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.

Acknowledgment. This investigation was supported by Grant CA 21430, awarded by the National Cancer Institute, HHS, and by funds from Bristol Laboratories. We thank Dr. John D. Douros of the NCI for help in obtaining L1210 leukemia and B16 melanoma testing.

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.

(6) Named according to the system proposed by 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, U.; Pidacks, C.; Lancaster, J. E. *J. Am. Chem. Soc.* **1962**, *84*, 3185.
(7) Cosulich, D. B.; Patrick, J. B.; Williams, R. P. U.S. Patent 3 332 944 (July 25, 1967).

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-

(1) A brief report of part of the present study has appeared: M. Sakaguchi, C. A. Larroquette, and K. C. Agrawal, 181st National Meeting of the American Chemical Society, Atlanta, GA, Mar 29–Apr 3, 1981, American Chemical Society, Washington, DC, 1981, Abstr MEDI 39.
(2) Leukemia Society Fellow.
(3) J. W. Fowler, G. E. Adams, and J. Denekamp, *Cancer Treat. Rev.*, 3, 227 (1976).
(4) K. C. Agrawal, K. B. Bears, R. K. Sehgal, J. N. Bown, P. E. Rist, and W. D. Rupp, *J. Med. Chem.*, 22, 583 (1979).
(5) K. C. Agrawal, B. C. Millar, and P. Neta, *Radiat. Res.*, 78, 532 (1979).
(6) R. K. Sehgal, M. W. Webb, and K. C. Agrawal, *J. Med. Chem.*, 24, 601 (1981).
(7) R. K. Sehgal and K. C. Agrawal, *J. Pharm. Sci.*, in press.
(8) S. Dische, M. I. Saunders, M. E. Lee, G. E. Adams, and I. R. Flockhart, *Br. J. Cancer*, 35, 567 (1977).
(9) M. Sakaguchi, M. W. Webb, and K.C. Agrawal, *J. Med. Chem.*, 25, 1339 (1982).

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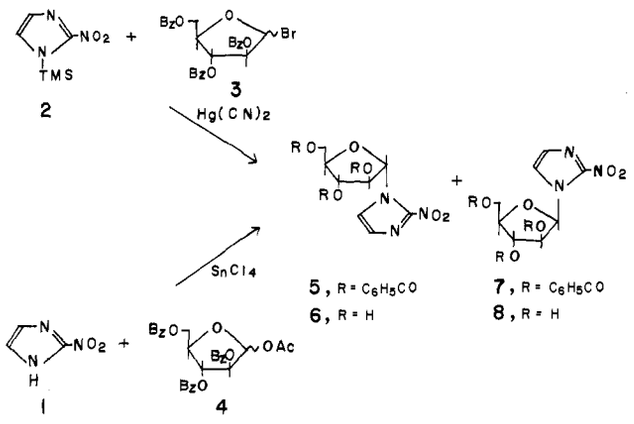
Scheme I

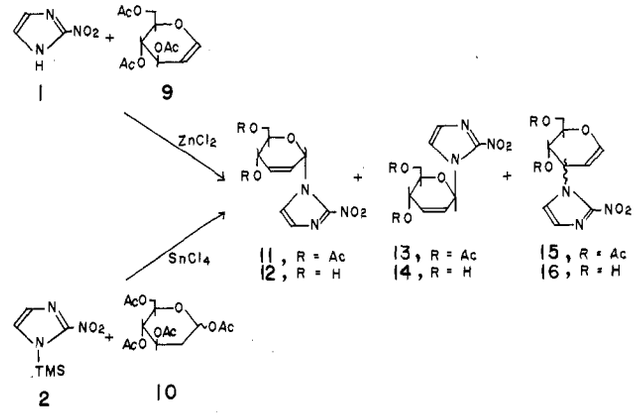


[a] TMS = MeSi.

logues of 2-nitroimidazole. The arabinofuranosyl moiety was selected primarily to stabilize the 2-NO_2 function by either a hydrogen bonding between the OH group at the 2′-position and the NO_2 function or by creating a steric hindrance in the vicinity of the NO_2 group in an effort to protect it from enzymatic reduction. The stabilizaton and steric protection of the 2-NO_2 function may yield derivatives with reduced in vivo toxicity, since the hypoxic cytotoxicity has been related to the reduction of the NO_2 group.[10] Morevoer, since the arabinofuranosyl moiety has been shown to confer both the anticancer and antiviral activities in cytosine arabinoside and adenosine arabinoside, respectively, it was considered appropriate to synthesize the 2-nitroimidazole analogue. An attempt was also made to synthesize a 2-deoxy-D-glucose analogue of 2-nitroimidazole, since 2-deoxy-D-glucose has been shown to induce an increased tumor cell kill after irradiation.[11]

