Potential Radiosensitizing Agents. 2. Synthesis and Biological Activity of Derivatives of Dinitroimidazole with Oxiranes[1]

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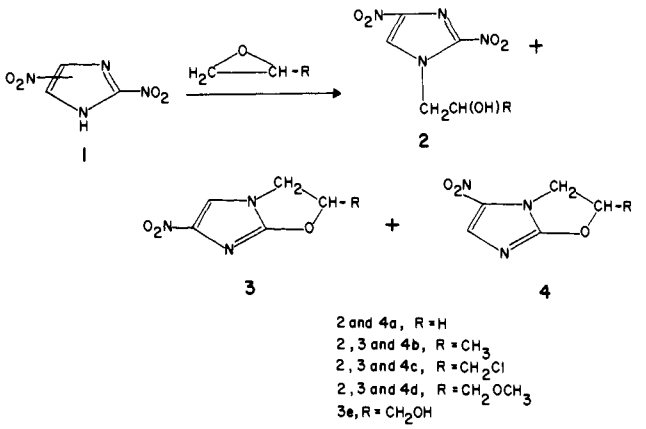
A series of 1-substituted 2,4-dinitroimidazole analogues have been synthesized and tested for their radiosensitizing ability for selectively sensitizing hypoxic mammalian cells to the lethal effect of radiation. The reaction of 2,4-(5)-dinitroimidazole (1) with a variety of oxiranes upon heating in absolute ethanol yielded the expected 1-substituted 2,4-dinitroimidazoles (2) and also resulted in the formation of a novel class of isomeric nitroimidazo[2,1-*b*]oxazoles (3 and 4) by intramolecular cyclization. The results of radiosensitizing activity of these agents against hypoxic Chinese hamster cells (V-79) indicated that 2,4-dinitroimidazoles were better sensitizers than the nitroimidazo[2,1-*b*]oxazoles, suggesting the necessity of the 2-nitro function in the molecule. The 1-(2-hydroxy-3-methoxypropyl)-2,4-dinitroimidazole (**2d**) was found to be the most effective radiosensitizer of this series.

The radiosensitizing effect of a variety of nitro aromatic derivatives has been actively investigated during the past few years, in an effort to selectively sensitize the relatively resistant hypoxic tumor cells toward radiotherapy.[2-4] Among the chemical sensitizers tested so far, 1-(2-hydroxy-3-methoxypropyl)-2-nitroimidazole (misonidazole) has been found to be an effective radiosensitizer of hypoxic cells[2,3] and is currently being evaluated clinically.[5,6] However, the large doses of misonidazole required for activity were found to be a limiting factor because of resulting neurotoxicity. Peripheral neuropathy was encountered in a relatively large number of patients at the dose levels tested.[5,6] Furthermore, misonidazole has been shown to be a mutagenic compound.[7] We, therefore, have undertaken a systematic approach to design and synthesize various analogues of nitroimidazoles in order to study the relationship between structure and biological activity that might lead to a more advantageous radiosensitizing agent.

The structure–activity studies of a series of nitrobenzene analogues have shown that the electron-negative substituents increased the radiosensitizing effectiveness,[8] thus confirming the earlier postulation that the electron affinity of the molecule was important.[9] A direct correlation between the sensitizing efficiency and electron affinity of the radiosensitizers has been shown by pulse radiolysis studies on one-electron transfer reactions.[10]

As part of our effort to search for more active and less toxic sensitizers, initially, a series of 2-substituted 5-nitroimidazoles were synthesized by replacing the 2-CH_3 group of metronidazole by a variety of groups (CH_2OH, CH_2Cl, CH_2OAc, $COCH_3$, $NHCOCH_3$) possessing potential for electronic, hydrophobic, or hydrophilic interactions.[11]

