New 2-Substituted Indoloquinone Mitomycin Analogues

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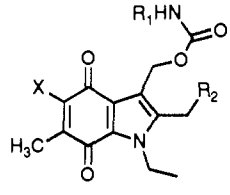
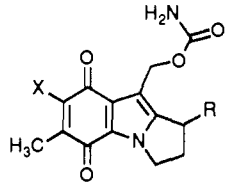
Previously reported 2-(hydroxymethyl)indoloquinones, prepared as their acetates or carbamates, were less active than 2-methyl analogues in bacterial cultures and they had no activity in mice, despite functionality appropriate for DNA cross-linking. On the basis of the hypothesis that these compounds might have been too reactive chemically for selective alkylation of DNA, we prepared new analogues with substituents that could give variation in the reduction potential of the quinone ring, which might control their rate of bioactivation. The 5-methoxyindoloquinones were much more potent cytotoxics than mitomycin C against human tumor cell lines, but they were inactive against P388 leukemia in mice. Two 5-aziridinylindoloquinones were also more potent than mitomycin C against the cell lines and one of them was active in the P388 model upon in vivo assay. The corresponding 5-amino analogues were less potent than mitomycin C against both the cell lines and murine P388 leukemia. A 2-(1-hydroxyethyl)carbamate was prepared by a 20-step synthesis. It was about one-fourth as potent as mitomycin C against two cell lines.

Among the earliest mitomycin analogues prepared was a series of indoloquinones in which substituents were varied at all available positions on the nucleus.[1-8] Most of these compounds were active against Gram-positive bacteria in cultures and the best of them (for example 1)



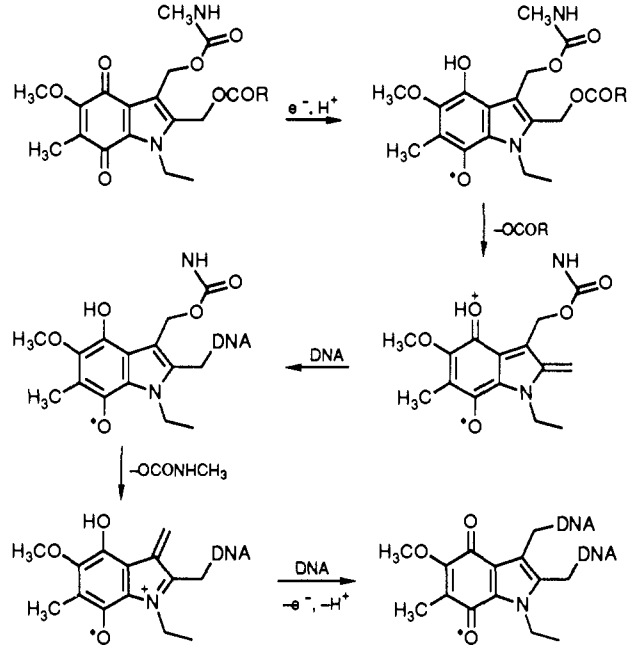


1: X = $\overline{NCH_2CH_2}$, R_1 = CH_2CH_2OH, R_2 = H
2: X = CH_3O, R_1 = CH_3, R_2 = $OCOCH_3$
3: X = CH_3O, R_1 = CH_3, R_2 = $OCONHCH_3$
4: X = CH_3O, R_1 = CH_3, R_2 = H
5: X = CH_3O, R = $OCOCH_3$
6: X = CH_3O, R = H
7: X = CH_3O, R = $OCONHCH_3$
8: X = $\overline{NCH_2CH_2}$, R = $OCOCH_3$
9: X = $\overline{NCH_2CH_2}$, R = $OCONH_2$

had oral activity in mice against *Streptococcus pyogenes* and *Staphylococcus aureus*, including a tetracycline-resistant species.[9] Substituents that conferred the best activity included methyl or ethyl at N-1, methyl at C-2, (carbamoyloxy)methyl at C-3, methoxy or aziridine at C-5, and methyl at C-6. A variety of carbamates, such as methyl, methylpiperazinyl, and hydroxyethyl, enhanced potency. Despite this significant antibacterial activity, the indoloquinones showed no activity against the 72j mammary adenocarcinoma in C_3H mice.[9]

One subset of the indoloquinones that showed rather disappointing activity was the 2-substituted analogues.[5] In principle, some of them, including the 2-(acetoxymethyl) and 2-[[(*N*-methylcarbamyl)oxy]methyl] compounds **2** and **3**, should have been able to cross-link DNA through their

Scheme I



2- and 3-methylene groups (Scheme I). Consequently, high potency in antibacterial assays was expected.[10] However, none of the 2-substituted analogues was as active as the 2-methyl analogue **4** across a spectrum of Gram-positive bacteria in vitro. The concept of enhanced activity for mitomycin analogues with two leaving groups on an indoloquinone chromophore was later demonstrated for 1-acetoxy-7-methoxymitosene (**5**),[10] which was significantly more active than 7 methoxymitosene (**6**) against P388 leukemia in mice.[11] This compound was as potent as mitomycin C, although it gave an inferior T/C value. The related 2-(acetoxymethyl)indoloquinone **2** was inactive against the 72j mammary adenocarcinoma.[9]

One possible explanation for the inferior biological activity of 2-substituted indoloquinone analogues is that they are too reactive chemically. This property could result in nonspecific alkylation of a variety of nucleophiles before the activated molecules could reach appropriate locations on DNA for producing lethal effects. High chemical reactivity of the 2-position was evident from an attempt to

(1) Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1984**, *86*, 3878.
(2) Allen, G. R., Jr.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 1.
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(4) Allen, G. R., Jr.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 14.
(5) Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Med. Chem.* **1967**, *10*, 14.
(6) Poletto, J. F.; Allen, G. R., Jr.; Weiss, M. J. *J. Med. Chem.* **1968**, *11*, 882.
(7) Remers, W. A.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 804.
(8) Roth, R. H.; Remers, W. A.; Weiss, M. J. *J. Org. Chem.* **1966**, *31*, 1012.
(9) Weiss, M. J.; Redin, G. S.; Allen, G. R., Jr.; Dornbush, A. C.; Lindsay, H. L.; Poletto, J. F.; Remers, W. A.; Roth, R. H.; Sloboda, A. E. *J. Med. Chem.* **1968**, *11*, 742.
(10) Mott, J.; Remers, W. A. *J. Med. Chem.* **1978**, *21*, 493.
(11) Hodges, J. C.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 1184.