Chemistry. Synthesis of arabinofuranosyl nucleosides was initially attempted by reacting 2-nitroimidazole (**1**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose (**4**) in the presence of stannic chloride as an acid catalyst (Scheme I). This procedure was similar to the one employed by Poonian et al.[12] for the synthesis of the arabinofuranosyl derivatives of imidazole analogues by reacting the base with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose. However, this reaction produced a very poor yield of the desired nucleosides, the α isomer (**5**) in 1.4% yield and the β isomer (**6**) in 0.7% yield. This low yield may be due to the utilization of the benzoyl analogue (**4**) instead of the benzyl derivative, which was necessitated for the deblocking step because of the presence of the nitro function in the resulting nucleosides. In contrast, reaction of 1-bromo-2,3,5-tri-*O*-benzoylarabinofuranose (**3**) with the trimethylsilyl derivative of **1** (**2**) in the presence of mercuric cyanide produced a reasonable yield (40%) of a mixture of the nucleosides **5** and **7**. In this reaction, the yield of the α isomer (**5**) predominated the β isomer (**7**) by a ratio of 5:1 as anticipated because of the trans rule of nucleoside synthesis.[13] The mixture of nucleosides **5** and **7** was separated by silica gel column chromatography and then debenzoylated with sodium methoxide in methanol at 0 °C to produce the corresponding arabinofuranosyl ana-

Scheme II



[a] TMS = Me_3Si.

logues **6** and **8**, respectively. The anomeric configuraton at C-1′ of the arabinose moiety in nucleosides **5** and **7** was determined by proton NMR spectroscopy. It has been reported that the anomeric proton of the β isomer of arabinofuranose nucleosides always appeared downfield from the anomeric proton of the corresponding α isomer.[14] The anomeric proton of **7** was 0.12-ppm downfield from the corresponding signal in **5**. In addition, the large spin–spin coupling constant for protons of C-1′ and C-2′ (J = 4.6 Hz) in nucleoside **7** in comparison to the α-isomer **5** ($J_{1'-2'}$ = 0.4 Hz) confirmed the anomeric assignment.[15]

In efforts to synthesize a 2-deoxy-D-glucose analogue of **1**, the trimethylsilyl derivative (**2**) was reacted with 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucose (**10**) in the presence of stannic chloride (Scheme II). This reaction was attempted on the basis of a published procedure[16] in which 1-bromo-3,4,6-triacetyl-2-deoxy-D-glucose was fused with the silver salt of 5,6-dimethybenzimidazole to yield an anomeric mixture of 1-(2′-deoxy-D-glucopyranosyl)-5,6-dimethylbenzimidazole. Similarly, synthesis of 2-deoxy-D-ribofuranose analogues have also been reported.[17] However, under the conditions employed for the reaction of **2** with **10**, the products isolated were not the 2-deoxy-D-glucopyranosyl analogues but were found to be a mixture of the α isomer (**11**, 5%) and the β isomer (**13**, 15%) of 1-(2′,3′-dideoxy-4′,6′-di-*O*-acetyl-D-*erythro*-hex-2′-enopyranosyl)-2-nitroimidazole. In addition, a third minor product (**15**, <1%) was also isolated from the preparative TLC and was confirmed to be 1,2,3-trideoxy-4,6-di-*O*-acetyl-3-(2′-nitro-1′-imidazolyl)-D-*erythro*-hex-1-enopyranose.

The synthesis of 2′,3′-unsaturated heterocyclic N-glycosides was first reported by Bowels and Robins[18] who empolyed various glycal derivatives in an acid-catalyzed fusion reaciton. By utilizing a similar procedure, Leutzinger et al.[19] reported the synthesis of the 9-(2′,3′-dideoxy-D-*erythro*-hex-2-enopyranosyl)guanine analogue without isolating the anomeric isomers. Fuertes et al.[20] separated the enantiomers obtained from the reaction of

(10) A. J. Varghese and G. F. Whitmore, *Cancer Res.*, **40**, 2165 (1980).
(11) V. K. Jain, W. Porschen, and L. E. Feinendegen, *Indian J. Exp. Biol.*, **15**, 714 (1977).
(12) M. S. Poonian, W. W. McComas, and M. J. Kramer, *J. Med. Chem.*, **22**, 958 (1979).
(13) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).
(14) C. W. Smith, R. W. Sidwell, R. K. Robins, and R. L. Tolman, *J. Med. Chem.*, **15**, 883 (1972).
(15) J. D. Stevens and H. G. Fletcher, *J. Org. Chem.*, **33**, 1799 (1968).
(16) G. Cooley, B. Ellis, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, **2**, 579 (1950).
(17) C. P. White and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4940 (1965).
(18) W. A. Bowles and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 1252 (1964).
(19) E. E. Leutzinger, R. K. Robins, and L. B. Townsend, *Tetrahedron Lett.*, **43**, 4475 (1968).