Scheme I



However, the 2-nitroimidazole derivatives were found to be more effective sensitizers. Since the CNS toxicity has been the critical limiting factor in the clinical use of misonidazole, a quaternary methiodide and an *N*-oxide of 1-(piperidinoethyl)-2-nitroimidazole were fabricated in an attempt to limit their crossing of the blood–brain barrier.[12] Although the latter derivative was 4-fold less toxic than misonidazole, it did not prove to be an effective sensitizer. A series of dinitroimidazoles were then synthesized in an effort to increase the electron affinity of the 2-nitroimidazole nucleus.[13] Dinitro derivatives of benzene have been reported to possess greater electron affinity than the corresponding nitrobenzene analogues, as measured by the Hammett σ constant.[8] Dinitropyrrole analogues were also found to be effective radiosensitizers in both in vitro and in vivo systems.[14] Among the dinitroimidazoles, 1-(2-hydroxyethyl)-2,4-dinitroimidazole was the most effective radiosensitizer producing an enhancement ratio of 2.0 at 100 μM concentration when tested against the Chinese hamster cells (V-79) in vitro.[15] This agent was found to more efficient than misonidazole at this concentration.[15] Therefore, in the present study we have synthesized a

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series of 2,4-dinitroimidazoles by reaction of 2,4(5)-dinitroimidazole with a variety of oxiranes and have compared the radiosensitizing effectiveness of the resultant derivatives by utilizing the Chinese hamster cells in vitro as the test system in an effort to elucidate the structure–activity relationship in this series.

Chemistry. The alkylation of 2,4(5)-dinitroimidazole (1) by reaction with ethylene oxide produced the expected 2,4-dinitro-1-(2-hydroxyethyl)imidazole (**2a**) and also resulted in the formation of a cyclized product which was confirmed to be the 2,3-dihydro-5-nitroimidazo[2,1-*b*]oxazole (**4a**)[13] (Scheme I). In a similar manner, reactions were carried out by reacting 1 with a variety of oxiranes. Initially, treatment of 1 with propylene oxide in absolute ethanol either in the presence or absence of a catalytic amount of sodium hydroxide at room temperature produced a mixture of **2b** and **4b**. The isomeric compound **3b** was not obtained from this reaction. The reaction of 1 with epichlorohydrin was attempted in absolute ethanol at room temperature for 48 h and remained incomplete as followed by TLC. However, this reaction went to completion upon heating, and the reaction products were separated by preparative TLC to afford the alcohol **2c** and the isomeric imidazo[2,1-*b*]oxazoles **3c** and **4c**. Similarly, reaction of 1 with 1,2-epoxy-3-methoxypropane in absolute ethanol at room temperature for 24 h was negligible. However, on heating this solution, the reaction was completed to give a mixture of three products which were separated by preparative TLC to yield the alcohol **2d** and the isomeric imidazo[2,1-*b*]oxazoles **3d** and **4d**. The structures of these isomeric compounds were confirmed by utilizing proton chemical shifts. The 5- and 6-nitroimidazo[2,1-*b*]oxazoles were differentiable by the significant downfield shift of the methylene protons closer to the imidazole ring, caused by the electron-withdrawing effect of the nitro group, an effect which is higher for the 5-nitro than for the 6-nitro isomers.[16] We have also observed that the 5-nitro isomers are generally freely soluble in solvents such as chloroform and methanol, whereas the corresponding 6-nitro isomers are appreciably less soluble in the same solvents.

Since in these reactions the alcohols **2c** and **2d** were obtained as minor components, we attempted various experiments to improve yields of these alcohols for biological evaluation. Accordingly, reaction of 1 in neat epichlorohydrin or 1,2-epoxy-3-methoxypropane during 96 and 48 h at room temperature, respectively, afforded higher yields (approximately 50%) of **2c** and **2d**. The products were separated from excess oxiranes by silica gel column chromatography. Reaction of 1 with 1,2-epoxy-3-hydroxypropane was also accomplished at room temperature, since elevated temperatures were found to polymerize the oxirane. Surprisingly, this reaction afforded only one isomer, **3e**.

