Notes

Metal Complexes of Mitomycins

Bhashyam S. Iyengar,† Takeo Takahashi,[1†] William A. Remers,*† and William T. Bradner‡

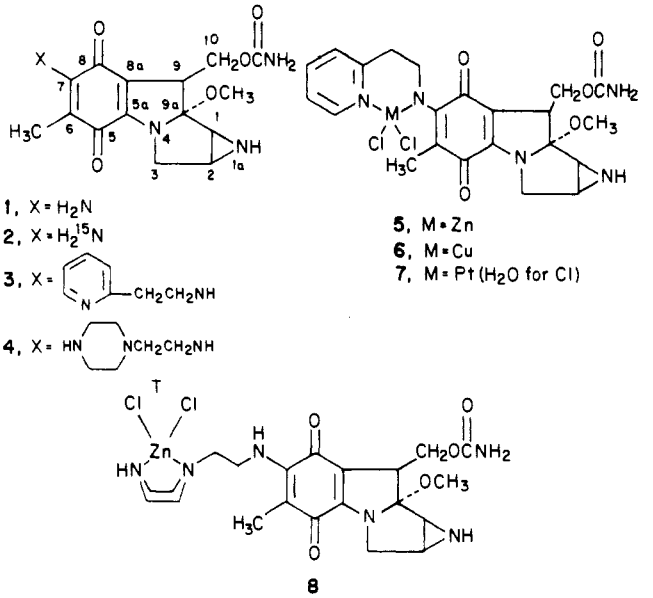
Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721, and Bristol-Myers Company, Syracuse, New York 13221-4755. *Received December 17, 1984*

The preparation of stable complexes between the N^7-[2-(2-pyridyl)ethyl] and N^7-(2-piperazinylethyl) derivatives of mitomycin C and metal ions such as Cu(II), Zn(II), and Pt(II) was accomplished. Mitomycin C did not form stable complexes, but it rearranged to a mitosene capable of complex formation. Some of these complexes had antitumor activity in mice. However, they were less active than mitomycin C. Weak associations between mitomycin C and metal ions were demonstrated by ^{13}C and ^{15}N NMR spectrometry.

A variety of antitumor drugs exert their cytotoxic effects, at least in part, by oxidative cleavage of DNA. These cleavages involve molecular oxygen and metal ions such as Fe(II), Zn(II) and Cu(II) that are chelated by the drugs. Typical examples of such drugs are bleomycin and streptonigrin.[2,3] A recent article showed that Cu(II) ions strongly promoted the strand scission of bacteriophage ϕX174 by mitomycin C (1) and sodium hydrosulfite.[4] This finding is consistent with earlier reports that reduction and reoxidation of mitomycin C results in the generation of hydrogen peroxide and other reactive species.[5,6]

Our continuing interest in the mitomycins led us to investigate the possibility that mitomycin C or some of its derivatives might form stable metal complexes. If this could be accomplished and if these complexes were taken up by cells, an increased cytotoxic effect might be obtained. Preliminary evidence for complex formation with mercury was found in the anomalous polarographic reduction of certain mitomycin C analogues with additional nitrogens in the 7-substituent.[7] The preparation of suitable analogues **3** and **4** by treatment of mitomycin A with 2-(2-pyridyl)ethylamine and piperazinylethylamine, respectively, was readily accomplished. Evidence that the primary amino group rather than the secondary amino group of the latter reagent had displaced the 7-methoxy group of mitomycin A was afforded by the blue color (rather than green)[8] of **4** and the presence in its ^1H NMR spectrum of one hydrogen at δ 1.57–2.13 (broad singlet). Treatment of **3** with zinc chloride or 1 equiv of cupric chloride in anhydrous methanol gave solids whose combustion analysis agreed with 1:1 complexes. Excess cupric chloride gave a complex of undetermined structure containing more than 1 equiv of copper. A platinum(II) complex also was prepared from **3**. It was nicely crystalline, but there were two molecules of KCl per molecule of complex in the crystal. Piperazinylethyl analogue **4** gave a 1:1 complex with zinc chloride. It is most likely structure **8** because the piperazinyl nitrogens are more basic than N^7 on the quinone ring.