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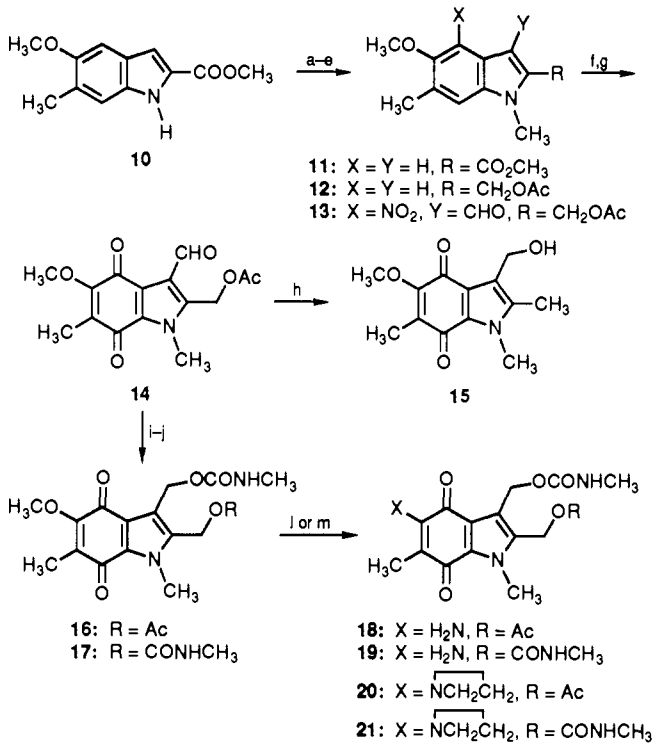
Scheme II[a]



[a] Reagents: (a) Me_2SO_4, NaH, toluene; (b) LAH, THF; (c) Ac_2O, py; (d) $POCl_3$·DMF, py, CH_2Cl_2; (e) 90% HNO_3, AcOH; (f) Sn, HCl, EtOH; (g) $ON(SO_3K)_2$, pH 6.0; (h) $NaBH_4$, MeOH, and then $FeCl_3$, HCl; (i) 9-BBN, THF, and then 30% H_2O_2; (j) CH_3NCO, Et_3N, CH_2Cl_2; (k) 0.1 M NH_4OH, MeOH; (l) NH_3, MeOH; (m) aziridine, CH_2Cl_2.

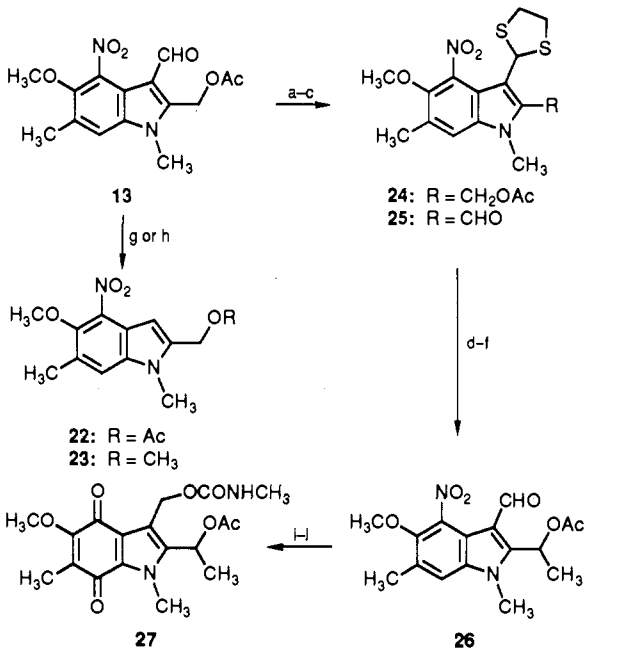
tosylate the 2-(hydroxymethyl) group with tosyl chloride in pyridine at 0 °C. Only the pyridinium derivative was isolated.[5]

If the antitumor activity of a 2-substituted indoloquinone suffers from excess chemical reactivity, there are, in principle, at least two ways to decrease the reactivity to a level at which greater selectivity toward biological nucleophiles might be obtained. One way might be to increase the difficulty of reducing the indoloquinone chromophore. As shown in Scheme I, this process is an essential step in the bioactivation of a mitomycin analogue. The quinone reduction potential can be controlled by the 5-substituent and we chose the methoxy, amino, and aziridinyl groups to investigate this parameter. A second way to modify chemical reactivity is to change the 2-substituent. Two variations were examined at this position: one involved an *N*-methylcarbamate rather than an acetate and the other involved a secondary-alcohol derivative rather than a primary-alcohol derivative. The latter change is based on the assumption that the steric effect of an additional methyl group would slow reaction of the methylene group, formed by loss of the substituent on C-2, with biological nucleophiles. For this purpose the 2-(1-acetoxyethyl) group was chosen, as represented in compound **27**. In each of the analogues just described, a methyl group was planned for the N-1 substituent, although the 2-substituted compounds in the literature had 1-ethyl groups. We felt that the smaller methyl group would cause less steric hindrance for chemical reactions at C-2, especially as that position was elaborated into an ethyl group (Scheme IV).

Chemistry

The starting point for synthesis of the indoloquinones was ethyl 5-methoxy-6-methylindole-2-carboxylate (**10**),

Scheme III[a]



[a] Reagents: (a) $HSCH_2CH_2SH$, TsA; (b) NaOH, CH_3CN; (c) PCC, CH_2Cl_2; (d) MeMgBr, THF, (e) Ac_2O, py; (f) $HgCl_2$, $CaCO_3$, CH_3CN, H_2O; (g) $HOCH_2CH_2OH$, TsOH, benzene, reflux; (h) MeOH, TsOH, toluene, reflux, (i) Pd–C, H_2, MeOH; (j) $ON(SO_3K)_2$, pH 6.0; (k) $NaBH_4$, MeOH; (l) CH_3NCO, Et_3N, CH_2Cl_2.

which has been used in the preparation of many mitosenes and some previous indoloquinones. It is made in five steps from 2,5-xylenol by a Reissert synthesis.[12] From **10**, the synthesis was parallel to the one used initially by Allen et al. for the earlier 2-substituted indoloquinones.[10] It proceeded by way of **11** and **12**, affording **13** in 37% oveall yield from **10** (Scheme II). The conversion of **13** into quinone aldehyde **14** was accomplished by Sn/HCl reduction (rather than Fe/HCl) followed by Fremy's salt oxidation. In the previous study, the 3-carboxaldehyde group was reduced to a hydroxymethyl group by sodium borohydride.[10] We found, however, that sodium borohydride reduced the 2-(acetoxymethyl) group as well as the carboxaldehyde group of **14** to give 3-(hydroxymethyl)-2-methyl derivative **15**. This problem was solved by using 9-borabicyclo[3.3.1]nonane as the reducing agent. Oxidative workup (30% H_2O_2) gave the desired 2-(acetoxymethyl)-3-(hydroxymethyl) derivative, which was isolated as the methylcarbamate **16** in 43% yield. Alkaline hydrolysis followed by treatment with methyl isocyanate then gave bis(methylcarbamate) **17**. The preparation of the 5-amino and 5-aziridino analogues **18** through **21** was carried out readily by using ammonia and ethyleneimine.