The generality and novelty of the reaction of oxiranes with 2,4(5)-dinitroimidazole led us to examine the mechanism by which these unusual products were being formed. From the experimental results it appeared that a logical sequence for these events is an initial reaction leading to the alcohol which could then undergo thermally induced intramolecular cyclization (Scheme II). Indeed, reaction of **2b** in absolute ethanol in the presence of excess propylene oxide, under reflux, afforded primarily **3b**. Similarly, reaction of **2c** and **2d** in absolute ethanol in the presence of excess of epichlorohydrin and 1,2-epoxy-3-methoxypropane, under reflux, afforded **3c** and **3d** respectively. However, formation of the cyclized products **4a–d** could not be satisfactorily explained by this reaction pathway. To rationalize the formation of **4a–d** it is suggested that the alternate pathway might initially involve abstraction of a proton from 1 to form an anion and subsequent direct attack of the oxiranes on one of the nitrogens of the imidazole nucleus, as depicted in Scheme II. Intramolecular cyclization in a concerted fashion may then result in the formation of **3** and/or **4**, depending upon the position of the involved N. Application of heat to the reaction mixture, however, favors the formation of **3**.

Scheme II

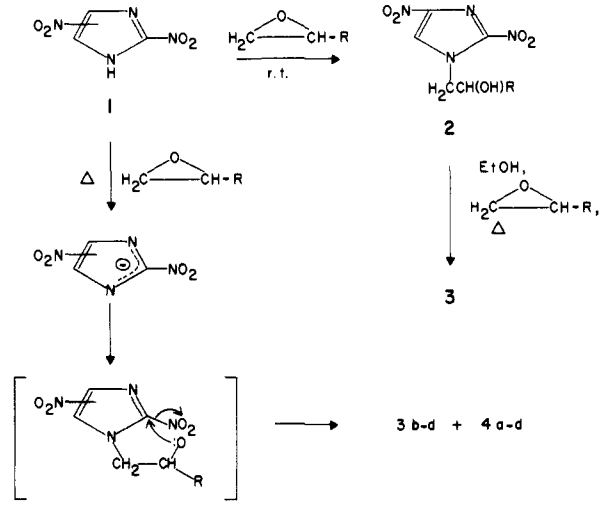

Table I. Biological Activity of Nitroimidazole Derivatives against Chinese Hamster Cells in Vitro

no.	ED_{50}, mM	radiosensitization: concn, mM	radiosensitization: enhancement ratio
2a	1.2	0.1	2.0
2b	1.1	0.5	2.1
2c	0.25	0.1	1.5
2d	2.2	0.1	1.8
		0.5	2.1
3b	1.5	0.1	1.2
3c	1.3	0.1	1.1
3d	1.5	0.1	1.1
3e	2.8	1.0	1.0
4a	1.0	0.25	1.6
4b	0.62	0.5	1.1
4c	0.61	0.5	1.1
4d	0.68	1.0	1.0

Biological Results and Discussion

The assessment of the radiosensitizing effectivity of the newly synthesized compounds depended upon their ability to sensitize hypoxic Chinese hamster cells (V-79) toward ionizing radiation. The results are listed in Table I. Initially the toxicity experiments were conducted to determine the highest concentration of various nitroimidazoles which may be essentially nontoxic to the growth of Chinese hamster cells in culture upon exposure for 2 h. The toxicity experiments were performed both in air and in nitrogen to determine any differential cytotoxicity of nitroimidazole analogues under these conditions. These agents did not exhibit differential hypoxic cytotoxicity upon exposure for up to 2 h at the concentrations employed in the irradiation experiments. It has been reported that, in general, the selective toxicity of nitroimidazoles toward hypoxic cells is observed at longer periods of exposure time in culture and at relatively high concentra-

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tions.[17] In this investigation, however, we have not attempted to determine the hypoxic cytotoxicity of these agents and, therefore, exposure times of longer than 2 h were not carried out. The ED_{50} values shown in Table I represent the drug concentration needed to achieve 50% kill of Chinese hamster cells under oxygenated conditions upon exposure for 2 h. Compound **2c** with a chloromethyl group in the side chain was the most toxic agent of this series, requiring a 0.25 mM concentration to kill 50% of the exposed cells. Conversion of the chloromethyl to a hydroxymethyl function (**3e**) resulted in a compound with the least toxicity. The ED_{50} values of the remaining agents of this series were between 0.61 and 2.2 mM, suggesting that these compounds could reasonably be employed for in vitro radiosensitization studies at the nontoxic concentrations.