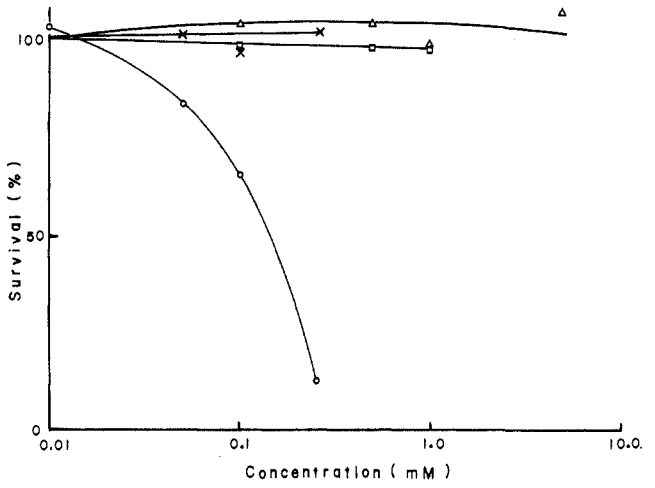


Figure 1. The effect of 2-nitroimidazole arabinofuranosides on the survival of Chinese hamster cells when exposed to various drug concentratons for 2 h under oxic condition: (O–O) **5**; (Δ–Δ) **6**; (x–x) **7**; (□–□) **8**.

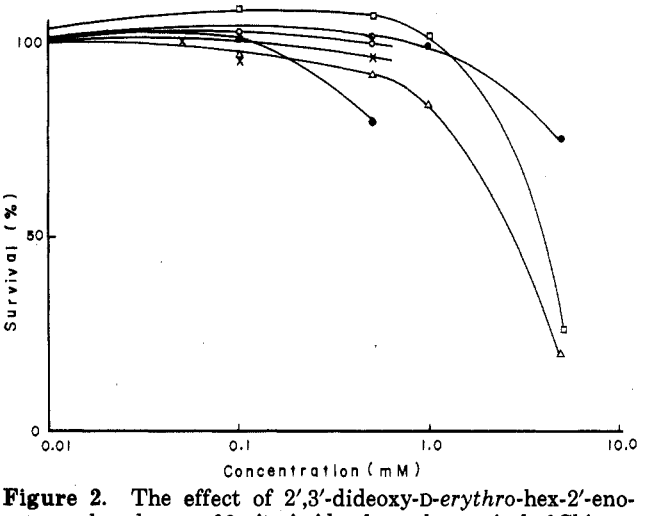


Figure 2. The effect of 2′,3′-dideoxy-D-*erythro*-hex-2′-enopyranosyl analogues of 2-nitroimidazole on the survival of Chinese hamster cells when exposed to various drug concentrations for 2 h under oxic conditions: (O–O) **11**; (Δ–Δ) **12**; (x–x) **13**; (□–□) **14**; (●–●) **15**; (⊙–⊙) **16**.

