Mitomycin C and Porfiromycin Analogues with Substituted Ethylamines at Position 7

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A series of 7-(2-substituted-ethyl)amino analogues of mitomycin C and porfiromycin was prepared and screened in standard antitumor systems. Certain of these analogues showed better activity than mitomycin C against P-388 leukemia, L-1210 leukemia, and/or B-16 melanocarcinoma in mice. Compounds also were tested for their leukopenic effects in mice, the limiting toxicity of mitomycin C. Some of them were less leukopenic and some were more leukopenic than this clinical agent. No statistically significant correlations could be made between physicochemical properties and antitumor activities of the analogues.

In the preceding article in this series, we defined the goal of mitomycin analogue development as the preparation of compounds that are at least as potent and efficaceous as mitomycin C in P-388 leukemia but which cause significantly less leukopenia. New 7-substituted compounds were chosen because position 7 controls the reduction of the quinone ring, thus offering a chance to gain some selectivity between normal cells and certain cancer cells. In this article, a variety of structural types were explored as substituents on the 7-amino group of mitomycin C and porfiromycin. A number of new lead compounds were identified as the targets for future analogue development, and preliminary structure–activity relationships were considered.[1]

One of the structural types that showed a good potential for analogue development was the substituted ethylamine at position 7. Although this type does not have an easily reducible quinone, certain individual compounds had good activity against mouse leukemias. We had prepared two different types of substituted ethylamines: the 2-phenylethylamine analogue of mitomycin C (**18**) and the 2-chloroethylamine analogues of mitomycin C (**2**) and porfiromycin (**3**). The former type was as effective as mitomycin C in prolonging the life span of mice bearing P-388 leukemia, although it was somewhat less potent than mitomycin C. The latter type showed some antitumor activity, but the two examples were not as potent or efficaceous as mitomycin C.[1] Examples of related compounds in the literature were limited to the 2-hydroxyethylamino analogue of mitomycin C (**5**), which was active against sarcoma-180[2] but inactive against L-1210 leukemia,[3] and the parent 7-ethylamino analogue (**1**), which was active in the sarcoma-180 and Hirosaki ascites sarcoma assays.[2,4]

Our approach to analogue development was to prepare an extended series of compounds in which the 2-position of the ethylamino group was substituted with a variety of different functional groups. These groups were chosen to give compounds with a wide range of lipophilicity. The resulting analogues were tested for activity against P-388 leukemia and for the production of leukopenia in mice, and then structure-activity correlations were attempted. The new analogues are listed in Table I. They were prepared by our previously published method involving treatment of a methanol solution of mitomycin A or *N*-methylmitomycin A with excess amine.[1] If the amine was supplied as its hydrochloride, excess triethylamine was added to compete for the hydrogen chloride. When ethylenediamine was used, the desired blue product **13** appeared initially (TLC evidence) but soon disappeared to be replaced by an orange substance. A satisfactory preparation of **13** was obtained by using only 1 equiv of ethylenediamine in methylene chloride solvent. It was necessary to carefully purify the products of all reactions by preparative-layer chromatography; otherwise, traces of the highly potent and toxic mitomycin A could influence the testing results. Table I also gives the yields, melting points, and NMR data for the newly introduced 7-substituents. In all cases, the peak at δ 4.02 for the 7-methoxy group of the starting material was absent. As reported previously, certain mitomycin analogues adhered tenaciously to solvent, even under high vacuum.[1] They could not be heated because of instability. Thus, some of the elemental analyses must be corrected for the presence of solvent. These solvates are indicated in Table I. In addition to the compounds listed in Table I, the known ethylamino (**1**) and 2-hydroxyethylamino (**5**) analogues were prepared by the literature method for comparison testing in our own assays.

