 with concentrated HCl, the aqueous solution was extracted with EtOAc. The combined organic phase was then washed with half-saturated Na_2CO_3 and saturated NaCl and then dried. Evaporation gave 0.22 g of oil which was filtered through 40 g of silica (CH_2Cl_2) to give 0.17 g (33%) of **60**: NMR δ 1.21 (t, J = 7 Hz, CH_2CH_3), 1.9 (m, $NCH_2CH_2CH_2$), 2.0–3.4 (m's, NCH_2, CH_2COOEt), 3.91 (s, OCH_3), 4.09 (q, J = 7 Hz, CH_2CH_3), 4.2 (br m, NCH), 6.31 (s, 2- and 4-ArH), 6.9–7.6 (m, 5,6,7-ArH), 8.0 (dd, J = 7 Hz (ortho), J = 2 Hz (meta), 8-ArH); mass spectrum, found m/e 313.1674 (M^+), $C_{19}H_{23}NO_3$ requires m/e 313.1672.

1-Methoxy-3-[2-(carboxymethyl)-1-pyrrolidinyl]-naphthalene (61). A solution of 87 mg (1.3 mmol) of 85% KOH in 2 mL of water and 25 mL of 95% ethanol was added to 0.172 g of ester **60**, and the mixture was heated at reflux under nitrogen for 45 min. The solution was evaporated to an oil which was dissolved in water and washed with CH_2Cl_2. The aqueous layer was taken to pH 1.5 and extracted with CH_2Cl_2 (6×), and the CH_2Cl_2 solution was dried and evaporated to yield 0.16 g of **61** (103%). This material was one spot by TLC and was used without further purification.

6-Hydroxy-2,3,3a,4-tetrahydrobenzo[*g*]pyrrolo[1,2-*a*]-quinolin-5(1*H*)-one (63) and 62. The acid **61** (0.16 g, 0.565 mmol) was dissolved in 2 g of a 10% solution of P_2O_5 in methanesulfonic acid and left for 70 h. The reaction mixture was slowly added to ice-cold saturated Na_2CO_3 and extracted with CH_2Cl_2 (5×), and the combined organic phase was washed, dried, and evaporated. Chromatography on a 60-g silica column with CH_2Cl_2 yielded the phenol **63** (0.098 g, 69%). Elution with 2% acetone in CH_2Cl_2 gave the expected product **62** (0.028 g, 19%) identical with material isolated from the previous cyclization.

The phenol **63** was recrystallized from EtOAc/hexane: mp 152–153 °C; NMR δ 1.2–3.9 (aliphatic protons), 5.82 (s, H para to OH), 6.8–7.3 (m, 3 H, ArH), 8.03 (d, J = 8 Hz, 1 H, H peri to OH), 14.2 (s, OH); UV λ_{max} 244 nm (ϵ 39400), 292 (44600), 315 (11400), 332 (4830), 467 (2560). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 6.0; N, 5.5. Found: C, 76.0; H, 6.1; N, 5.5.

4-Formyl-6,11-dimethoxy-2,3,3a,4-tetrahydrobenzo[*g*]-pyrrolo[1,2-*a*]quinolin-5(1*H*)-one (56). The ketone **54** (1.57 g, 5.28 mmol) was combined with NaH (1.1 g, 46 mmol), 3.40 mL (42.1 mmol) of ethyl formate, 140 mL of anhydrous Et_2O, and 40 μL of MeOH, and the solution was refluxed under nitrogen for 2 h with stirring. After 18 h at room temperature, methanol was added until no further gas evolution was noted followed by 50 mL of water. The layers were separated, and the organic phase was extracted once with 50 mL of 2 M NaOH. The combined aqueous phase was taken to pH 5 with 6 M HCl and extracted with EtOAc (3 × 40 mL), and the combined organic phase was washed, dried, and evaporated. The residue was filtered through 20 g of silica (1% MeOH in CH_2Cl_2 eluent) to give after evaporation 1.51 g (89%) of **56**. Due to this compound's instability, it was used directly in the next step: NMR δ 1.9 (m, $NCH_2CH_2CH_2$), 3.4–4.4 (CH_2NCH), 3.68 and 4.00 (2 s, OCH_3), 7.0–8.1 (m, ArH), 8.45 (2 s, C=CHOH); mass spectrum, found m/e 325.1322 (M^+), $C_{19}H_{19}NO_4$ requires m/e 325.1313.