Although the structures proposed for metal complexes **5–7** are reasonable, according to the basicity of the pyridine nitrogen and the formation of a six-membered ring, it was important to determine that the complexes formed with N^7 and the pyridyl nitrogen rather than on the other side of the mitomycin, for example involving the aziridine nitrogen and the carbamate group. As discussed below,



mitomycin C (1) does not form stable complexes, which rules out the latter possibility. Further support for structures **5–7** was obtained by preparing the naphthoquinone analogue **12** of mitomycin derivative **13**. This compound was synthesized from 2-(2-pyridyl)ethylamine and methylnaphthoquinone. It readily gave zinc(II) and copper(II) complexes **13** and **14**, respectively.

Our initial attempt at mitomycin C complexation, based on treating a methanol solution with 2 equiv of zinc chloride, resulted in a slow color change from blue to red-violet. Removal of the solvent gave a purple solid whose ultraviolet absorption spectrum (Experimental Section) showed that a rearrangement from the mitosane

† University of Arizona.
‡ Bristol-Myers Company.

(1) Visiting professor from the Pharmaceutical Institute, University of Sendai, Sendai, Japan.
(2) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Iitaka, Y.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 1073.
(3) Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. *Can. J. Chem.* **1976**, *54*, 219.
(4) Veda, K.; Morita, J.; Yamashita, K.; Komano, T. *Chem.-Biol. Interact.* **1980**, *29*, 145.
(5) Lown, J. W.; Begleiter, A.; Johnson, D.; Morgan, A. R. *Can. J. Biochem.* **1976**, *54*, 110.
(6) Tomasz, M. *Chem.-Biol. Interact.* **1976**, *13*, 89.
(7) Iyengar, B. S.; Sami, S. M.; Remers, W. A.; Bradner, W. T.; Schurig, J. E. *J. Med. Chem.* **1983**, *26*, 16.
(8) Iyengar, B. S.; Sami, S. M.; Tarnow, S. E.; Remers, W. A.; Bradner, W. T.; Schurig, J. E. *J. Med. Chem.* **1983**, *26*, 1453.

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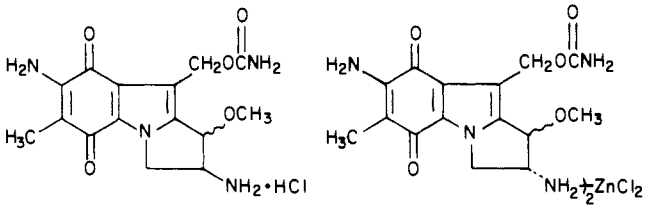

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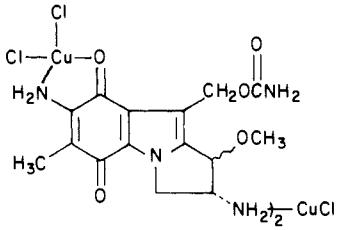

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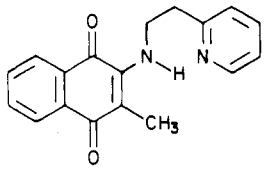

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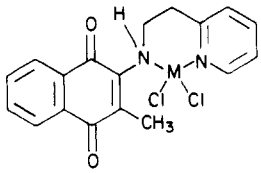
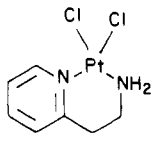


13, M = Zn
14, M = Cu



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to the mitosene system had occurred.[9] Combustion analysis and ^1H NMR established that this solid was a 2:1 complex between 2,7-diamino-1-methoxymitosene and zinc chloride, with both cis and trans mitosene isomers present (**10**). The zinc is considered to be complexed with the 2-amino group, which is much more basic (pK_a = 7) than any other nitrogen in the molecule. This result can be interpreted in the following way. Mitomycin C does not have a sufficiently basic nitrogen to form a stable complex with zinc (the aziridine nitrogen has pK_a = 1.5).[10] On prolonged standing in methanol, the Lewis acid Zn(II) catalyzes the conversion of mitomycin C in to 2,7-diamino-1-methoxymitosene, which now is basic enough to form a zinc complex.