Table II shows the activities of the 7-(ethylamino)mitosanes against P-388 leukemia in mice. The assays were not run concurrently, but each compound was standardized against Mitomycin C in the same assay. Therefore, compounds should not be directly compared with each other but compared on the basis of how each one related to mitomycin C. This procedure is necessary because of the substantial variation in the maximum therapeutic effect of mitomycin C (**21**) from one experiment to another. From Table II it is evident that three compounds, **4**, and **8** and **14**, are clearly superior to mitomycin C in prolonging the life span of mice bearing P-388 leukemia. Compounds **5**, **16**, **13**, and **18** are approximately equal to mitomycin in this respect. Only **8** is equal to mitomycin C in potency, as measured by the minimum effective dosage for T/C $\geq$ 125%. The therapeutic ratios (OD/MED) of compounds **1**, **8**, **14**, and **15** are superior to that of mitomycin C, and for compounds **4**, **5**, **12**, **16**, **18**, and **19**, they are equal to that of mitomycin C. Complete details of the P-388 assay are given as supplementary material (see paragraph at the end of paper concerning supplementary material).

In the assay for leukopenia, compounds **2** and **16** are less leukopenic than mitomycin C at their optimal doses. Compounds **4**, **6**, and **15** are more leukopenic than mitomycin C, and the remaining compounds are comparable.

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(1) Iyengar, B. S.; Lin, H. J.; Cheng, L.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 975.
(2) Oboshi, S.; Matsui, M.; Ishii, S.; Masago, N.; Wakaki, S.; Uzu, K. *Gann* **1967**, *58*, 320.
(3) Kojima, R.; Driscoll, J.; Mantel, N.; Goldin, A *Cancer Chemother. Rep.* **1972**, *3*, 121.
(4) Usubuchi, I.; Sobajima, Y.; Hongo, T.; Kawaguchi, T.; Sugawara, M.; Matsui, M.; Wakaki, S.; Uzu, K. *Gann* **1967**, *58*, 307.

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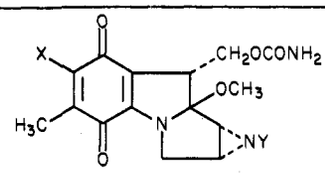
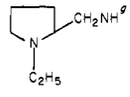
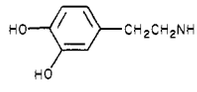
Table I. Properties of the 7-(Ethylamino)mitosanes[a]