A synthesis of 2-(1-acetoxyethyl) analogue **27** from nitro aldehyde **13** is outlined in Scheme III. The main problem in designing this synthesis was to create an aldehyde group at the 2-position for subsequent Grignard reaction, while protecting the existing 3-carboxaldehyde. Conversion of the 3-carboxaldehyde to a ketal was an obvious solution, but it proved to be more difficult than we had supposed. This aldehyde is deactivated by conjugation with the indole nitrogen, which means that mild conditions are insufficient for ketalization. Thus, **13** did not react with ethylene glycol and *p*-toluenesulfonic acid until a toluene solution was heated at reflux temperature. The product

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

Table I. Activities of Indoloquinones against Human Tumor Cell Lines[a]

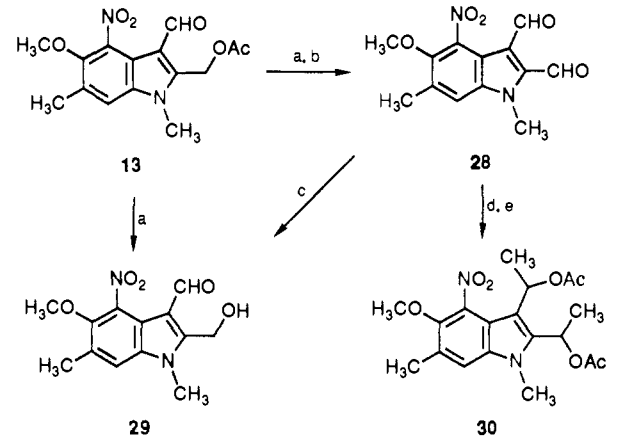
compd	IC_{50} values in μg/mL against cell lines						
	A549	B16-BN	B16-F10	HCT-116	Moser	SW1271	SW900
16			0.20	0.065	0.09	0.47	0.04
17			<0.03	<0.03	<0.03	0.14	<0.03
18	>3.1	14.0	>31	>31	12.8	>31	
19	1.6	9.5	13.3	3.7	3.1	7.9	
20	<0.02	0.27	0.39	0.065	0.035	0.73	
21	0.03	1.6	0.66	0.17	0.13	2.7	
mit C	0.47	3.6	1.5	1.1	2.8	8.1	0.24

[a] The assay used a crystal violet staining procedure. It is described in detail in Catino, J. J.; Francher, D. M.; Edinger, K. J.; Stringfellow, D. A. *Cancer Chemother. Pharmacol.* **1985**, *15*, 240. The stain was solublized with 0.2 mL of 0.1 M AcOH–EtOH (1:1 v/v) and optical densities were determined at 590 nm with a Dynatech MR 600 microliter plate reader. IC_{50} values were calculated by linear-regression analysis of absorption data. The vehicle was DMSO except for mitomycin C, which had DMSO/saline. Values for indoloquinolines represent an average of two experiments in each cell line and the mitomycin C values are averages of two to seven experiments, depending on the cell line. Abbreviations for the cell lines correspond to the following tumor types: A549, SW1271, and SW900 = human lung carcinoma; B16-BM and B16-F10 = murine melanoma; HCT-116 and Moser = human colon carcinoma.

(**22**) of this reaction resulted from decarbonylation rather than acetal formation. Similarly, decarbonylation occurred when **13** was treated with methanol and *p*-toluenesulfonic acid in refluxing toluene. In this case, the product (**23**) had also undergone exchange of methanol for the acetoxyl group (which is another demonstration of high reactivity for 2-substituents). Fortunately, we were able to prepare thioacetal **24** in 89% yield from **13**, ethanedithiol, and *p*-toluenesulfonic acid in methylene chloride at room temperature. Alkaline hydrolysis of the acetoxyl group followed by oxidation of the alcohol with pyridine chlorochromate gave the 2-carboxaldehyde **25**, which was converted into the corresponding 2-(1-acetoxyethyl)-indole-3-carboxaldehyde derivative **26** by treatment with methylmagnesium bromide followed by acetylation of the hydroxyl group and removal of the thioketal with mercuric chloride in acetonitrile–water containing calcium carbonate. This deprotection proved to be unreliable and the best yield obtained in this step was only 35%. The conversion of **26** to the final product **27** was accomplished by standard methods including catalytic hydrogenation of the nitro group, Fremy's salt oxidation of the resulting amine to a quinone, reduction of the aldehyde with sodium borohydride, and treatment of the resulting hydroxymethyl derivative with methyl isocyanate and triethylamine in methylene chloride. The overal yield for this conversion was 7.5%.

An alternative approach to the synthesis of **27** involved alkaline hydrolysis and oxidation with pyridine chlorochromate to give the indole-2,3-dicarboxaldehyde **28** (Scheme IV). Indole-2,3-dicarboxaldehydes are relatively rare, with only the parent compound[13] and its *N*-methyl derivative known.[14] The only information on the relative reactivity of the two carbonyl groups is the observation that the 2-carboxaldehyde reacted selectively with ethyl azidoacetate.[15] In the hope that the 3-carboxaldehyde group might be selectively reduced, we treated **28** with 9-borabicyclononane. The product **29**, however, resulted from selective reduction of the 2-carboxaldehyde group. The structure of **29** was confirmed by its formation from hydrolysis of **13**. No selectivity was observed in the reaction of dialdehyde **28** with a large excess of methylmagnesium bromide. Both aldehyde groups were converted into hydroxyethyl groups. The crude product was converted into its diacetate **30**, which was isolated in 17% yield. Treatment of **28** with fewer equivalents of methylmagnesium bromide gave no detectable products; only starting material was found.

Scheme IV[a]



[a] Reagents: (a) NH_4OH, CH_3CN; (b) PCC, CH_2Cl_2; (c) 9-BBN, THF; (d) MeMgBr, THF; (e) Ac_2O, py.

Table II. Activities of Indoloquinone **27** against Human Tumor Cell Lines[a]

compd	IC_{50} values in μg/mL	
	A549	HCT-116
27	0.075	0.060
27	0.065	0.060
mitC	0.015	0.015
mitC	0.080	0.010

[a] The assay used a tetrazolium staining procedure. It is described in detail in Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827. Abbreviations for cell lines are given in Table I.

Biology

The IC_{50} values for cytotoxic activity of the new indoloquinones against a panel of human tumor cell lines are compared with those of mitomycin C in Table I. Their activities are surprisingly good. Both the 5-methoxyindoloquinones (**16** and **17**) and the 5-aziridinoindoloquinones (**20** and **21**) are more potent than mitomycin C against every cell line. The 5-aminoindoloquinones (**18** and **19**), however, were less potent than mitomycin C. Compound **17**, which has two carbamate groups, is clearly the most potent one. In the pairs of compounds, **16**, **17** and **18**, **19**, the biscarbamates are more active than the acetoxy carbamates; however, the reverse is true for the pair 20, 21. The cytotoxic activity of 2-(acetoxyethyl) analogue **27** is compared separately against mitomycin C in Table II,

(13) Werner, W. *Chem.-Ztg.* **1974**, *98*, 616.
(14) Dupas, G.; Duflos, J. *J. Heterocycl. Chem.* **1980**, *17*, 93.
(15) Dupas, G.; Duflos, J.; Queguiner, G. *J. Heterocycl. Chem.* **1983**, *20*, 967.