The formation of **10** offered us an opportunity to examine a literature reaction in which it was reported that mitomycin C in CH_3CO_2D formed *trans*-2,7-diamino-1-methoxymitosene (**9**) (among other products), which must have resulted from direct migration of the 9a-methoxy group to C-1 because no deuterium was incorporated at C-1.[11] When we repeated the reaction of mitomycin C with zinc chloride in CD_3OD, the resulting **10** showed a complete absence of the 1-OCH_3 signal (δ 3.4) in the ^1H NMR spectrum, which demonstrates that 1-OCD_3 came from the solvent rather than 1-OCH_3 from migration. This result does not necessarily disprove the literature report, which was not done in deuteriomethanol. However, it restricts the possible generality of the migration process.

Returning to the preparation of complexes, we treated mitomycin C in methanol with 2 equiv of cupric chloride. Again a slow color change occurred. The greenish colored product had an ultraviolet absorption spectrum characteristic of a mitosene and combustion analysis showed 1.5$CuCl_2$/molecule of mitomycin derivative. The product is assigned structure **11** on the basis of this evidence and the ^1H, ^{13}C, and ^{15}N NMR studies described below.

Although stable complexes could not be prepared from mitomycin C, it was possible to demonstrate weaker interactions by NMR spectroscopy. The ^1H NMR spectrum of mitomycin C in Me_2SO-d_6 was unchanged by the addition of 1 equiv of zinc chloride; however, 1 equiv of cupric chloride caused a significant change in the 7-NH_2 group protons. The peak at δ 7.1 was broadened and reduced to about half its intensity, while another peak of equal intensity appeared at δ 7.7. These results suggest that zinc does not interact appreciably with mitomycin C, but copper complexes partially with an exchange rate slower than the NMR process. Additional evidence on this point was obtained by the use of 7-$^{15}NH_2$ mitomycin C (**2**), which was prepared by treating mitomycin A with $^{15}NH_3$.[12] The

Table I. Activity of Mitomycin Derivatives and Their Metal Chelates against P-388 Murine Lukemia

compd	dose, mg/kg per inj	effect MST (% T/C)	av wt change, g
3	25.6	>375 [4/6]	−2.7
	12.8	256	−1.8
	6.4	213	−1.1
	3.2	163 (319)	−0.9
	1.6	163	−0.4
	0.8	138	−0.3
	0.4	125	−0.6
	0.2	125	−0.5
4	25.6	138	−0.6
	12.8	125	1.2
	6.4	113	2.1
	4.8	(213)	
5	25.6	161	−1.3
	12.8	156	−0.4
	6.4	139	−0.6
	3.2	133 (194)	0.1
	1.6	122	0.8
6	25.6	128	−1.4
	12.8	122	0.2
	4.8	(156)	
7	25.6	125	−0.2
	12.8	110	0.5
	4.8	(230)	
8	25.6	100	−0.6
	12.8	90	1.2
	4.8	(213)	
9	25.6	130	0.6
	12.8	115	0.4
	6.4	110	1.9
	4.8	(>165)	
10	25.6	178	−0.7
	12.8	144	0.4
	6.4	133	0.7
	3.2	139 (194)	2.0
	1.6	122	0.5
11	25.6	toxic	−3.1
	12.8	100	0.3
	6.4	100	0.8
	3.2	100 (194)	0.9
15	32	130	−0.5
	16	120	−0.7
	8	100	1.3
	4.8	(230)	

[a] Determined at Bristol-Meyers Co., Syracuse, NY. A tumor inoculum of 10^6 ascites cells was implanted ip in CDF_1 female mice. Six mice were used at each dose of the mitosane, and 10 control mice were injected with saline. A control group of six mice at each dose received mitomycin C in the same experiment: MST = median survival time; max effect (% T/C) = MST treated/MST control × 100 at the optimal dose (opt dose); MED = minimum effective dose (% T/C 125); TR = therapeutic ratio (opt dose/MED). The number of 30-day survivors at the optimal dose is given in brackets beside the maximum effect.

(9) Webb, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pldacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 1962.

(10) Underberg, W. J. M.; Lingeman, H. *J. Pharm. Sci.* **1983**, *72*, 553.

(11) Stevens, C. L.; Taylor, K. G.; Munk, M. E.; Marshall, W. S.; Noll, K.; Shah, G. D.; Shah, L. G.; Uzu, K. *J. Med. Chem.* **1964**, *8*, 1.