Preliminary experiments for radiosensitization were then carried out to determine the efficacy of each compound as an hypoxic cell radiosensitizer. Cultures of Chinese hamster cells were exposed to the maximum nontoxic drug concentration (limited to 1 mM or less) and made hypoxic by flushing with 95% N_2 and 5% CO_2 for 2 h. Complete survival curves were obtained for each compound at the various radiation doses from 400 to 3000 rad. The survival characteristics of the cell line utilized in these experiments were same as described previously.[15] The enhancement ratios for each compound were calculated by dividing the D_0 value (the radiation dose required to reduce survival by a factor of 0.37 in the exponential region) for the control hypoxic cells with the D_0 value for the cells irradiated in presence of the radiosensitizer. The oxygen enhancement ratio in these experiments was 3.0. Thus, the higher the enhancement ratio, the more potent will be the radiosensitizer. The data in Table I indicate that, in general, the various analogues of **3** and **4** are poor radiosensitizers, with enhancement ratios varying from 1.0 to 1.6. However, the 2,4-dinitroimidazole derivatives (**2**) were found to be potent radiosensitizers. The chloromethyl analogue **2c** was the least active and most toxic in this group. The radiosensitization activities of **2a**, **2b**, and **2d** were found to be similar, each achieving an enhancement ratio of 2.0 to 2.1 at the concentration of 0.1 to 0.5 mM. Although **2a** is most effective radiosensitizer at a 0.1 mM concentration, it is relatively more toxic at higher concentrations.[15] However, compound **2d** was the least toxic of this group, as indicated by the amount of drug required to inhibit 50% of the colony formation. Moreover, **2d** is effective at lower concentrations, since it produced an enhancement ratio of 1.8 at 0.1 mM concentration. To achieve a similar degree of sensitization under these conditions with misonidazole, a 5-fold concentration is needed. The present work has demonstrated that the series of 2,4-dinitroimidazoles possesses potent radiosensitizing activity in vitro and that further in vivo studies of some of these analogues specifically of **2d**, may provide an agent with better therapeutic effectivity than misonidazole.

Experimental Section

Infrared spectra were obtained using a Beckman IR-10 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded at 60 mHz on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6E spectrometer at 70-eV ionization potential using direct-inlet injection. The elemental analyses were performed by Integral Microanalytical Laboratories, Raleigh, NC. 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 was performed 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 UV light (254 nm). Evaporation of solvents was done under reduced pressure using a rotary evaporator.

Reaction of 2,4(5)-Dinitroimidazole (1) with Propylene Oxide. To a solution of 1 (0.5 g, 3.2 mmol) in 50 mL of absolute ethanol was added 10 mL of propylene oxide. The reaction mixture was stirred at room temperature for 48 h and monitored by TLC ($CHCl_3$). The solvent was removed in vacuo to leave a residual oil consisting of a mixture of **2b** and **4b**. The residue was subjected to preparative TLC using chloroform as eluant. Resulting fractions were extracted with chloroform and methanol, and spectral analysis (IR, NMR) indicated the upper fraction as **4b** and the lower fraction as **2b**. Compound **4b** was obtained as an oil, which was crystallized (ethyl ether/hexane) to yield 124 mg (23%): mp 68–69 °C; IR (KBr) 1540 and 1340 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.53 (s, C_5 H), 5.58 (m, CHO), 4.36 (m, NCH_2), 1.69 (d, CH_3); MS, *m/e* 169 (M^+), 153 (M – O), 123 (M – NO_2), 122 [M – (NO_2 + H)]. Anal. ($C_6H_7N_3O_3$) C, H, N.

Compound **2b** was also obtained as an oil after evaporating the solvent under vacuum and was crystallized (ethyl ether) to yield 319 mg (53%): mp 72–73 °C; IR (KBr) 3480 (OH), 1530 and 1320 cm^{-1} (NO_2); NMR (CD_3OD) δ 8.02 (s, C_5 H), 5.07 (m, CHO), 4.28 (m, NCH_2), 1.41 (d, CH_3); MS, *m/e* 216 (M^+), 201 (M – CH_3), 169 [M – (NO_2 + H)]. Anal. ($C_6H_8N_4O_5$) C, H, N.