Table III. Activity of Indoloquinones and Mitosenes against P388 Murine Leukemia[a]

compd	max effect: % T/C compd (mit C)	dose, km/kg	MED, mg/kg
16	105 (200)	51.2	
17	100 (200)	6.4	
18	105 (210)	25.6	
19	120 (210)	25.6	
20	114 (200)	12.8	
21	145 (210)	32.0	14.5
5	165 (229)	6.4	0.8
7	167 (228)	6.4	1.6
8	122 (224)	6.4	
9	144 (183)	51.2	0.8

[a] A tumor inoculum of 10^6 ascites cells was implanted in CDF_1 female mice. Six mice were used at each dose of the compound, given on day 1 only, and 10 control mice received saline. A control group of six mice at each dose in each experiment received mitomycin C. The optimal dose of mitomycin C is 3.2–4.8 mg/kg and its minimum effective dose is 0.2. MST = median survival time; max effect (% T/C) = MST treated/MST control × 100 at the optimal dose. MED = minimal effective dose (% T/C = 125). There were no survivors among the indoloquinone or mitosene treated mice. Mitomycin C, however, showed one or more survivors in certain experiments.

because a different and more sensitive assay method was used for it. It is about one-fourth as potent as mitomycin C.

Activities of the indoloquinone analogues in the P388 murine leukemia assay are given in Table III, with the activities of mitomycin C in the same experiments, where it was the positive control, given in parentheses. The indoloquinone activities should be compared on the basis of how each one relates to its mitomycin C control, rather than by direct comparison. However, the variations in mitomycin C activity are not large. Also included in Table III are the previously reported activities of four mitosenes (**5**, **7–9**) that closely resemble the indoloquinones.[11] They are important for evaluating the generality of any structure–activity relationships that might be found for the indoloquinones. The most obvious result in Table III is that the 5-methoxyindoloquinones, which had shown high potency in cell culture, were completely inactive in mice. One of the two 5-aminoindoloquinones (**19**), which was not very potent in cell culture, showed some prolongation of life in mice, although it was not quite high enough to meet the standard criterion for activity (T/C = 125). The one indoloquinone that can be considered active (T/C = 145) is 5-aziridinyindoloquinone **21**. It has activity nearly as good as some of the mitosenes, although all of these compounds are less active than mitomycin C. From the limited data in Table III, it appears that in both indoloquinones and mitosenes the biscarbamate functionality is superior to the acetoxy monocarbamate functionality. However, the clear superiority of the aziridinyl substituent in the indoloquinones is not apparent in the mitosenes. It was not possible to test compound **27** in the P388 assay because the lengthy synthesis (20 steps from 2,5-xylenol) did not provide sufficient sample.

Conclusions

The impressive activity of indoloquinones **16**, **17**, **20**, and **21** against cultures of human tumor cells probably can be attributed to their ability to give bifunctional alkylation of DNA. Why this superior activity does not extend to murine P388 leukemia is not clear; however, the most likely explanations are rapid metabolism or clearance and rapid reactivity of these indoloquinones. These suggestions are supported by the absence of host toxicity (weight loss or early deaths) at even the highest dose tested for compounds **16**, **18–21**. Indoloquinone **17** did reach a maximum tolerated dose at 0.4 mg/kg, but the compound did not demonstrate any antitumor activity; higher doses of this compound were toxic to the mice. Thus the absence of host toxicity at doses several fold higher than mitomycin C despite in vitro potency several fold greater than mitomycin C is indicative of rapid metabolism (elimination) or very rapid reactivity of the test agents.

Among the indoloquinones, the 5-methoxy analogues should be the most readily reduced for bioactivation, followed by the 5-aziridinyl analogues and then the 5-amino analogues. Polarographic half-wave potentials have not been measured for the indoloquinones, but they should be the same as those for the correspondingly substituted mitosenes, because the chromophores are identical. Thus, the methoxy analogues should have $E_{1/2}$ values of −0.40 V,[16] which is nearly the same as that of mitomycin C[17] (benzoquinone chromophore). The aziridinyl analogues should have $E_{1/2}$ values of −0.45 V and the amino analogues should have $E_{1/2}$ values of −0.54 V.[16] Aminoquinone derivatives in both the indoloquinone and mitosene series lack antitumor activity in mice, possibly because it is difficult for them to be reductively activated. The most readily reduced compounds, the methoxyquinones, have the best murine antitumor activity among the mitosenes, but they have the worst murine antitumor activity among the indoloquinones. This difference could be caused by nonspecific alkylation because of excessive chemical reactivity for the methoxyindoloquinones, as discussed in the introduction. Decreasing the ease of chromophore reduction by changing to the aziridinyl substituent might have brought the indoloquinones into a better range of chemical reactivity, thus affording improved murine antitumor activity. That the aziridinyl substituent does not enhance the antitumor activity of mitosenes can be rationalized by the fact that one of their two alkylating groups is a secondary carbon atom. They might require the more readily reduced methoxyquinone chromophore to balance the decreased alkylating ability. The better activity for biscarbamates over acetoxy monocarbamates in both series might result from differences in either their hydrophilicity or their ability to act as leaving groups. Although the results described above do not conclusively prove our starting hypothesis that the antitumor activity of indoloquinones can be improved by moderating their chemical reactivity, this line of thinking has led to analogues with impressive activity in human tumor cell lines and it has provided the first indoloquinone with murine antitumor activity.

Experimental Section

General Methods. Solvents were distilled prior to use. Solutions were concentrated under reduced pressure on a rotary evaporator. Thin-layer chromatography (TLC) was performed on precoated silica gel plates (Analtech), 20 cm × 10 cm × 250 μm for analytical and 20 × 20 × 0.2 cm for preparative separations, with the following solvent systems: (A) EtOAc–CH_2Cl_2 (2:8 v/v) and (B) EtOAc–CH_2Cl_2 (1:9 v/v). ^1H NMR spectra were recorded on either a 60-MHz Varian EM360L or a 90-MHz JEOL FX90Q spectrometer using $CDCl_3$ as solvent and TMS as internal standard; IR spectra were measured in KBr disks on a Beckman IR33 spectrophotometer. Microanalyses were determined by Desert Analytics, Tucson, AZ, and they were within ±0.4% of theoretical values unless stated otherwise. Melting points were measured on a Mel-Temp melting point apparatus and are un-

(16) Iyengar, B. S.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1986**, *29*, 1864.
(17) Iyengar, B. S.; Lin, H.-J.; Cheng, L.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 975.

corrected. Mass spectra were obtained on Varian 311 or Finnigan-MAT 90 mass spectrometers.

Methyl 1,6-Dimethyl-5-methoxyindole-2-carboxylate (11). A solution of 10 (5.0 g, 23 mmol) in dry benzene (275 mL) was treated with NaH (1.92 g of 57% oil dispersion, 46 mmol). The suspension that formed was heated at reflux and treated dropwise with dimethyl sulfate (7 mL, 74 mmol). The mixture was stirred at reflux for 2 h after the addition was complete. It was then cooled and diluted with water. The organic layer was separated, washed with water, and concentrated under reduced pressure to give a sticky, off-white solid. An ether solution of this solid was filtered through a mixture of magnesium sulfate and activated charcoal. The filtrate was concentrated and the solid residue was crystallized from methanol. A second crop was obtained by concentrating the filtrate. The total yield of 11 was 4.5 g (85%) of white crystals: mp 110–112 °C; IR (KBr) 1700, 1500, 1470, 1250–1200, 840–820 cm^{-1}; NMR ($CDCl_3$) δ 2.34 (s, 3), 3.83 (s, 3), 3.87 (s, 3), 4.0 (s, 3), 6.93 (s, 1), 7.13 (br s, 2) ppm. Anal. ($C_{13}H_{15}NO_3$) H, N, C: calcd, 66.94; found, 67.45.