^{15}N peak of **2** occurred at δ −283.5 (reference to $NH_4{}^{15}NO_3$) in Me_2SO-d_6 and it was unchanged by the addition of zinc chloride. However, the addition of cupric chloride caused a shift to δ −292.0 and broadening of the peak.

Effects of metal ions on the ^{13}C NMR spectrum of mitomycin C also were investigated. The ^{13}C NMR spectrum of mitomycin C had been analyzed previously.[12] Addition of zinc chloride to mitomycin C in Me_2SO-d_6 produced a significant diminution in the peaks for C-1 (35.3 ppm) and C-2 (31.6 ppm), without the appearance of any new peaks in the spectrum. However, when the spectrum was taken at a 45° pulse rather than at the usual 30° pulse, the C-1 and C-2 peaks appeared at their full intensity. This result suggests that a weak interaction between the zinc and the aziridine nitrogen occurs at an exchange rate comparable to the NMR process. It was difficult to obtain a sharp ^{13}C NMR spectrum when cupric chloride was added to mitomycin C in Me_2SO-d_6. The spectrum that was obtained showed broadening and diminished intensity for the signals from carbons 1, 2, 3, 7, and 8a, which suggest copper complexation with both the 7-amino and aziridino nitrogens.

Biological Activity. The activities of the new mitomycin derivatives and their metal complexes are given in Table I. The activity of the mitomycin control at its optimal dose is given in parentheses beside each compound. Assays were not all run concurrently and the therapeutic effects vary from one experiment to another, depending on the tumor inoculum. Therefore, compounds should be compared according to how each one relates to the mitomycin C control rather than directly. It is apparent from Table I that the pyridylethyl analogue **3** has excellent antitumor activity with a wide therapeutic index. However, piperazinylethyl analogue **4** is much less active than mitomycin C. The zinc and copper complexes, **5** and **6**, respectively, from **3** showed antitumor activity, although both were lower than the mitomycin C controls. Platinum complex **7** was barely active. The simple platinum chloride complex **15** of 2-(2-pyridyl)ethylamine was prepared in order to see if this functionality has any other intrinsic antitumor activity. It can be considered as an analogue of cisplatin.[13] Table I shows that it has low activity at the 30 mg/kg dose. The zinc chloride complex **8** from **4** was inactive, as were the naphthoquinone derivatives **13** and **14** (not given in Table I). Of the two mitosene metal complexes, zinc complex **10** had moderately good activity at 25.6 mg/kg (T/C = 178) and it was still active at 8-fold dilution. In contrast, copper complex **11** was inactive.

Conclusion

The preparation of stable metal complexes from mitomycin analogues with additional nitrogen atoms in the 7-substituent has been demonstrated. Mitomycin C forms weak complexes that undergo rearrangement to mitosenes in methanol. Although some of these complexes showed antitumor activity, the desired improvement in activity over mitomycin C was not obtained. It is conceivable that they might have good intrinsic activity inside the cell nucleus, but their cellular uptake is limited by the positive charges they bear. Cellular uptake was not measured. Two alternative approaches to the formation of mitomycin metal complexes are under investigation in our laboratory. One involves the preparation of analogues with strong enough complexing ability that they can scavenge metal ions from cellular components after cellular uptake. A potential drawback of this approach is that these potent metal binders might form complexes that would limit their uptake into cells or diffusion into the nucleus. It is possible that the low activity of piperazinylethyl analogue **4** results from this process (suggested by a referee). The stability constants for complexes of **4** and the much more active pyridylethyl analogue **3** have not been measured, but the piperazinyl group with two strongly basic amines should bind metals such as Zn(II) and Cu(II) much more strongly than the system of **3**, which has one pyridyl nitrogen and one nearly neutral nitrogen on the quinone ring (pK_a = −1.3).[10] The second approach is to prepare more lipophilic, neutral metal complexes that might partially dissociate to charged species within cells. Complexes of mercury or gold might serve this purpose.

Experimental Section

General Procedures. Melting points were determined on a Laboratory Instruments Mel-Temp apparatus and are uncorrected. UV and visible spectra were taken on a Beckman DU-8 spectrophotometer. ^1H and ^{13}C NMR spectra were taken on a JEOL FX90Q spectrometer. Chemical shifts are reported as ppm downfield from Me_4Si. ^{15}N NMR spectra were taken on a Bruker WM250 spectrometer. Elemental analyses were performed by the Analytical Center, University of Arizona or Mic Anal, Tucson, AZ.