4-Diazo-6,11-dimethoxy-2,3,3a,4-tetrahydrobenzo[*g*]-pyrrolo[1,2-*a*]quinolin-5(1*H*)-one (57). The α-formyl ketone **56** (1.31 g, 4.03 mmol) was dissolved in 90 mL of CH_2Cl_2, and then 0.99 g (5.0 mmol) of *p*-toluenesulfonyl azide[39] and 1.2 mL (8.6 mmol) of triethylamine were added. This stirred solution was left for 48 h, and the oil resulting from evaporation of the solution was chromatographed on 200 g of alumina (acidic, activity I, CH_2Cl_2 eluent) to give several highly colored fractions. A fraction consisting of diazo ketone **57** plus a trace of two colored byproducts was isolated (0.18 g, 14.0%): NMR δ 2.1 (m, $NCH_2CH_2CH_2$), 3.2 (m, NCH_2), 3.80, 4.07 (2 s, OCH_3), 4.83 (m, NCH), 7.4, 8.0 (2 m, 2 H each, ArH); IR (CH_2Cl_2) 2080 (s, C=N$_2$), 1610 cm^{-1} (C=O).

Methyl 5,10-Dimethoxy-2,3,11,11a-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzo[*f*]indole-11-carboxylate (58). The diazo ketone **57** (0.18 g, 0.56 mmol) was dissolved in 90 mL of dry MeOH (freshly distilled from CaH_2 and degassed with nitrogen). This solution was irradiated for 10 min with a 450-W Hanovia ultraviolet lamp (Pyrex filter) at 25–30 °C with stirring and slow nitrogen bubbling after which the solution was evaporated to give a red glass (0.11 g). Upon chromatography (40 g of silica, CH_2Cl_2, and then up to 2% acetone in CH_2Cl_2) three fractions were obtained: fraction 1, 0.011 g; fraction 2, 0.018 g; fraction 3, 0.034; total yield, 0.063 g (34%). The first and third fractions had nearly identical spectra and represent *cis*- and *trans*-**58**: NMR δ 2.0 ($NCH_2CH_2CH_2$), 3.77, 3.90, 3.93 (3 s, OCH_3), 3.5 (m, NCH_2), 4.3 (m, $NCHCHCOOCH_3$), 7.3, 7.9 (2 m, 2 H each, ArH); mass

(39) M. Regitz, J. Hocker, and A. Liedhegener, "Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 179.

spectrum, found m/e 327.1464 (M^+), $C_{19}H_{21}NO_4$ requires m/e 327.1465.

2-Allyl-3-methoxy-1,4-naphthoquinone (45). The hydroquinone dimethyl ether **26** (0.67 g, 1.9 mmol) in 25 mL of CH_2Cl_2 was shaken with 10 mL of 6 M HNO_3 for 1 min. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (3×), and the combined organic phase was washed, dried, and evaporated to give 0.52 g of an orange oil. Chromatography (25 g of silica, CH_2Cl_2) gave **45** as a solid which was recrystallized from hexane/EtOAc: 0.062 g (14%); mp 80–81 °C; NMR δ 3.29 (d, J = 6 Hz, $CH_2CH{=}CH_2$), 4.05 (s, OCH_3), 5.1 (m, $CH{=}CH_2$), 5.9 (br m, $CH{=}CH_2$), 7.6, 8.0 (2 m, 3 H, 1 H, ArH); IR (Nujol) 1690, 1640, 1600, 1590, 1570 cm^{-1}; UV λ_{max} 391 nm (ϵ 1750), 333 (3040), 278 (18 300), 274 (19 700), 256 (sh, 20 900), 251 (23 100). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.3; H, 5.3.

Registry No. **3**, 72881-45-9; **7**, 13243-65-7; **8**, 72866-61-6; **9**, 72866-62-7; **10**, 59641-26-8; **13**, 72866-63-8; **14**, 72866-64-9; **15**, 72866-65-0; L-**19**, 69940-12-1; **20**, 2065-37-4; L-**21**, 72866-66-1; (*S*)-**24**, 72866-67-2; (*S*)-**25**, 72866-68-3; L-**26**, 72866-69-4; (*S*)-**27**, 72866-70-7; (*S*)-**28**, 72866-71-8; [*S*(*cis*)]-**29**, 72881-46-0; [*S*(*trans*)]-**29**, 72866-72-9; (*S*)-**30**, 72866-73-0; L-**31**, 72866-74-1; L-**33**, 72866-75-2; L-**34**, 72866-76-3; L-**37**, 72866-77-4; L-**38**, 72866-78-5; L-**39**, 72866-79-6; *cis*-**40**, 72866-80-9; **44**, 72866-81-0; **47**, 72866-82-1; **48**, 72881-47-1; **49**, 72881-48-2; **50**, 72866-83-2; **51**, 72866-84-3; **52**, 72866-85-4; **53**, 72866-86-5; **54**, 72866-87-6; **55**, 72866-88-7; **56**, 72866-89-8; **57**, 72866-90-1; *cis*-**58**, 72866-91-2; *trans*-**58**, 72866-92-3; **59**, 72866-93-4; **60**, 72866-94-5; **61**, 72866-95-6; **62**, 72866-96-7; **63**, 72866-97-8; ketene dimethyl acetal, 922-69-0; pyrrolidine, 123-75-1; 1,4-naphthoquinone, 130-15-4; L-proline methyl ester, 2577-48-2; allyl bromide, 106-95-6; hydroxylamine hydrochloride, 5470-11-1; methoxyamine hydrochloride, 593-56-6; trimethyl orthoformate, 149-73-5; phenyl chloroformate, 1885-14-9; ethyl 2-pyrroleacetate, 4728-25-0; ethyl 3-pyrroleacetate, 71616-57-4; homoproline ethyl ester acetate, 72866-98-9.