1,6-Dimethyl-2-(hydroxymethyl)-5-methoxyindole Acetate (12). A solution of 11 (1.9 g, 8.2 mmol) in ether (125 mL) was treated with 0.6 g of lithium aluminum hydride. The mixture was stirred at reflux temperature for 2 h, cooled, diluted with EtOAc, and extracted with H_2O. The aqueous phase was extracted with a mixture of Et_2O and EtOAc, and the combined organic layers were dried ($MgSO_4$) and concentrated to give 1.3 g of crude alcohol. Without further purification, this product was stirred overnight with Ac_2O (20 mL) and pyridine (20 mL). The mixture was poured into ice water and the precipitate that formed was dissolved in EtOAc. This solution was washed twice with H_2O, dried ($MgSO_4$), and concentrated. The oily residue gave yellow crystals on treatment with ether–hexane. Recrystallization from the same solvents afforded 1.26 g (70%) of 12: mp 108–112 °C; IR (KBr) 1730, 1470, 1240, 1200, 1080, 1000, 940, 815 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3), 2.42 (s, 3), 3.73 (s, 3), 3.88 (s, 3), 5.23 (s, 2), 6.77 (s, 1), 6.97 (s, 1), 7.06 (s, 1) ppm. Anal. ($C_{14}H_{17}NO_3$) C, H, N.

1,6-Dimethyl-2-(hydroxymethyl)-5-methoxy-4-nitroindole-3-carboxaldehyde Acetate (13). To DMF (1 mL) chilled in an ice bath was added $POCl_3$ (0.4 mL). The mixture was stirred for 15 min and treated with a solution of 12 (1.0 g) and pyridine (2 mL) in CH_2Cl_2 (20 mL). After 1 h it was poured into saturated NaOAc solution (200 mL) at 0 °C and stirred for 3 h. The organic layer was separated, washed with 3 N HCl and water, dried ($MgSO_4$), and concentrated. Recrystallization of the residue from CH_2Cl_2–E_2O (1:1) and hexane gave 725 mg of the aldehyde. Without further purification, this product was dissolved in acetic acid (15 mL) and treated with 0.7 mL of 90% HNO_3. After 30 min the solution was poured into water. The solid that formed was purified by chromatography on silica gel with $CHCl_3$ as solvent. Recrystallization of the product from methanol gave 770 mg (62%) of 13 as yellow crystals: mp 223–230 °C dec; IR (KBr) 1750, 1670, 1540, 1220, 1010–955 cm^{-1}; NMR ($CDCl_3$) δ 2.09 (s, 3), 2.47 (s, 3), 3.83 (s, 3), 3.87 (s, 3), 5.55 (s, 2), 7.26 (s, 1), 10.1 (s, 1) ppm. Anal. ($C_{15}H_{16}N_2O_6$) C, H, N.

1,6-Dimethyl-4,7-dioxo-2-(hydroxymethyl)-5-methoxyindole-3-carboxaldehyde Acetate (14). A suspension of finely ground 13 in ethanol (250 mL) was stirred with tin metal (3.0 g, 30-mesh granules) and 3 N HCl (65 mL) for 2 h. The resulting yellow solution was decanted from excess tin and treated dropwise with a saturated solution of $NaHCO_3$ until a white precipitate formed. A $CHCl_3$ extract (100 mL × 3) of the mixture was washed with H_2O (100 mL × 2), dried ($MgSO_4$), and concentrated. The crude amine product was dissolved in acetone (180 mL) and treated with a solution of potassium nitrosodisulfonate (4.5 g) in pH 6.0 phosphate buffer (180 mL of 3.0 M NaH_2PO_4). The mixture was stirred 2 h, diluted with H_2O, and extracted with CH_2Cl_2. This extract was washed with 5% $NaHCO_3$ solution (200 mL × 2) followed by H_2O (200 mL × 2), dried (Na_2SO_4), and concentrated to give an orange solid. Column chromatography of this crude product on silica gel (70–270 mesh) with $CHCl_3$ as solvent gave, after concentration of the major orange band, 548 mg (58%) of 14 as orange crystals: mp 127–128 °C dec; IR (KBr) 3020, 1740, 1675, 1640, 1260, 1240 cm^{-1}; NMR ($CDCl_3$) 1.94 (s, 6), 3.97 (s, 6), 5.47 (s, 2), 10.53 (s, 1) ppm. Anal. ($C_{15}H_{16}NO_6$) C, H, N.

4,7-Dioxo-3-(hydroxymethyl)-5-methoxy-1,2,6-trimethylindole (15). A solution of 14 (25 mg, 0.08 mmol) in 10 mL of methanol was deaerated by bubbling N_2 for 30 min. Sodium borohydride (30 mg, 0.8 mmol) was added and the mixture was stirred under N_2 for 30 min, during which it turned colorless. Acetone (10 mL) was added to destroy the excess borohydride and the mixture was exposed to air for 15 min. The solvents were removed under reduced pressure, and the residue was purified by preparative TLC with solvent system B. The major orange band was extracted with MeOH–CH_2Cl_2 and this extract was filtered and concentrated to give 10 mg of 15 as an orange solid that had an identical melting point (124–141 °C) and NMR spectrum [($CDCl_3$) δ 1.97 (s, 3), 2.23 (s, 3), 3.87 (s, 3), 4.0 (s, 3), 4.60 (br s, 2)] as the previously described material: mp 124–145 °C; NMR ($CDCl_3$) δ 1.93 (s, 3), 2.23, (s, 3), 3.87 (s, 3) 4.0 (s, 3), 4.58 (br s, 2).[3]

2,3-Bis(hydroxymethyl)-1,6-dimethyl-5-methoxy-4,7-dioxoindole 2-Acetate 3-Methylcarbamate (16). A solution of 14 (200 mg, 0.66 mmol) under N_2 was cooled to −10 °C and treated with 9-borabicyclo[3.3.1]nonane in THF (2.6 mL of 0.5 M solution, 1.3 mmol). The mixture was stirred and allowed to come to room temperature over 30 min. It was then cooled in an ice bath and treated with 30% H_2O_2 (10 mL added in 1-mL portions). After 10 min, H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (75 mL × 3). This extract was dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC with system B. The major orange band was removed and extracted with MeOH–CH_2Cl_2. This extract was filtered and concentrated to give 46.5 mg (43%) of the 3-(hydroxymethyl) compound as orange crystals: mp 110–115 °C; IR (KBr) 3300–3100, 1740, 1640, 1240 cm^{-1}; NMR ($CDCl_3$) δ 1.94 (s, 6), 3.94 (s, 6), 4.65 (s, 2), 5.05 (s, 2) ppm. This product was converted directly into the corresponding methylcarbamate. A solution of it in 10 mL of CH_2Cl_2 at 5 °C was treated with 0.25 mL of Et_3N followed by 0.25 mL of methylisocyanate. After being stirred at 5 °C for 30 min and at ambient temperature for 16 h, the mixture was poured into 5 mL of water with stirring. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic layers were dried ($MgSO_4$) and concentrated. The solid residue was purified by preparative TLC on silica gel with solvent system A. A MeOH–CH_2Cl_2 extract of material from the main band (orange) was filtered and concentrated to afford 42 mg (76%) of 16 as orange crystals: mp 174–179 °C dec; IR (KBr) 3360, 1720, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.76 (s, 3), 2.06 (s, 3), 3.97 (s, 3), 4.03 (s, 3), 5.29 (s, 2), 5.32 (s, 2), 5.6 (br s, 1, exchanges with D_2O) ppm. The analytical sample contained 1.0 mol of CH_3OH. Anal. ($C_{17}H_{20}N_2O_7 \cdot CH_4O$) C, H; N: calcd, 7.06; found, 6.60.