[7-^{15}N]Mitomycin C (2). A solution of mitomycin A (150 mg, 0.43 mmol) in 25 mL of anhydrous methanol was treated with 2 mL of triethylamine and $^{15}NH_4Cl$ (200 mg, 3.7 mmol). After 30 h, the solution was concentrated under reduced pressure and the residue was purified by preparative thin-layer chromatography on silica gel with CH_3OH–$CHCl_3$ (2:8) as solvent. The major blue band, which was identical in R_f with mitomycin C, was scraped from the plate, eluted with CH_3OH–CH_2Cl_2, and concentrated to give 134 mg (93%) of the product.

Zinc Chloride Complex of 2,7-Diamino-1-methoxymitosene (10). A solution of mitomycin C (1; 50 mg, 0.15 mmol) in 8 mL of anhydrous methanol was stirred with zinc chloride (42 mg, 0.3 mmol) under N_2 for 36 h. The resulting purple mixture was concentrated under reduced pressure and the residue was washed with two 5-mL portions of acetonitrile and dried under vacuum. This procedure gave 30 mg (50%) of **10** as purple solid with no definite melting point: NMR (Me_2SO-d_6) showed the 1-OCH_3 at 3.40 and the 1-H as a multiplet (cis and trans isomers) at 4.5; UV (CH_3OH) 309.7, 247.2, 215.5 nm. Anal. ($C_{15}H_{17}N_4O_5$·0.5ZnCl_2·H_2O)H, N; C: calcd, 42.95; found, 42.22; Zn: calcd, 7.79; found, 8.27.

When this experiment was repeated in CD_3OD, the product showed no signal for the 1-OCH_3 group at 3.40.

Cupric Chloride Complex of 2,7-Diamino-1-methoxymitosene (11). A solution of mitomycin C (50 mg, 0.15 mmol) in 8 mL of anhydrous methanol was stirred with copper(II) chloride (40 mg, 0.3 mmol) under N_2 for 20 h. The resulting greenish mixture was concentrated under reduced pressure and the residue was stirred with 10 mL of acetonitrile for 10 min. It was washed again with acetonitrile (5 mL × 2) and dried. This procedure gave 30 mg (38%) of **11** as greenish solid with no definite melting point: UV (CH_3OH) 520.0, 317.6, 243.0, 201.4 nm. Anal. ($C_{15}H_{18}N_4O_5$·1.5$CuCl_2$·2H_2O) C, H; N: calcd, 9.79; found 9.33; Cu: calcd, 16.66; found, 14.5.

N^7-[2-(2-Pyridyl)ethyl]mitomycin C (3). A solution of 150 mg of mitomycin C and 0.5 mL (excess) of 2-(2-aminoethyl)-pyridine in 10 mL of methanol was stirred under N_2 for 1 h and then concentrated under reduced pressure. Purification of the residue by preparative thin-layer chromatography on silica gel with CH_3OH–$CHCl_3$ (2:8) as solvent gave 140 mg (74%) of **3** as dark blue solid that decomposed above 200 °C: NMR (Me_2SO-d_6) showed peaks for the new substituent at 2.90–3.6 (m, 4), 7.0–7.3 (br s, 3), 7.6–8.1 (br s, 1), 8.5 (d, 1), and CH_2Cl_2 solvate at 5.3 (s). Anal. ($C_{22}H_{25}N_5O_5$·0.42CH_2Cl_2) C, H; N: calcd, 14.74; found, 15.20.

Zinc Chloride Complex of N^7-[2-(2-Pyridyl)ethyl]mitomycin C (5). A solution of N^7-2-(2-pyridylethyl)mitomycin C

(12) Keller, P. J.; Hornemann, U. *J. Nat. Prod.* **1983**, *46*, 567.
(13) Cleare, M. J. In "Structure–activity Relationships of Antitumor Agents", Reinhoudt, D. N., Connors, T. A., Pinedo, H. M., van de Poll, K. W., Eds.; Martinus Nijhoff Publishers: The Hague, 1983; pp 59–91.