Structural Study of Carbanionic Species α to a Phosphoryl Group. The Anion of Diethyl [(Carbomethoxy)methyl]phosphonate. Comparison with Phosphorus-Ylidic Esters and Acetoacetic Ester Anions

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The structure of the anion of diethyl [(carbomethoxy)methyl]phosphonate in solution has been studied by ^1H, ^{13}C, and ^{31}P NMR and by IR. Two slowly interconverting species, **2a** and **2b**, can be observed when the gegenion K^+ is complexed to [2.2.2]cryptand in THF, pyridine, and Me_2SO. From the various coupling constants and IR frequencies it appears that, for these two species, the carbon α to phosphorus is planar, and the carbon–carbon and carbon–oxygen bonds are partially double; the $\Delta G_c^{\ddagger}$ value indicates that their interconversion takes place by rotation around the partial C–C double bond. All these characteristics show a close similarity with phosphorus ylidic ester **3**. In the three examined solvents (Me_2SO, pyridine, and THF), either an externally solvated chelate **2A** (Li^+/Me_2SO; c = 0.5 M), occasionally accompanied by free ion (K^+/Me_2SO; c = 0.5 M), or aggregates (Li^+ or K^+/THF; c = 0.5 M) are observed, thus showing a similarity with acetoacetate anion **4** under similar conditions. From the determined dissociation coefficient in Me_2SO, it can be concluded that K^+ is as strongly chelated by the anion formed from diethyl [(carbomethoxy)methyl]phosphonate as by the acetoacetate anion, though its carbon α to phosphorus bears more negative charge.

The reactivity of Wittig–Horner reagents,[1] i.e., anionic species **1** (where R is alkoxy or aryl and A is an electron-

$$[R_2P(O)\text{—}CH\text{—}A]^-M^+$$
$$\mathbf{1}$$

withdrawing group) formed from electron-withdrawing substituted phosphonates and phosphine oxides, has been shown to be dependent on the solvent and the associated cation.[2] In order to understand this behavior, we have undertaken a structural study of these species in solution by NMR and IR spectroscopy.

In a previous work[3] on nitrile and benzylic phosphonate anions (**1**, R = OC_2H_5, A = CN or Ph), a striking similarity between the structures of these species and of the corresponding P ylides has been shown. In the present work, we examine the structure of the phosphono ester anion **2** (**1**, R = OC_2H_5, A = $COOCH_3$) according to solvent and associated cation.

$$[(C_2H_5O)_2P(O)CHCOOCH_3]^-M^+$$
$$\mathbf{2}$$

This species could be expected to chelate a cation by two oxygen atoms: such a possibility has already been suggested by Kirilov and Petrov[4] and by ourselves in a preliminary communication.[5] Thus, the structure of **2** will be compared not only to that of ylidic analogue **3**[6] but also

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(1) W. S. Wadsworth, *Org. React.*, **25**, 73 (1978), and quoted references.
(2) (a) B. Deschamps, Nguyen Trong Anh, and J. Seyden-Penne, *Tetrahedron Lett.*, 527 (1973); (b) M. Cossentini, B. Deschamps, Nguyen Trong Anh, and J. Seyden-Penne, *Tetrahedron*, **33**, 409 (1977); (c) B. Deschamps and J. Seyden-Penne, *ibid.*, **33**, 413 (1977); (d) B. Deschamps, *ibid.*, **34**, 2009 (1978); Thèse, Orsay, France, 1977; (e) A. Loupy, K. Sogadji, and J. Seyden-Penne, *Synthesis*, 126 (1977).
(3) T. Bottin-Strzalko, M. J. Pouet, J. Seyden-Penne, and M. P. Simonnin, *J. Org. Chem.*, **43**, 4346 (1978), and quoted references.
(4) M. Kirilov and G. Petrov, *Monatsh. Chem.*, **103**, 1651 (1972).
(5) T. Bottin-Strzalko, J. Seyden-Penne, and M. P. Simonnin, *J. Chem. Soc., Chem. Commun.*, 905 (1976).

0022-3263/80/1945-1270$01.00/0