no.	X	Y	yield, %	recrystn solvents	solvent impurity	mp, °C	^{1}H NMR signals for the new substituent; signals for the solvent impurity, δ[b]
1	CH_3CH_2NH	H	ref 2				
2	$ClCH_2CH_2NH$	H	ref 1				
3	$ClCH_2CH_2NH$	CH_3	ref 1				
4	FCH_2CH_2NH[c]	H	74	$CHCl_3$-CH_3OH		>340 dec	3.3-3.9 (m, 2), 4.2 (t, 2), 6.5 (br s, 1)
5	$HOCH_2CH_2NH$	H	ref 2				
6	$CH_3OCH_2CH_2NH$	H	73	CH_2Cl_2-CH_3OH		106-109 dec	3.42 (s, 3), 3.5-3.9 (br s, 4), 6.27-6.77 (br s, 1)
7	$(CH_3O)_2CHCH_2NH$	H	83	CH_2Cl_2-CH_3OH		>220 dec	3.45 (s, 6), 3.33-3.93 (m, 2), 4.33-4.85 (br s, 1), 6.15-6.66 (br s, 1)
8	$HSCH_2CH_2NH$	H	44	CH_2Cl_2-CH_3OH	$0.5CH_2Cl_2$	152-154 dec	(Me_2SO-d_6) 2.53-3.10 (br s, 4), 7.30-7.50 (br s, 1); 5.55 (s)
9	$HSCH_2CH_2NH$	CH_3	54	CH_2Cl_2-CH_3OH		85-87 dec	2.57-3.10 (br s, 4), 6.20-6.93 (br s, 1)
10	$C_2H_5SCH_2CH_2NH$[d]	H	73	CH_2Cl_2-CH_3OH	$0.5CH_3OH$	103-106 dec	1.27 (t, 3), 2.40-2.9 (m, 4), 3.4-3.93 (m, 2), 6.56 (t, 1); 3.33-3.43 (br s), 4.00-4.10 (br s)
11	$C_2H_5SCH_2CH_2NH$[e]	CH_3	69	CH_2Cl_2-CH_3OH	$0.5CH_3OH$	114-116 dec	1.27 (t, 3), 2.40-2.93 (m, 4), 3.40-3.93 (m, 2), 6.5-6.8 (br s, 1); 3.33-3.40 (br s), 4.00-4.10 (br s)
12	$NCCH_2CH_2NH$	H	65	CH_2Cl_2-CH_3OH	$0.5CH_3OH$	68-73 dec	2.1-2.77 (m, 4), 6.57 (t, 1); 3.32-3.43 (br s), 4.02-4.10 (br s)
13	$H_2NCH_2CH_2NH$[f]	H	65	CH_2Cl_2	$1CH_2Cl_2$	202-205 dec	1.47 (br s, 2), 3.50 (br s, 2); 5.55
14	$(CH_3)_2NCH_2CH_2NH$	H	ref 7				
15	c-C_4H_8N-CH_2CH_2NH	H	61	CH_2Cl_2-CH_3OH	$1CH_3OH$	>200 dec	1.57-1.93 (m, 4), 2.23-3.03 (m, 8), 6.92 (5, 1); 3.33-3.40 (br s), 4.00-4.10 (br s)
16		H	41	CH_2Cl_2-CH_3OH		>300 dec	1.07 (t, 3), 1.4-2.33 (m, 5), 2.36-3.03 (m, 4); 3.3-3.83 (m, 2), 6.77-7.20 (br s, 1)
17	c-$O(CH_2CH_2)_2N$-CH_2CH_2NH[h]	H	55	CH_2Cl_2-CH_3OH	$1CH_3OH$	74-76 dec	2.27-2.73 (br s, 8), 3.47-4.03 (br s, 4), 7.27 (t, 1); 3.30-3.40 (br s), 4.00-4.10 (br s)
18	Ph-CH_2CH_2NH	H	ref 1				
19		H	63	CH_2Cl_2-CH_3OH		>250 dec	0.6-1.53 (m, 4), 6.20-6.50 (br s, 1), 7.18 (br s, 5)
20	*p*-HO-Ph-CH_2CH_2NH[i]	H	81	none	$2H_2O$	120-125 dec	($CDCl_3$ + CD_3OD) 2.5-2.9 (m, 4), 6.5-7.2 (dd, 4), NH and OH protons not apparent
21		H	64	acetone-ether	$1.5H_2O$	>125 dec	($CDCl_3$ + CD_3OD) 2.5-2.9 (m, 4), 6.2-6.9 (m, 3), NH and OH protons not apparent

[a] Analytical results were within ±0.40% of theoretical values for all elements (C, H, N), except as shown in subsequent footnotes. In some examples, the solvent impurities indicated in the table had to be added to reconcile the calculated and found values for these elements. NMR signals for the solvent impurities are given in the table. It was not possible to obtain exact ratios for protons in the solvent impurities with respect to those in the compound by integrating the spectra. [b] The solvent was $CDCl_3$ unless specified otherwise. [c] N: calcd, 14.39; found, 13.96. [d] C: calcd, 53.42; found, 53.00. [e] C: calcd, 54.42; found, 53.93. [f] C: calcd, 46.76; found, 47.41. [g] H: calcd, 7.01; found, 7.54. [h] N: calcd, 14.60; found, 14.10. [i] N: calcd, 11.42; found, 11.83.

Some of the compounds listed in Table II also were tested against L-1210 leukemia in mice. Their activities in this assay are given in Table III. Although no compound, including mitomycin C, shows impressive activity in this assay, the mercaptoethylamine analogue 8 was clearly better than mitomycin C. Compounds **6**, **7**, **10**, **11**, **15**, and **20** appear to be approximately as active as mitomycin C. The superior activity of analogue 8 in both leukemia systems prompted its evaluation against B-16 melanoma in mice. As shown in Table IV, this analogue