(3, 100 mg, 0.23 mmol) in 8 mL of anhydrous methanol was treated with zinc chloride (60 mg, 0.44 mmol). The mixture was stirred under N_2 for 24 h and then concentrated under reduced pressure. The residue was stirred with 10 mL of acetonitrile, filtered, washed with more acetonitrile (2 × 5 mL), and dried under vacuum. This procedure gave 45 mg (34%) of **5** as a bluish solid which decomposed at 200–210 °C: UV (CH_3OH) 538–556 (br), 369.2, 317.5, 253 nm; the ^1H NMR spectrum was nearly identical with that of **3**. Anal. ($C_{22}H_{25}N_5O_5 \cdot ZnCl_2 \cdot H_2O$) C, H; N: calcd, 11.79; found, 10.67; Zn: calcd, 11.01; found, 11.5.

Cupric Chloride Complex of N^7-[2-(2-Pyridyl)ethyl]mitomycin C (6). A solution of N^7-[2-(2-pyridyl)ethyl]mitomycin C (**3**; 30 mg, 0.068 mmol) in 1 mL of anhydrous ethanol under N_2 was treated dropwise with a solution of copper(II) chloride (11 mg, 0.08 mmol) in 1 mL of anhydrous ethanol. The mixture was stirred 30 min and then filtered. The solids were washed repeatedly with 2-mL portions of cold anhydrous ethanol and dried under vacuum to give 20 mg (50%) of **6** as a green solid with no definite melting point: UV (CH_3OH) 571.68, 387.52 nm. Anal. ($C_{22}H_{25}N_5O_5 \cdot 1.25CuCl_2 \cdot H_2O$) C, H, N, Cl. The extra 0.25 mol of $CuCl_2$ could not be removed by repeated washing with ethanol.

Preparation of the Platinum(II) Complex N^7-[2-(2-Pyridyl)ethyl]mitomycin C (7). A solution of N^7-[2-(2-pyridyl)ethyl]mitomycin C (**3**; 54 mg, 0.12 mmol) in 1 mL of *p*-dioxane was stirred with a solution of potassium tetrachloroplatinate(II) (70 mg, 0.17 mmol) in 1.2 mL of water for 16 h under N_2. The greenish crystalline solid that formed was washed with water (5 mL × 2) and methanol (5 mL × 2) and dried under vacuum. This procedure gave 35 mg (40%) of **7** as a complex containing KCl and H_2O and decomposing at 230–240 °C. Anal. ($C_{22}H_{25}N_5O_5 \cdot Pt(H_2O)_2 \cdot 2KCl \cdot H_2O$) C, N, Cl; H: calcd, 3.73; found, 3.03.

N^7-[2-(1-Piperazinyl)ethyl]mitomycin C (4). A solution of mitomycin A (100 mg, 0.29 mmol) and 1-(2-aminoethyl)piperazine (52 mg, 0.40 mmol) in 50 mL of diethyl ether was stirred 16 h under N_2. The solution was concentrated under reduced pressure and the residue was purified by preparative thin-layer chromatography on silica gel with CH_3OH–$CHCl_3$ (2:8) as solvent. This procedure gave 82 mg (68%) of **4** as a blue solid: mp 138–141 °C dec: NMR ($CDCl_3$) showed peaks for the new substituent at 1.57–2.13 (br s, 1), 2.20–2.60 (br s, 1), 260–3.03 (br s, 4), 6.93 (t, 1); UV (CH_3OH) 550, 367.5, 220.5 nm. Anal. ($C_{21}H_{30}N_6O_5 \cdot 1.5H_2O$) C, H; N: calcd, 17.74; found, 15.83.

Zinc Chloride Complex of N^7-[2-(1-Piperazinyl)ethyl]mitomycin C (8). A solution of N^7-[2-(1-piperazinyl)ethyl]mitomycin C (**4**; 45 mg, 0.1 mmol) in 2 mL of *p*-dioxane was treated with a solution of zinc chloride (40 mg, 0.29 mmol) in 10 mL of anhydrous methanol. The mixture was stirred 1 h and filtered, and the solid was washed with methanol (2 mL × 2) and methylene chloride (5 mL × 2) and dried under vacuum. This procedure gave 16 mg (30%) of **8** as a gray solid that decomposed at 225–235 °C: UV (CH_3OH) 543, 367.5, 350 (sh), 233 nm. Anal. ($C_{21}H_{30}N_6O_5 \cdot ZnCl_2 \cdot CH_2Cl_2$) C, H, N.