1,6-Dimethyl-2,3-bis(hydroxymethyl)-5-methoxy-4,7-dioxoindole Bis(methylcarbamate) (17). A solution of 16 (100 mg) in 10 mL of MeOH containing 1 mL of 0.1 N NH_4OH was stirred for 1 h. TLC indicated complete reaction of the starting material. The solution was concentrated under reduced pressure and the residual orange solid was dried under high vacuum for 3–4 h. Without further purification, it was dissolved in CH_2Cl_2, chilled to 5 °C, and treated with Et_3N (0.5 mL) followed by methyl isocyanate (0.5 mL). The mixture was stirred at 5 °C for 30 min and at ambient temperature for 16 h, diluted to 50 mL with CH_2Cl_2, and washed with 10 mL of water. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The solid residue was purified by preparative TLC on silica gel using solvent system A. A MeOH–CH_2Cl_2 extract of the main band (orange) was filtered and concentrated to give 47.5 mg (41%) of 17 as orange crystals: mp 185–188 °C dec; IR (KBr) 3360, 3310, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (s, 3), 2.75 (d, 3), 2.80 (d, 3), 3.97 (s, 3), 4.02 (s, 3), 4.5–4.9 (br s, 2, exchanges with D_2O), 5.27 (s, 2), 5.33 (s, 2) ppm. Anal. ($C_{17}H_{21}N_3O_7 \cdot 0.25\ H_2O$) C, H, N.

5-Amino-2,3-bis(hydroxymethyl)-1,6-dimethyl-4,7-dioxoindole 2-Acetate 3-Methylcarbamate (18). A solution of 16 (50 mg) in methanol (10 mL) was treated with excess ammonia. After 36 h the mixture was concentrated under reduced pressure and the residue was purified by TLC on silica gel with solvent system A. From the main band (purple) was obtained a solid that gave, after crystallization from MeOH–Et_2O, 9.6 mg (21%) of 18 as purple crystals: mp 190–200 °C dec; IR ($CDCl_3$) 3400, 3320, 3270, 1710, 1690 cm^{-1}. The NMR spectrum was identical with

that of **16** except that the peak at 4.03 (s, 3, methoxyl) was replaced by a broad singlet at 4.6–5.0 for two protons (NH_2). The analytical sample contained 0.25 mol of MeOH. Anal. ($C_{16}H_{19}N_3O_6 \cdot 0.25CH_4O$) C, H, N.

5-Amino-2,3-bis(hydroxymethyl)-1,6-dimethyl-4,7-dioxoindole Bis(methylcarbamate) (19). This compound was prepared by the procedure described for **18**. From 50 mg of **17** was obtained, after recrystallization from MeOH, 16.2 mg (34%) of **19** as purple crystals: mp 94–98 °C dec; IR (KBr) 3360–3250, 1690 cm^{-1}. The NMR spectrum was identical with that of **17** except that the peak at 4.01 (s, 3, methoxyl) was replaced by a singlet at 4.7–5.1 for two protons. Anal. ($C_{16}H_{20}N_4O_6 \cdot 0.75\ H_2O$) C, N; H: calcd, 5.74; found, 6.46.

5-Aziridinyl-2,3-bis(hydroxymethyl)-1,6-dimethyl-4,7-dioxoindole 2-Acetate 3-Methylcarbamate (20). A solution of **16** (50 mg) in CH_2Cl_2 (10 mL) was treated with excess ethylenimine. After 3 h, the mixture was concentrated under reduced pressure and the residue was purified by TLC on silica gel with solvent system A. From the main band (purple) was obtained a solid that gave, after recrystallization from MeOH, 17.0 mg (33%) of **20** as purple crystals: mp 195–201 °C dec; IR (KBr) 3350, 1730, 1710 cm^{-1}. The NMR spectrum was identical with that of **16**, except that the peak at 4.03 (s, 3, methoxyl) was preplaced by a singlet at 2.30 for four protons (aziridine). The analytical sample was recrystallized from Et_2O–toluene. It contained 1.0 mol of Et_2O and 0.8 mol of toluene. Anal. ($C_{18}H_{21}N_3O_6 \cdot C_4H_6O \cdot 0.8C_7H_8$) C, H, N.

5-Aziridinyl-1,6-dimethyl-2,3-bis(hydroxymethyl)-4,7-dioxoindole Bis(methylcarbamate) (21). This compound was prepared by the procedure described for **20**. From 50 mg of **17** was obtained, after recrystallization from MeOH–Et_2O, 10.8 mg (21%) of **21** as purple crystals: mp 190–200 °C dec; IR (KBr) 3400, 3320, 3270, 1710, 1690 cm^{-1}. The NMR spectrum was identical with that of **17**, except that the peak at 4.02 (s, 3, methoxyl) was replaced by a singlet at 2.30 for four protons (aziridine). The analytical sample was crystallized from Et_2O–toluene. It contained 1.0 mol of Et_2O and 0.5 mol of toluene. Anal. ($C_{19}H_{22}N_4O_6 \cdot C_4H_6O \cdot 0.5C_7H_8$) C, H, N.

2-(Acetoxymethyl)-1,6-dimethyl-5-methoxy-4-nitroindole (22). A solution of 11 (100 mg), ethylene glycol (10 mL), and *p*-toluenesulfonic acid (10 mg) in dry benzene (100 mL) was heated at reflux for 1 h, cooled, and extracted with 1 N NaOH (50 mL × 2) followed by H_2O (50 mL × 2). The organic layer was dried (Na_2SO_4) and concentrated and the crude solid residue was purified by column chromatography on silica gel with CH_2Cl_2 as solvent. Concentration of the eluate from the major yellow band gave **22** as yellow crystals: mp 85–89 °C; IR (KBr) 1730, 1510, 1220 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3), 2.45 (s, 3), 3.7 (s, 3), 3.85 (s, 3), 5.25 (s, 2), 6.81 (s, 1), 7.3 (s, 1). Anal. ($C_{14}H_{16}N_2O_5$) C, H; N: calcd, 9.58; found, 9.09.