3,4-di-*O*-acetyl-D-xylal with 6-chloropurine and reported three major compounds, 6-chloro-9-(4′-*O*-acetyl-2′,3′-dideoxy-α- and -β-D-*glycero*-pent-2′-enosyl)purine and 1,2,3-trideoxy-4-*O*-acetyl-3-(6′-chloro-9′-purinyl)-D-*threo*-pent-1-enopyranose. In our attempts to synthesize the 2′,3′-unsaturated 2-nitroimidazolyl N-glycosides **11** and **13** by an alternate route than the reaction with 2-deoxyglucose analogue **10**, we have reacted 3,4,6-tri-*O*-acetyl-D-glucal (**9**) with **1** in a fusion reaction catalyzed with zinc chloride. The results obtained under these conditions are different than described earlier[19] in that three different isomeric compounds were isolated from the reaction mixture by utilizing a combination of column and preparative layer chromatography techniques. These compounds were identified by NMR to be the α isomer (**11**, 9.8%), β isomer (**13**, 14%), and the 3-substituted pyranose analogue **15** (3%). The formation of anomeric isomers **11** and **13** in this reaction would be expected due to the allylic expulsion of the C-3 acetate group from **9** during nucleoside formation. However, the formation of **15** would be expected to involve a carbonium ion intermediate,[20] which would lead to the formation of two stereoisomeric glycals having the ribo and arabino configuration. The α and β configurations of **11** and **13** were established on the basis of a large spin–spin coupling constant for protons of $C_{1'}$ and $C_{2'}$ (J = 12.0 Hz) for the β isomer and a relatively smaller J value of 5.9 Hz for the α isomer. In addition, the protons of the β isomer consistently appeared downfield from the protons of the α isomer. The structure of **15** was assigned so that the 2-nitroimidazole moiety was bonded to the $C_{3'}$ position of the sugar and was found to be a mixture of the two stereoisomers. This structure was based upon the NMR data, which suggested a glycal-type α,β-unsaturated ether linkage due to the chemical shifts of the olefinic protons at δ 6.99 and 6.04. The $C_{1'}$ H signal appeared as a doublet at δ 6.99. The $C_{2',3'}$ protons appeared as multiplet between δ 6.04 and 6.42. Attempts were not made to separate the mixture of stereoisomers of **15** because of the extremely low yield obtained in this reaction. The esters **11**, **13** and **15** upon hydrolysis in methanolic ammonia at 0 °C overnight yielded the corresponding products **13**, **14**, and **16**. The structures of these agents were confined by IR and NMR data in a similar pattern as described in the case of the esters.

(20) M. Fuertes, G. Garcia-Munoz, R. Madronero, and M. Stud, *Tetrahedron*, **26**, 4823 (1970).

Table I. Partition Coefficients and Radiosensitizing Activity against Chinese Hamster Cells in Vitro of 2-Nitroimidazole Nucleosides

compd	PC[a]	radiosensitization concn,[b] mM	radiosensitization SER[c]
5		0.05	1.0
6	0.11	1.0	1.6
7		0.1	1.1
8	0.07	1.0	1.8
11		0.5	1.9
12	0.22	0.5	2.0
13		0.5	1.6
14	0.22	1.0	2.0
15		0.5	1.8
16	0.24	1.0	1.7
misonidazole[d]	0.43	1.0	1.9

[a] Partial coefficients. [b] Concentrations employed were maximum nontoxic dose limited to 1 mM or less. [c] Sensitizer enhancement ratios were determined from the radiation survival curves by dividing the D_0 value of the control hypoxic cells with the D_0 value obtained for the hypoxic cells irradiated in presence of the sensitizer. The values shown were averaged from at least two or more sets of experiments. [d] Data for misonidazole, the reference compound of the series, are included for comparative purposes.

Biological Results and Discussion

The cytotoxic effects of 2-nitroimidazole arabinofuranosides against Chinese hamster (V-79) cells in vitro are shown in Figure 1. The esters **5** and **7** were tested up to a maximum soluble concentraiton of 0.5 mM. The anomeric specificity for cytotoxicity due to the esters was observed in that the α isomer (**5**) was significantly more toxic than the β isomer (**7**) in inhibiting the colony formation. However, this isomeric specificity for cytotoxic effect was not observed in the case of arabinofuranosides **6** and **8**, which were relatively nontoxic and did not inhibit the colony formation up to a concentration of 1 mM. Conversely, the 2′,3′-dideoxy-hex-2′-enopyranosyl esters **11**, **13**, and **15** were essentially nontoxic up to a maximum soluble concentration of 0.5 mM, whereas the hydrolyzed products **12** and **14** were comparatively more toxic than the arabinofuranosides (Figure 2). Compound **16**, however, did not show this increased toxicity.

The radiosensitizing efficacy of these agents was determined against V-79 cells in vitro under hypoxic con-