Table II. Antitumor Activity and Leukopenia of 7-(Ethylamino)mitosanes[a]

no.	P-388 leukemia: max % T/C compd	P-388 leukemia: max % T/C (mit C)	P-388 leukemia: opt dose, mg/kg	P-388 leukemia: MED, mg/kg	P-388 leukemia: TR: opt dose/MED	leukopenia % change in WBC at opt dose on day 3
1	250	322	12.8	0.8	32	NA
2	190	245	12.8	1.6	8	−7
3	205	>300 (4)	51.2	6.4	8	NA
4	>316 (5)	268 (2)	6.4	0.4	16	−58
5	228	228	25.6	1.6	16	−38
6	205 (1)	268 (2)	12.8	0.8	16	−57
7	200 (1)	224	6.4	0.8	8	−44
8	313 (2)	181	12.8	0.2	64	−35
9	179	268 (2)	25.6	3.2	8	NA
10	205	268 (2)	12.8	1.6	8	−35
11	200	322	25.6	6.4	4	NA
12	232 (1)	268 (2)	6.4	0.4	16	−40
13	178	156	3.2	0.4	8	NA
14	233	161	12.8	0.4	32	NA
15	194	211	12.8	0.4	32	−64
16	217	211	12.8	0.8	16	−29
17	150	211	25.6	6.4	4	NA
18	194	194	25.6	1.6	16	NA
19	200	233	25.6	1.6	16	NA
20	218	288	25.6	1.6	16	NA
21	139	233	12.8	12.8	1	NA
22 (mit C)	161-322	(0-4)	3.2	0.2	16	−42

[a] Determined at Bristol Laboratories, 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 parentheses beside the maximum effect. Complete testing results, including each dose used for therapeutic effect, number of 5- and 30-day survivors, and average weight difference between the test and control group, are available as supplementary material (see paragraph at end of paper).

Table III. Activity against L-1210 Leukemia in Mice[a]

no.	NSC	max effect, % T/C	opt dose, mg/kg	MED, mg/kg	TR: opt dose/MED
6	339670	143, 145	12	6	2
7	329040	151	24	6	4
8[b]	329697	168	9.6	1.6	6
9	339669	129, 136	48	12	4
10	339668	141, 155	24	12	2
11	342733	143, 145	48	24	2
12	339671	130, 137	12	3	4
14	344017	136, 146	12	6	2
15	326239	125	5	5	1
17	326240	132	96	48	2
20	345817	125, 151	48	12	4
22 (mit C)	026980	124-153[c]	3-6	3	1-2

[a] Determined according to standard NCI protocol at Arthur D. Little, Cambridge, MA. Both values are shown for assays that were repeated. [b] Determined according to the same protocol (one dose on day 1) at Bristol Laboratories, Syracuse, NY. This compound also is active on dosage schedules of once every day for 9 days and once every 3 days for 9 days. [c] A range based on numerous determinations.

Table IV. Comparative Activities of Compounds 8, 6, 10, and Mitomycin C against B-16 Melanoma in Mice[a]

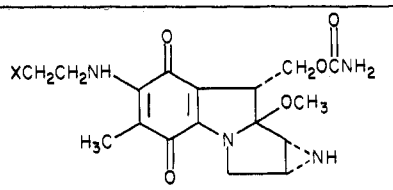
no.	dose,[b] (mg/kg)/day	effect: MST, % T/C	cures[c]	av wt change, g
8	12.0	218	9/10	−1.9
	6.0	218	9/10	−0.5
	3.0	218	5/10	−0.5
	1.5	190	2/10	−0.1
	0.75	193	0	0
22 (mit C)	3.0	193	0	−1.3
	1.5	164	0	−0.3
	0.75	126	0	0.4
6	12.0	190	10/10	−2.0
	6.0	190	5/10	−1.7
	3.0	190	2/10	−0.4
10	12.0	190	9/10	−1.7
	6.0	175	3/10	−1.2
	3.0	144	0	−0.8
22 (mit C)	3.0	190	6/10	−2.2
	1.5	160	0	−1.1
	0.75	127	0	−0.7

[a] Determined according to standard NCI protocol at Arthur D. Little, Cambridge, MA. [b] Injections given ip on days 1, 4, and 7. Doses higher than the maximum one shown were toxic. Ten mice were used at each dose. [c] Tumor-free survivors on day 45.

has outstanding activity in this assay, being superior to mitomycin C in the number of "cures" (tumor-free survivors on day 45) and the therapeutic ratio. Compounds **6** and **10** also were more active than mitomycin C in a subsequent assay.