3-Methyl-2-[[2-(2-pyridyl)ethyl]amino]-1,4-naphthoquinone (12). A solution of 510 mg of 3-methyl-1,4-naphthoquinone and 2 mL (excess) of 2-(2-aminoethyl)pyridine in 25 mL of anhydrous methanol was heated at reflux temp while O_2 was bubbled through it. After 1 h the resulting brown solution was cooled and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel with CH_3OH–$CHCl_3$ (2:8) as solvent. The major orange band gave 320 mg (37%) of **12** as a orange solid: mp 82–85 °C; NMR (acetone-d_6) 2.2 (s, 3), 3.10 (t, 2), 3.9–4.2 (br s, 2), 7.14–8.15 (m, 8), 8.5 (d, 1). Anal. ($C_{18}H_{16}N_2O_2 \cdot 0.5CH_3OH$) C; H: calcd, 5.88; found, 5.36; N: calcd, 9.08; found, 8.53.

Zinc Chloride Complex of 3-Methyl-2-[[2-(2-pyridyl)ethyl]amino]-1,4-naphthoquinone (13). A solution of 3-methyl-2-[[2-(2-pyridyl)ethyl]amino]-1,4-naphthoquinone (**12**; 159 mg, 0.47 mmol) in 15 mL of anhydrous methanol was stirred with zinc chloride (200 mg, 1.47 mmol) for 16 h. The mixture was concentrated under reduced pressure and the residue was stirred with 100 mL of diethyl ether, filtered, washed with diethyl ether (10 mL × 3), and dried. This procedure gave 102 mg (51%) of **13** as an orange solid: mp 200–210 °C dec. The ^1H NMR spectrum was essentially unchanged from that of **12**. Anal. ($C_{18}H_{16}N_2O_2 \cdot ZnCl_2 \cdot 0.5CH_3OH$) C, H, N, Zn.

Cupric Chloride Complex of 3-Methyl-2-[[2-(2-Pyridyl)ethyl]amino]-1,4-naphthoquinone (14). A solution of 3-methyl-2-[[2-(2-pyridyl)ethyl]amino]-1,4-naphthoquinone (**12**; 30 mg, 0.1 mmol) and copper(II) chloride (14 mg, 0.1 mmol) in 1.0 mL of dry *N,N*-dimethylformamide was stirred for 12 h and then concentrated under reduced pressure. The oily residue was extracted with 25 mL of absolute ethanol and the precipitate that formed was filtered and dried under reduced pressure. This procedure gave 13 mg (30%) of **14** as a dark red solid with no definite melting point. Anal. ($C_{18}H_{16}N_2O_{23} \cdot CuCl_2 \cdot 1.7H_2O$) C, N; H: calcd, 4.28; found, 3.75; Cl: calcd, 15.50; found, 16.39.

Platinum(II) Chloride Complex of 2-(2-Aminoethyl)pyridine (15). A solution of 2-(2-aminoethyl)pyridine (4.4 mg, 0.36 mmol) and potassium tetrachloroplatinum (150 mg, 0.36 mmol) in 4 mL of water was stirred under N_2 for 12 h. The resulting precipitate was collected, washed with ice-cold water (1 mL × 2) and methanol (1 mL × 2), and dried under vacuum. This procedure gave 70 mg (50%) of **15** as a pale yellow solid that decomposes at 245–255 °C. Anal. ($C_7H_{10}N_2 \cdot PtCl_2$) C, H, N.

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Registry No. 1, 50-07-7; 2, 99016-64-5; 3, 93073-99-5; 4, 93073-98-4; 5, 99016-68-9; 6, 99016-69-0; 7, 99016-70-3; 8, 99016-71-4; 9 (isomer 1), 99095-22-4; 9 (isomer 2), 99095-23-5; 10 (isomer 1), 99016-66-7; 10 (isomer 2), 99095-24-6; 11, 99016-67-8; 12, 99016-65-6; 13, 99016-72-5; 14, 99016-73-6; 15, 63443-81-2; 1-(2-aminoethyl)piperazine, 140-31-8; mitomycin A, 4055-39-4; 2-(2-aminoethyl)pyridine, 2706-56-1; 2-methyl-1,4-naphthoquinone, 58-27-5.