ditions (Table I). The radiaiton survival curves were obtained for each compound with radiation doses in the range of 400 to 2700 rad. The sensitizer enhancement ratios (SER) were then calculated by dividing the D_0 value (the radiation dose required to reduce the survival by a factor of 0.37 in the exponential region of the curve) for the control hypoxic curve with the D_0 value obtained for the cells irradiated in the presence of the radiosensitizer under hypoxia. The SER for misonidazole, the reference compound of this series, was 1.9 under these conditions. The radiosensitization data in Table I suggest that the hex-2-enopyranosyl analogues were superior to arabinofuranosides as sensitizers. In the latter series, the nucleosides **6** and **8** were more active sensitizers than the corresponding benzoate esters **5** and **7**. This may be related to the concentrations employed, since the esters were tested at lower concentraitons due to the cytotoxicity. However, the acetyl esters of hex-2′-enopyranosyl analogues **11**, **13**, and **15** were active sensitizers at 0.5 mM, producing SERs of 1.9, 1.6, and 1.8, respectively. Compounds **12** and **14** were found to be the most active agents of this series, each producing an SER of 2.0 at 0.5 and 1.0 mM concentration, respectively. Thus, both these agents were superior to misonidazole as radiosensitizers in this test system. However, compound **12** was twice as active as **14**, since to achieve the same degree of sensitization, one-half the concentration of **12** was required.

The relationship of partition coefficients as a guide to the development of radiosensitizers has recently been described.[21] We have therefore determined the partition coefficients of these nucleosides. It is obvious from the data in Table I that within this series there is no correlation of in vitro radiosensitization with partition coefficient. However, the partition coefficient of 0.22 for compounds **12** and **14** suggest that these agents are more hydrophilic than misonidazole and, thus, may be relatively less neurotoxic. These results therefore encourage further continued investigation in the development of 2-nitroimidazole nucleosides as potential radiosensitizers.

Experimental Section

Infared spectra were obtained on a Beckman IR-10 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded at 60 mHz on a Varian A-60 spectrometer, with tetramethylsilane as the internal reference. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6E spectrometer at 70-eV ionization potential with direct-inlet injection. The elemental analyses were performed by Baron Consulting Co., Orange, CT, and are within ±0.4% of the calculated value when specified by symbols. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical thin-layer chromatography was performed on glass plates coated with a 0.25-mm layer of silica gel GF_{254} and preparative layer chromatography on 20 × 20 cm glass plates coated with a 2-mm layer of silica gel PF_{254} (E. Merck AG, Darmstadt, Germany). The compounds were detected by visual examination under short- and long-wavelength UV light. Evaporation of solvents was done under reduced pressure with a rotary evaporator.

1-(2′,3′,5′-Tri-*O*-benzoyl-α-D-arabinofuranosyl)-2-nitroimidazole (5) and 1-(2′,3′,5′-Tri-*O*-benzoyl-β-D-arabinofuranosyl)-2-nitroimidazole (7). To a crude solution of **2** [prepared from 1.72 g (0.015 mol) of **1**, according to Prisbe et al.[22]] in anhydrous acetonitrile (100 mL) was added a solution of 5.25 g (0.01 mol) of 1-bromo-2,3,5-tri-*O*-benzoyl-D-arabinofuranose[23] (**3**) in anhydrous acetonitrile (50 mL) and 3.60 g (0.01 mol) of mercuric cyanide. The resulting solution was stirred for 2 days at room temperature and then evaporated to dryness. A filtered solution of the residue in chloroform (300 mL) was washed successively with 30% potassium idoide (100 mL × 3), saturated aqueous sodium bicarbonate (100 mL × 3), and water (100 mL × 3). The organic phase was dried (anhydrous Na_2SO_4) and evaporated to dryness. The residual syrup was chromatographed on a column (5 × 50 cm) of silica gel G (600 g) with a gradient of benzene–ethyl acetate (10:1 to 0:1) (2.5 L). The initial fracitons contained a non-UV-absorbing material, as monitored by TLC, and were discarded. This was followed by fractions containing the β anomer **7**. These fractions were pooled together and evaporated, and the residue was purified by preparative TLC to yield 0.40 g (7.2%) of **7**, which was recrystallized from ether–petroleum ether: mp 124 °C; UV (EtOH) λ_{max} 237 nm (ε 25 568), 275 (7841), 284 (7784), 314 (6903); IR (KBr) 1715 ($OCOC_6H_5$), 1470 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 4.60-5.10 (m, 3 H, $C_{4',5'}$ H), 5.69 (m, 1 H, $C_{2'}$ H), 6.15 (dd, 1 H, $C_{3'}$ H), 7.08 (d, 1 H, $C_{1'}$H, $J_{1'-2'}$ = 4.6 Hz), 7.32–8.19 (m, 17 H, 3 C_6H_5 and $C_{4,5}$ H); MS, *m/e* 511 (M − NO_2). Anal. ($C_{29}H_{23}N_3O_9$) C, H, N.