In the previous article in this series, it was shown that for mitosenes with a wide variety of amine substituents at position 7 a rough correlation could be made between the quinone reduction potential, the minimum effective dose for activity against P-388 leukemia, and the diminution of leukopenia. Such a correlation seems unlikely with the substituted ethylamino analogues because the substituent is remote from the quinone ring. However, the substituents should influence the lipophilicity of the molecules, and a correlation between octanol–water partition coefficient (log *P*) and minimum effective dose might be possible. Table V lists some of the analogues with an unsubstituted aziridine nitrogen in increasing order of potency according to minimum effective dose (MED). Also given are the calculated log *P* values, half-wave reduction

Table V. Structure-Activity Relationships among 7-(Ethylamino)mitosanes



no.	X	MED,[a] mg/kg	log P[b]	$E_{1/2}$,[c] V	leukopenia[d] % change
18	C_6H_5	1.6	2.48	−0.44	NA
10	C_2H_5S	1.6	1.66	−0.41	−35
2	Cl	1.6	0.74	NA	−7
5	OH	1.6	−0.81	NA	−38
1	H	0.8	0.35*	−0.44	NA
6	CH_3O	0.8	−0.12	−0.44	−57
14	$(CH_3)_2N$	0.4	−0.15	doublet	NA
4	F	0.4	0.18	−0.41	−58
12	CN	0.4	−0.49	−0.40	−40
13	NH_2	0.4	−0.84	NA	NA
8	SH	0.2	0.63	−0.40	−35

[a] Activity against P-388 mouse leukemia from Table II. [b] Distribution between 1-octanol and water containing phosphate buffer at pH 7.4. Determination by the method of Hansch, C.; Muir, R. M.; Fujita, T.; Malongy, P. P.; Geiger, F.; Struch, M. *J. Am. Chem. Soc.* 1963, *85*, 2817, is indicated by an asterisk. Other values are estimated from log P for 1 and aliphatic π values from the literature [Fujita, T.; Iwasa, J.; Hansch, C. *J. Am. Chem. Soc.* 1964, *86*, 5175; Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley-Interscience: New York, 1979]. [c] Determined by differential pulse polarography on a Model 174A EG8G polarographic analyzer. The electrolyte was 1.0 M KCl solution and the standard was 10^{-3} M $CdCl_2$ in 1.0 M KCl. Mitomycin analogues were 10^{-3} M in 1.0 M KCl. $E_{1/2}$ values are given relative to the saturated calomel electrode. The following conditions were used: potential scan, 0.1 V/in.; potential scan rate, 1 mV/s; voltage range, 1.5 V; initial potential, −0.1 or −0.2 V; modulation amplitude, 25; rate of mercury drops, 60/min. [d] Decrease in white cells from Table II.

potentials ($E_{1/2}$), and extent of leukopenia. As anticipated, there is almost no variation in $E_{1/2}$. This result would predict a uniform degree of relatively high leukopenia, but the data do not agree well with this prediction. Compounds **4** and **6** are highly leukopenic, but **2** is not leukopenic and the other compounds are moderately leukopenic. There appears to be a trend between potency and log P, with the least lipophilic compounds having the lowest MED values. However, a multiple linear-regression analysis revealed no statistically significant correlation. The most obvious exception to this trend is **5**, the hydroxyethylamino analogue. This is not the only instance in which the hydroxy substituent deactivates a mitosane. For example, the stepwise addition of hydroxy groups to phenethylamine analogue **18** gives **20**, which has a decreased therapeutic effect, and then **21**, which is barely active and has low potency. We do not know why the hydroxy group deactivates, although interactions such as hydrogen bonding and complex formation are possible causes. The other main exception to the trend of greatest potency for the most hydrophilic compounds is mercaptoethylamino analogue **8**, which has better potency than predicted by its log P. An explanation for this observation is not apparent, but it is possible that **8** is converted into the corresponding disulfide. This change in structure certainly would modify its physicochemical properties. An alternative explanation that **8** actually has the isomeric 7-(2-aminoethyl)thio structure was ruled out by its ultraviolet absorption maximum of 368 nm in methanol. This

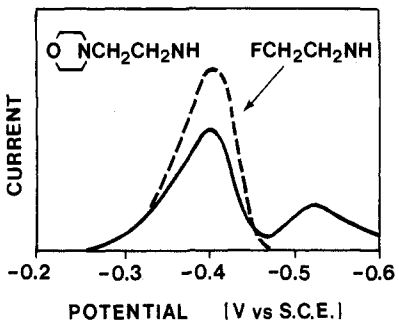


Figure 1. Plot of the first derivative of current against potential in the polarographic reduction of mitosanes. Peak maxima correspond to $E_{1/2}$.

value is identical with that of ethylamino analogue **1** but much different from that of a 7-alkoxymitosane, such as mitomycin A (319 nm).