1,6-Dimethyl-5-methoxy-2-(methoxymethyl)-4-nitroindole (23). A solution of 11 (100 mg) in toluene (50 mL) containing dry methanol (5 mL) and *p*-toluenesulfonic acid (20 mg) was heated at reflux for 45 min, cooled, and extracted with 1 N NaOH (50 mL × 2) followed by H_2O (50 mL × 2). The organic layer was dried (Na_2SO_4) and concentrated. The solid residue was purified by column chromatography on silica gel with CH_2Cl_2 as solvent. Concentration of eluate from the major yellow band gave **23** as yellow crystals: mp 72–75 °C; IR (KBr) 1510, 1330, 1100 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3), 3.3 (s, 3), 3.75 (s, 3), 3.90 (s, 3), 4.50 (s, 2), 6.7 (s, 1), 7.31 (s, 1); EIMS M^+ 264. The analytical sample was recrystallized from acetone–hexane. It contained 0.1 mol of acetone. Anal. ($C_{13}H_{16}N_2O_4 \cdot 0.1C_3H_6O$) C, H, N.

1,6-Dimethyl-2-(hydroxymethyl)-5-methoxy-4-nitroindole-3-carboxaldehyde Ethylene Dithioacetal Acetate (24). A solution of **13** (2.0 g, 6.25 mmol) in CH_2Cl_2 (100 mL) was treated with 1,2-ethanedithiol (4.0 mL) and *p*-toluenesulfonic acid monohydrate (100 mg). The mixture was stirred for 1 h and then treated with saturated sodium bicarbonate solution (150 mL). The organic layer was separated, washed with water (100 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil that solidified on treatment with ice-cold MeOH (10 mL). After filtration and drying under vacuum, 2.2 g (89%) of **24** was obtained as yellow solid, mp 203–205 °C dec: IR (KBr) 1730, 1520, 1370, 1220 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (s, 3), 2.5 (s, 3), 3.2–3.6 (m, 4), 3.7 (s, 3), 3.9 (s, 3), 5.6 (s, 2), 5.8 (s, 1), 7.3 (s, 1) ppm. The analytical sample was recrystallized from acetone–hexane. It contained 0.3 mol of acetone. Anal. ($C_{17}H_{20}N_2O_5S_2 \cdot 0.33\ C_3H_8O$) C, H, N.

1,6-Dimethyl-5-methoxy-4-nitroindole-2,3-dicarboxaldehyde 3-Ethylene Dithioacetal (25). A solution of **24** (2.0 g) in acetonitrile (150 mL) and 1 N NaOH (100 mL) was stirred 75 min and then diluted with 400 mL of ice-cold water. The yellow precipitate was washed with cold water (25 mL × 2) and dried. This procedure gave 1.69 g (86%) of crude 2-(hydroxymethyl) derivative: mp 186–190 °C; IR (KBr) 3490, 1520, 1370 cm^{-1}; NMR δ 2.42 (s, 3), 3.32–3.61 (m, 4), 3.75 (s, 3), 3.85 (s, 3), 5.1 (s, 2), 5.83 (s, 1), 7.22 (s, 1) ppm. A mixture 1.5 g (4.2 mmol) of this product, dry CH_2Cl_2 (100 mL), and pyridinium chlorochromate (1.1 g, 5.1 mmol) was stirred for 2 h. The resulting dark brown mixture was applied to a Florisil column, which was washed with CH_2Cl_2 until TLC showed no more fast-moving spots. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CH_2Cl_2 as solvent. Concentration of eluate from the main band gave 0.54 g (36%) of **25** as yellow solid: mp 191–194 °C dec; IR (KBr) 1670, 1530, 1390 cm^{-1}; NMR ($CDCl_2$) δ 2.5 (s, 3), 3.3–3.7 (m, 4), 3.8 (s, 3), 3.9 (s, 3), 5.8 (s, 1), 7.3 (s, 1), 11.0 (s, 1) ppm. Anal. ($C_{15}H_{16}N_2O_4S_2$) C, H, N.

2-(1-Acetoxyethyl)-1,6-dimethyl-5-methoxy-6-nitroindole-3-carboxaldehyde (26). To an ice-cooled solution of **25** (540 mg, 1.53 mmol) in dry THF (20 mL) was added methylmagnesium bromide (0.8 mL of 3 M solution, 2.3 mmol). The mixture was stirred at ice-bath temperature for 0.5 h and at ambient temperature for 1.5 h. An ice-cold solution of saturated NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (75 mL × 4). The combined extract was dried (Na_2SO_4) and concentrated under reduced pressure and the residual solid was purified by column chromatography on silica gel with CH_2Cl_2 as solvent. Concentration of eluate from the major band gave a pale yellow solid. This solid was dissolved in dry pyridine (2 mL) and the solution was cooled in an ice bath and treated with acetic anhydride (1 mL). After being stirred at ice-bath temperature for 1 h and at ambient temperature for 15 h, the solution was poured into ice water (100 mL) and extracted with CH_2Cl_2 (50 mL × 4). The combined extract was washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give 326 mg (52%) of the 1-acetoxyethyl derivative as pale yellow crystals: mp 162–165 °C; IR (KBr) 1740, 1525, 1370, 1220 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (d, 3), 2.06 (s, 3), 2.65 (s, 3), 3.3–3.8 (m, 4), 3.85 (s, 3), 4.0 (s, 3), 6.4 (s, 1), 6.95 (q, 1), 7.2 (s, 1) ppm. This compound was converted directly into **26**. A solution of 300 mg (0.73 mmol) of it in acetonitrile–water (30 mL, 4:1 v/v) was stirred with mercury(II) chloride (400 mg, 1.47 mmol) and calcium carbonate (150 mg, 1.5 mmol) for 4 h, at which time TLC indicated that no starting material remained. The mixture was filtered, and the solids were washed with acetonitrile (5 mL × 2). The combined organic layers were washed with saturated $NaHCO_3$ solution (25 mL × 2) followed by H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give 85 mg (35%) of **25** as dark yellow solid: mp 105–112 °C; IR (KBr) 1740, 1665, 1530–1540, 1370, 1220 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (d, 3), 2.1 (s, 3), 2.65 (s, 3), 3.8 (s, 3), 4.1 (s, 3), 6.5 (q, 1), 7.8 (s, 1), 10.4 (s, 1) ppm; exact mass calcd for $C_{16}H_{19}N_2O_6$ 334.1164, obsd 334.1125.

2-(1-Acetoxyethyl)-1,6-dimethyl-3-(hydroxymethyl)-5-methoxyindole-4,7-dione Methylcarbamate (27). A solution of **26** (60 mg) in methanol (75 mL) was treated with a small amount of 10% Pd–C catalyst and the mixture was shaken in a H_2 atmosphere at 30 psi for 90 min. The mixture was filtered and concentrated to give the 4-amino derivative as yellow solid, which was converted directly into the corresponding 4,7-dione. Thus, a solution of the yellow solid in acetone (25 mL) was added to a solution of potassium nitrosodisulfonate (500 mg) in 20 mL of 3.0 M NaH_2PO_4. After 2 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2. This extract was washed with 5% $NaHCO_3$ solution and with water, dried (Na_2SO_4), and concentrated to give an orange solid. This solid was purified by column chromatography on silica gel with $CHCl_3$ as solvent. Concentration of eluate from the main orange band gave a small amount of solid whose NMR spectrum ($CDCl_3$) showed no aromatic proton but showed an aldehyde proton at δ 10.5.