The continued elution from the column produced the α isomer (**5**), which was recrystallized from ether–hexanes to yield 1.83 g (32.9%): mp 82 °C; UV (EtOH) λ_{max} 238 nm (ε 24 450), 276 (5868), 284 (5966), 315 (6088); IR (KBr) 1715 ($OCOC_6H_5$); 1470 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 4.63–5.05 (m, 3 H, $C_{4',5'}$ H), 5.60 (br d, 1 H, $C_{2'}$ H), 5.91 (br s, 1 H, $C_{3'}$ H), 6.96 (d, 1 H, $C_{1'}$ H, $J_{1'-2'}$ = 0.4 Hz), 7.25–8.12 (m, 17 H, 3 C_6H_5 and $C_{4,5}$ H); MS, *m/e* 511 (M − NO_2). Anal. ($C_{29}H_{23}N_3O_9$) C, H, N.

1-α-D-Arabinofuranosyl-2-nitroimidazole (6). Compound **5** (0.557 g, 1 mmol) was added to 5 mL of 0.05 M methanolic sodium methoxide. The mixture was stirred at 0 °C for 2.5 h. The precipitate of the partially hydrolyzed product of **5** was filtered off, and the filtrate was purified by preparative TLC with chloroform–methanol (5:1) to give 115 mg (46.9%) of **6** as pale yellow needles: mp 160 °C; UV (EtOH) λ_{max} 225 nm (ε 3835), 320 (8319); IR (KBr) 3300 (OH), 1470 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 3.57 (d, 2 H, $C_{5'}$ H), 3.99–4.35 (m, 3 H, $C_{2'-4'}$ H), 5.35 (br m, 2 H, 2OH), 5.92 (br s, 1 H, OH), 6.29 (br s, 1 H, $C_{1'}$ H), 7.18 (d, 1 H, C_4 H), 7.70 (d, 1 H, C_5 H). Anal. ($C_8H_{11}N_3O_6$) C, H, N.

1-β-D-Arabinofuranosyl-2-nitroimidazole (8). Compound **7** (0.15 g, 0.27 mmol) was added to 2.5 mL of 0.025 M methanolic sodium methoxide. The mixture was stirred at 0 °C for 3 h and then purified by preparative TLC with chloroform–methanol (6:1) to yield 36 mg (54.6%) of **8** as white needles: mp 172 °C; UV (EtOH) λ_{max} 225 nm (ε 3844), 318 (8200); IR (KBr) 3300 (OH), 1470 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 3.72–4.35 (m, 5 H, $C_{2'-5'}$ H), 5.16–5.70 (m, 3 H, 3 OH), 6.60 (d, 1 H, $C_{1'}$ H), 7.18 (d, 1 H, C_4 H), 7.97 (d, 1 H, C_5 H). Anal. ($C_8H_{11}N_3O_6$) C, H, N.

Reaction of 3,4,6-Tri-*O*-acetylglucal (9) with 2-Nitroimidazole (1). To 2.26 g (0.02 mol) of **1**, 6.53 g (0.024 mol) of **9** was added and mixed thoroughly. The mixture was heated at 90–100 °C for 10 min under vacuum (water aspirator). The reaction mixture was cooled to room temperature, and a catalytic amount (50 mg) of $ZnCl_2$ was added. The mixture was then heated at 140–160 °C (oil bath) for an additional 45 min under vacuum (water aspirator) while stirring. The yellow suspension turned dark brown during the fusion. After the mixture was cooled, the compounds were extracted with 200 mL of chloroform. The organic layer was filtered to remove the unreacted material **1** (0.65 g) and then washed with a saturated aqueous solution of sodium bicarbonate (100 mL × 2) and water (100 mL × 2). The chloroform layer was dried (anhydrous Na_2SO_4) and evaporated to dryness. The residual syrup was chromatographed on a column (5 × 50 cm) of silica gel G (500 g) with a gradient of benzene/ethyl acetate (4:1 to 1:1) (1.5 L). Initial fractions contained primarily the unreacted **9**, followed by the α isomer (**11**), and then a mixture of **11**, **13**, and **15**. The esters were then separated on 12 preparative TLC plates (silica gel GF_{254}, 2-mm thick) with benzene/ethyl acetate (1:1) as a solvent. The initial fractions containing the α isomer and the material from the faster moving band of the preparative TLC plates were combined and recrystallized from ethyl ether to yield 0.62 g (9.8%) of **11**: mp 136 °C; UV (EtOH) λ_{max} 220 nm (ε 5385), 320 (6862); IR (KBr) 1740 (OAc), 1730 (OAc), 1650 (C=C), 1470 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.96 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 4.32 (m, 3 H, $C_{5',6'}$ H), 4.89 (dd, 1 H, $C_{2'}$ H), 5.25 (m, 1 H, $C_{4'}$ H), 6.14 (m, 1 H, $C_{3'}$ H), 6.66 (dd, 1 H, $C_{1'}$ H, $J_{1',2'}$ = 5.9), 7.17 (d, 1 H, C_4 H), 7.32 (d, 1 H, C_5 H); MS, *m/e* 325