Our polarographic measurements were based on the mitomycin C study conducted by Rao and co-workers.[5] Their study showed that the initial reduction of mitomycin C was a reversible two-electron process. The $E_{1/2}$ value obtained for mitomycin C, −0.368 V at pH 7, was somewhat smaller than ours, −0.45 V at pH 7. However, we used a 1 M KCl solution and they did not. All of the simpler substituted ethylamines that we measured gave a single peak in the $E_{1/2}$ determination. However, compounds **14**, **15**, and **17**, which have a basic amino group in the substituent, gave two peaks. This phenomenon is illustrated in Figure 1, wherein an analogue (fluoroethylamine, **4**) that gives a normal reduction is compared with an analogue (morpholinoethylamine, **17**) that gives an anomalous reduction. The cause of the anomalous reduction probably is complex formation with mercury on the electrode surface. Another difference from the usual result was shown by compound **19**, which had a relatively small $E_{1/2}$ of −0.359 V. The cyclopropane ring of this compound might be responsible for its comparative ease of reduction.

In summary, a number of 7-[(2-substituted-ethyl)-amino]mitosanes have been prepared and found active against P-388 and other mouse tumors. A rough trend between potency and hydrophilicity was observed. This limited trend is not very satisfying on theoretical grounds, but it has been helpful to us in analogue design. For example, it led us to prepare the fluoroethylamino and cyanoethylamino analogues **4** and **12**. Future papers in this series will be based on other types of 7-substituents.

Experimental Section

Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian (EM 360, 60 MHz) NMR spectrometer with tetramethylsilane as the standard. Elemental analyses were performed by the Analytical Center, University of Arizona, Tucson, AZ.

Preparation of Mitomycin C Analogues (General Method). A solution of mitomycin A (100 mg or 0.286 mmol) in 8 mL of anhydrous methanol was stirred with 0.6 mmol of amine or amine hydrochloride (in the case of amine hydrochloride, 0.5 mL of triethylamine was added to the reaction mixture) for 15 min to 3 h at room temperature. The mixture turned blue. The solvent was removed by evaporation under reduced pressure, and the crude product was purified by preparative thin-layer chromatography using precoated silica gel plates (20 × 20 cm and 2-mm thickness) as adsorbent and MeOH–$CHCl_3$ (2:8, v/v) as the developing solvent. The products were recrystallized from a mixture of methylene chloride and methanol. The yields and properties of these products are given in Table I.

(5) Rao, G. M.; Begleiter, A.; Lown, J. W.; Plambeck, J. A. *J. Electrochem. Soc.* **1977**, *124*, 199.

7-[(2-Aminoethyl)amino]-9a-methoxymitosane (13).[6] A solution of mitomycin A (50 mg, 0.143 mmol) in 5 mL of methylene chloride was added over 5 min with constant stirring to a solution of ethylenediamine (10 mg, 0.166 mmol) in 10 mL of methylene chloride. After 4 h, the purple precipitate that formed was collected, washed with methylene chloride, and dried under reduced pressure. Thin-layer chromatography in the system described above showed a single spot. The yield and properties of 13 are given in Table I.

Preparation of Porfiromycin Analogues (General Method). The porfiromycin analogues were prepared by an idential procedure with the one described above by reacting *N*-methylmitomycin A (100 mg or 0.275 mmol) with 0.6 mmol of amine hydrochloride in the presence of triethylamine (0.5 mL) in 8 mL of anhydrous methanol. The yields and properties of these compounds are given in Table I.