Without further purification, the indoloquinone aldehyde was dissolved in CH_3OH–CH_2Cl_2 (1:4 v/v), and N_2 was bubbled

through the solution for 15 min. A solution of sodium borohydride (30 mg) in water (2 mL) was added and the mixture was stirred vigorously for 40 min. Acetone (5 mL) was added, the solvents were removed under reduced pressure, and the residual solid was purified by preparative TLC with solvent system B. A MeOH–CH_2Cl_2 extract of the main orange band was filtered and concentrated to give 10 mg of the 3-(hydroxymethyl) derivative as an orange solid whose NMR spectrum showed a two-proton singlet at δ 4.6 (3-CH_2OH), but no aldehyde proton. This product was converted directly to the methylcarbamate by treatment with methyl isocyanate. It was dissolved in dry CH_2Cl_2 (5 mL), cooled in an ice bath, and treated with Et_3N (0.2 mL) followed by methyl isocyanate (0.2 mL). The mixture was stirred 1.5 h at ice-bath temperature and 18 h at ambient temperature and then diluted with CH_2Cl_2. The resulting solution was washed with H_2O (5 mL), the organic layer was separated, and the solvent was removed under reduced pressure. Purification of the residue by preparative TLC using solvent system B gave 5 mg (12% from **26**) of **27** as an orange solid: mp 82–88 °C dec; IR (KBr) 3360, 1740, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (d, 3, J = 7 Hz), 1.95 (s, 3), 2.06 (s, 3), 2.73 (d, 3, J = 3.5 Hz), 3.99 (s, 3), 4.06 (s, 3), 4.61 (br s, 1), 5.35 (s, 2), 6.20 (q, 1, J = 7 Hz) ppm; EIMS M^+ 378, $M^+ - CH_2CO$ 336, $M^+ - CH_3CO$ 335, $M^+ - CH_3NCO$, 321, $M^+ - CH_3NHCO_2H$ 303, $M^+ - CH_3NCO$ and CH_3CO_2H, 261; exact mass calcd for $C_{18}H_{22}N_2O_7$ 378.1427, obsd 378.1404.

1,6-Dimethyl-5-methoxy-4-nitroindole-2,3-dicarboxaldehyde (28). A solution of **13** (100 mg, 0.31 mmol) in THF (60 mL) was stirred with 0.5 M NH_4OH (2 mL) for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by preparative TLC with solvent system B. This procedure gave the 2-(hydroxymethyl) derivative as yellow crystals. It was converted directly to the dicarboxaldehyde. Thus, a solution of it in dry CH_2Cl_2 (60 mL) was treated with pyridinium chlorochromate (180 mg, 0.84 mmol) and the mixture was stirred for 3 h. The resulting brown solution was filtered through Florisil, the Florisil bed was washed with CH_2Cl_2 (3 × 25 mL), and the combined organic solutions were concentrated under reduced pressure. Purification of the crystalline residue by preparative TLC with solvent system B gave 50 mg (56%) of **28** as yellow crystals: mp 137–141 °C dec; IR (KBr) 2950, 1675, 1530, 1320 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (s, 3), 3.93 (s, 3), 4.13 (s, 3), 7.47 (s, 1), 10.36 (s, 1), 10.70 (s, 1) ppm. Anal. ($C_{13}H_{12}N_2O_5$) C, H; N: calcd, 10.14; found, 9.52.

1,6-Dimethyl-2-(hydroxymethyl)-5-methoxy-4-nitroindole-3-carboxaldehyde (29). A. Reduction of 28. A solution of **28** (10 mg, 0.036 mmol) in dry THF (15 mL) under N_2 was cooled to −10 °C and treated with 9-borabicyclo[3.3.1]nonane (0.2 mL of 0.5 M solution in THF, 0.1 mmol). After 1 h, 30% hydrogen peroxide (3 mL) was added dropwise at 0 °C. Water (50 mL) was added and the resulting solution was extracted with CH_2Cl_2 (20 mL × 3). This extract was dried (Na_2SO_4) and concentrated under reduced pressure. The solid residue was purified by preparative TLC with solvent system B. Extraction of the major yellow band with MeOH–CH_2Cl_2 followed by filtration and concentration gave 4 mg (39%) of **29** as a bright yellow solid: mp 172–175 °C; IR (KBr) 3300–3400, 1660 cm^{-1}; UV (MeOH) 215.5, 247.2, 302.2 nm (lit.[17] 215.0, 248, 298 nm); NMR ($CDCl_3$) δ 1.6 (br s, 1), 2.5 (s, 3), 3.84 (s, 3), 3.90 (s, 3), 4.94 (s, 2), 7.35 (s, 1), 9.89 (s, 1) ppm.

B. Hydrolysis of 13. A solution of **13** (20 mg) in 1 M NH_4OH in MeOH (10 mL) was stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue was purified by preparative TLC with solvent system B. A MeOH–CH_2Cl_2 extract of the main yellow band, followed by filtration and concentration gave 12 mg (69%) of **29** as bright yellow solid had an identical melting point and IR and UV spectra as the product prepared by reduction of **28**. The two samples had the same R_f in system B. An analytical sample was recrystallized from acetone. Anal. ($C_{13}H_{14}N_2O_5 \cdot 0.5\ C_3H_6O$) C, H, N.

2,3-Bis(1-acetoxyethyl)-1,6-dimethyl-5-methoxy-4-nitroindole (30). A solution of **28** (50 mg, 0.18 mmol) in 10 mL of dry THF under N_2 (10 mL) was cooled in an ice bath and treated with 3.0 M methylmagnesium bromide solution in THF (150 μL, 45 mmol). The mixture was stirred at 5 °C for 30 min and at room temperature for 1.5 h. An ice cold saturated NH_4Cl solution was added and the resulting mixture was extracted with CH_2Cl_2 (75 mL × 3). The combined extract was washed with H_2O, dried (Na_2SO_4), and concentrated to give a pale yellow residue. Dry pyridine (1 mL) was added and the solution was cooled in an ice bath and treated with acetic anhydride (0.5 mL). The mixture was stirred for 1 h at 5 °C and for 14 h at room temperature and then poured into ice-cold H_2O (100 mL). A CH_2Cl_2 extract (30 mL × 3) of the resulting mixture was washed with 5% HCl (25 mL × 2) and with H_2O (25 mL × 2), dried (Na_2SO_4), and concentrated under reduced pressure to give 12 mg (17%) of **30** as pale yellow crystals: mp 69–72 °C dec; IR (KBr) 1730, 1520, 1360, 1225 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (d, 6), 2.10 (s, 6), 2.50 (s, 3), 3.90 (s, 6), 5.0–5.4 (m, 1), 6.1–6.6 (m, 1), 7.3 (s, 1) ppm; FABMS (glycerol) MH^+ + glycerol 485, MH^+ 392.2, $M^+ - CH_3CO$ 349, $M^+ - CH_3CO_2H$ 333, $MH^+ - 2CH_3CO_2H$ 273. The analytical sample was recrystallized from toluene. It contained 0.25 mol of toluene. Anal. ($C_{19}H_{24}N_2O_7 \cdot 0.25C_7H_8$) C, H, N.

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