(21) J. M. Brown and P Workman, *Radiat. Res.*, 82, 171 (1980).
(22) E. J. Prisbe, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, 43, 4784 (1978).
(23) H. G. fletcher, Jr. *Methods Carbohydr. Chem.*, 2, 228 (1963).

(M^+). Anal. ($C_{13}H_{15}N_3O_7$) C, H, N.

The middle band from the plates was scraped off and extracted with ethyl acetate and the solvent was removed under vacuum. The residue was recrystallized from ethyl ether to yield 0.91 g (14%) of **13**: mp 124 °C; UV (EtOH) λ_{max} 220 nm (ϵ 4545), 318 (7273); IR (KBr) 1760 (OAc), 1740 (OAc), 1650 (C=C), 1470 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.92 (s, 3 H, OAc), 2.08 (s, 3 H, OAc), 3.93–4.26 (m, 3 H, $C_{5',6'}$ H), 5.02 (m, 1 H, $C_{2'}$ H), 5.58 (dd, 1 H, $C_{4'}$ H), 6.04 (m, 1 H, $C_{3'}$ H), 6.78 (d, 1 H, $C_{1'}$ H, $J_{1',2'}$ = 12.0), 7.18 (d, 1 H, C_4 H), 7.39 (d, 1 H, C_5 H); MS, m/e 325 (M^+). Anal. ($C_{13}H_{15}N_3O_7$) C, H, N.

The material from the lower band of the preparative TLC plates after recrystallization from ethyl ether yielded 0.19 g (3%) of **15**, mp 132 °C; UV (EtOH) λ_{max} 226 nm (ϵ 3823), 312 (6446); IR (KBr) 1745 (OAc), 1465 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 2.03 (s, 3 H, OAc), 2.12 (s, 3 H, OAc), 3.67–4.18 (m, 3 H, $C_{5',6'}$ H), 4.37 (dd, 1 H, $C_{4'}$ H), 6.04–6.42 (m, 2 H, $C_{2',3'}$ H), 6.99 (d, 1 H, $C_{1'}$ H), 7.16 (d, 1 H, C_4 H), 7.33 (d, 1 H, C_5 H). Anal. ($C_{13}H_{15}N_3O_7$) C, H, N.

Reacion of 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-D-glucose (10) with 1-(Trimethylsilyl)-2-nitroimidazole (2). Stannic chloride (3.5 mL, 30 mmol) was added to a solution of **2** [prepared from 2.0 g (17.7 mmol) of **1**] and 3.32 g (10 mmol) of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-glucose in 1,2-dichloroethane (100 mL). The mixture was heated at 60–70 °C for 45 min and then washed with saturated aqueous sodium bicarbonate and water. The organic phase was dried and evaporated to dryness. The preparative TLC plates with benzene/ethyl acetate (3:2) as the eluant gave two major bands. Extraction of the compound from the faster band with ethyl acetate produced 0.17 g (5.2%) of pure **11** as white needles, mp 136 °C. The slower band upon extraction with ethyl acetate yielded 0.49 g (15.1%) of **13** as white needles, mp 124 °C, and a last minor band yielded 30 mg (<1%) of **15**, mp 124 °C. These derivatives were found to be identical with the analogues isolated in the reaction with triacetylglucal.

1-(2',3'-Dideoxy-α-D-*erythro*-hex-2'-enopyranosyl)-2-nitroimidazole (12). A solution of **11** (325 mg, 1 mmol) in 15 mL of presaturated methanolic ammonia was stored at 0 °C overnight and then evaporated to dryness. The solid residue was crystallized from ethanol to yield 160 mg (66.3%) of **12** as colorless prisms: mp 152 °C; UV (EtOH) λ_{max} 216 nm (ϵ 4400), 315 (6300); IR (KBr) 3350–3100 (OH), 1640 (C=C), 1480 and 1355 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 3.74 (m, 4 H, $C_{5',6'}$ H and OH), 4.60 (br s, 1 H, OH), 4.85 (dd, 1 H, $C_{2'}$ H), 5.66 (m, 2 H, $C_{3',4'}$ H), 6.64 (dd, 1 H, $C_{1'}$ H), 7.20 (d, 1 H, C_4 H), 7.64 (d, 1 H, C_5 H). Anal. ($C_9H_{11}N_3O_5$) C, H, N.