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Registry No. 1, 4117-84-4; 2, 78142-83-3; 3, 78142-84-4; 4, 83603-86-5; 5, 27066-48-4; 6, 83586-79-2; 7, 83586-80-5; 8, 83586-81-6; 9, 83586-82-7; 10, 83586-83-8; 11, 83586-84-9; 12, 83586-85-0; 13, 83586-86-1; 14, 17287-42-2; 15, 83586-87-2; 16, 83586-88-3; 17, 83586-89-4; 18, 78142-92-4; 19, 83586-90-7; 20, 83586-91-8; 21, 83586-92-9; mitomycin A, 4055-39-4; *N*-methylmitomycin, 18209-14-8; 2-fluoroethanamine, 406-34-8; 2-methoxyethanamine, 109-85-3; 2,2-dimethoxyethanamine, 22483-09-6; 2-mercaptoethanamine, 60-23-1; 2-(ethylthio)ethanamine, 36489-03-9; 2-cyanoethanamine, 151-18-8; 1,2-ethanediamine, 107-15-3; *N,N*-dimethyl-1,2-ethanediamine, 108-00-9; 2-pyrrolidinylethanamine, 7154-73-6; 2-(aminomethyl)-1-ethylpyrrolidine, 26116-12-1; 2-morpholinoethanamine, 2038-03-1; phenethylamine, 64-04-0; 1-amino-2-phenylcyclopropane, 54-97-7; 2-(*p*-hydroxyphenyl)ethylamine, 51-67-2; 3,4-dihydroxyphenethylamine, 51-61-6.

Supplementary Material Available: Full screening data for compounds submitted to the P-388 (Table II) and L-1210 (Table III) assays (5 pages). Ordering information is given on any current masthead page.

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Potential Radiosensitizing Agents. 6. 2-Nitroimidazole Nucleosides: Arabinofuranosyl and Hexopyranosyl Analogues[1]

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New 2-nitroimidazole nucleosides have been synthesized as radiosensitizers of hypoxic mammalian cells in an attempt to reduce the neurotoxicity and to increase the therapeutic efficacy of this class of agents. The trimethylsilyl derivative of 2-nitroimidazole was condensed with 1-bromo-2,3,5-tri-*O*-benzoylarabinofuranose in the presence of mercuric cyanide to yield anomeric isomers of arabinofuranosides, which were separated by preparative thin-layer chromatography. Reaction of 2-deoxy-1,3,4,6-tetra-*O*-acetyl-D-glucose or 3,4,6-tri-*O*-acetyl-D-glucal with 2-nitroimidazole in the presence of an acid catalyst produced α and β isomers of 2′,3′-dideoxy-D-*erythro*-hex-2′-enopyranosides and an isomeric 3-substituted 1,2,3-trideoxy-D-*erythro*-hex-1-enopyranose. Hydrolysis of the esters was accomplished with sodium methoxide in methanol at 0 °C. The radiosensitizing efficacy of these agents was determined against Chinese hamster (V-79) cells in vitro. The 1-(2′,3′-dideoxy-α-D-*erythro*-hex-2′-enopyranosyl)-2-nitroimidazole was the most active agent of this series and was found to be superior to misonidazole as a radiosensitizer.

A series of 2-nitroimidazole derivatives has been shown to selectively sensitize hypoxic cells, present in solid tumors, toward the lethal effect of ionizing radiation.[3] We have recently reported the synthesis of a series of 2,4-dinitroimidazoles[4-6] and 2-acetyl-4-nitroimidazoles[7] in an effort to increase the electron affinity of the 2-nitroimidazole nucleus and, hence, the radiosensitizing activity. However, a major limitation in the therapeutic use of misonidazole, a 2-nitroimidazole derivative, has been the dose-related neurotoxicity.[8] To alleviate the CNS toxicity associated with this class of agents, we have initiated the synthesis and biological testing of a series of 2-nitroimidazole nucleosides. These included 1-β-D-glucopyranosyl, 1-β-D-glucothiopyranosyl, and a neuraminic acid derivative of 2-nitroimidazole.[9] It was hypothesized that nucleosides in general may not cross the blood–brain barrier effectively and, therefore, may provide analogues with enhanced therapeutic efficacy.

In this investigation we report the synthesis of arabinofuranosyl and 2′,3′-dideoxy-hex-2′-enopyranosyl ana-

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