1-(2',3'-Dideoxy-β-D-*erythro*-hex-2'-enopyranosyl)-2-nitroimidazole (14). A solution of **13** (325 mg, 1 mmol) in 15 mL of presaturated methanolic ammonia was stored at 0 °C overnight and then evaporated to dryness. The residue was purified by preparative TLC with chloroform/methanol (5:1) to yield 230 mg (95.4%) of **14** as amorphous compound: UV (EtOH) λ_{max} 214 nm (ϵ 3484), 314 (4590); IR (KBr) 3300 (broad, OH), 1645 (C=C), 1475 and 1355 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 3.42 (m, 4 H, $C_{5',6'}$ H and OH), 4.68 (br s, 1 H, OH), 4.93 (m, 1 H, $C_{2'}$ H), 5.77 (m, 2 H, $C_{3',4'}$ H), 6.80 (dd, 1 H, $C_{1'}$ H), 7.10 (d, 1 H, C_4 H), 7.52 (d, 1 H, C_5 H). Anal. ($C_9H_{11}N_3O_5$) C, H, N.

1,2,3-Trideoxy-3-(2'-nitro-1'-imidazolyl)-D-*erythro*-hex-1-enopyranose (16). A solution of **15** (162.5 mg, 0.5 mmol) in 10 mL of presaturated methanolic ammonia was kept at 0 °C overnight and then evaporated to dryness. The residue was crystallized from ethanol to yield 83 mg (69%) of **16**: mp 192 °C dec; UV (EtOH) λ_{max} 226 nm (ϵ 3085), 316 (5959); IR (KBr) 3350–3200 (OH), 1645 (C=C), 1475 and 1355 (NO_2) cm^{-1}; NMR (Me_2SO-d_6) δ 3.15–4.25 (m, 4 H, $C_{4'-6'}$ H), 4.77 (t, 1 H, $C_{6'}$ OH), 5.48 (d, 1 H, $C_{4'}$ OH), 6.15–6.60 (m, 2 H, $C_{2',3'}$ H), 7.08 (br s, 1 H, $C_{1'}$ H), 7.55 (d, 1 H, C_4 H), 8.00 (d, 1 H, C_5 H). Anal. ($C_9H_{11}N_3O_5$) C, H, N.

Partition Coefficients. We determined the partition coefficients by utilizing the procedure of Fujita et al.[24] The compounds were dissolved in phosphate buffer (0.1 M, pH 7.4) and then stirred with an equal volume of octanol at room temperature for 1 h. The concentration of the nitroimidazole nucleosides in the aqueous phase was determined spectrophotometrically.

Biological Experiments. Asynchronous monolayer cultures of Chinese hamster (V-79) cells were employed in all the experiments. The monolayers were derived from exponetially growing cultures. The techniques used for culturing and handling this cell line were followed as reported earlier.[5] To determine cytotoxicity, petri dishes containing approximately 200 V-79 cells were exposed to a range of concentraitons of each drug for 2 h at 37 °C. At the end of the specific time interval, the medium containing the drug was removed and replaced with 3 mL of fresh medium. Cultures were incubated for 6 days at 37 °C in an atmosphere of 95% air/5% CO_2. The resulting colonies were fixed in absolute ethanol, stained with Methylene blue, and counted.

The radiosensitizing studies were carried out by irradiating the cells inside sealed containers under hypoxia, with a cobalt-60 source at a dose rate of approximately 230 rad/min. The cells were plated in permanox petri dishes (60 × 15 mm, Lux Scientific Corp.), which were kept in containers capable of holding seven petri dishes. The hypoxia was achieved by flushing the containers with 95% N_2/5% CO_2 for 1 h at 37 °C in the presence of an appropriate concentraiton of the compound. The total drug exposure time was limited to 2 h. After irradiation, the medium containing the drug was removed and replaced wiht fresh medium. The cultures were incubated for 6 days at 37 °C in an atomosphere of 95% air/5% CO_2. The reuslting colonies were fixed in ethanol, stained with Methylene blue, and counted. Complete survival curves were obtained for each agent at radiation doses of 400 to 2700 rad. The D_0 value was calculated for each compound, and the ratio of the D_0 value of the hypoxic control cells to the D_0 value of the hypoxic drug-treated cells provided the sensitizer enhancement ratio of the corresponding agent.

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(24) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964).