Reaction of 2,4(5)-Dinitroimidazole (1) with Epichlorohydrin. A solution of 1 (0.5 g, 3.2 mmol) in 50 mL of absolute ethanol and 5 mL of epichlorohydrin was stirred at room temperature for 48 h. The reaction remained incomplete as followed by TLC ($CHCl_3$). However, the reaction was completed upon further heating the solution at 60 °C for 16 h. The solvent and excess epichlorohydrin were removed under reduced pressure to leave a residual oil, which was treated with 8 mL of 1:2 chloroform/methanol solution at 0 °C. The resulting crystalline product was filtered off and subsequently identified as **3c** by spectral analyses. The filtrate was concentrated and subjected to preparative TLC using chloroform as eluant. Resulting fractions were extracted with chloroform and methanol, and spectral analysis (IR, NMR) indicated that the faster moving band was **4c**. Compound **4c** was obtained as an oil, which was crystallized ($CHCl_3$/hexane) to yield 158 mg (25%): mp 98–99 °C; IR (KBr) 1515 and 1335 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 7.57 (s, C_5 H), 5.64 (m, CHO), 4.56 (m, NCH_2), 3.89 (d, CH_2Cl); MS, *m/e* 203 (M^+), 187 (M – O), 157 (M – NO_2). Anal. ($C_6H_6N_3O_3Cl$) C, H, N.

The middle band was obtained as a crystalline product and characterized by IR and NMR as **3c**, which was pooled with the crystalline material obtained before the preparative TLC and recrystallized (absolute ethanol) to yield 236 mg (37%): mp 170–171 °C; IR (KBr) 1505 and 1310 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.03 (s, C_5 H), 5.65 (m, CHO), 4.28 (m, NCH_2), 4.07 (d, CH_2Cl); MS, *m/e* 203 (M^+), 187 (M – O). Anal. ($C_6H_6N_3O_3Cl$) C, H, N.

The slower moving band was obtained as an oil and assigned structure **2c**, which was crystallized (ethyl ether) to yield 116 mg (15%): mp 121–122 °C; IR (KBr) 3540 (OH), 1532 and 1328 cm^{-1} (NO_2); NMR (CD_3OD) δ 7.95 (s, C_5 H), 4.49 (m, CHO), 4.10 (m, NCH_2), 3.28 (d, CH_2Cl); MS, *m/e* 250 (M^+), 234 (M – O), 203 [M – (NO_2 + H)]. Anal. ($C_6H_7N_4O_5Cl$) C, H, N.

Reaction of 2,4(5)-Dinitroimidazole (1) with 1,2-Epoxy-3-methoxypropane. A solution of 1 (0.5 g, 3.2 mmol) in 50 mL of absolute ethanol and 5 mL of 1,2-epoxy-3-methoxypropane was stirred at room temperature for 24 h. The formation of the reaction product was negligible as followed by TLC ($CHCl_3$). This reaction was subjected to completion upon further heating the mixture at 60 °C for 16 h. The solvent and excess oxirane were removed under reduced pressure to leave a residual oil. Workup in a similar manner as described in the case of reaction of 1 with epichlorohydrin afforded by fractional crystallization ($CHCl_3$/CH_3OH) part of a material which was characterized as **3d**. Preparative TLC of the filtrate using chloroform as eluant afforded a faster moving fraction as an oil, which was identified as **4d** and was crystallized (ethyl ether/hexane) to yield 166 mg (26%): mp 71–72 °C; IR (KBr) 1510 and 1335 cm^{-1} (NO_2); NMR ($CDCl_3$)

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δ 7.57 (s, C_6 H), 5.54 (m, CHO), 4.52 (m, NCH_2), 3.78 (d, CH_2O), 3.42 (s, CH_3); MS, *m/e* 199 (M^+), 183 (M - O), 125 [M - C(OH)CH_2OCH_3]. Anal. ($C_7H_9N_3O_4$) C, H, N.

The middle fraction was obtained as a crystalline product, which was characterized by IR and NMR as **3d**, and was recrystallized (absolute ethanol) to yield a total of 223 mg (35%): mp 159-160 °C; IR (KBr) 1500 and 1320 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.04 (s, C_5 H), 5.47 (m, CHO), 4.20 (m, NCH_2), 3.70 (d, CH_2O), 3.28 (s, CH_3); MS, *m/e* 199 (M^+), 183 (M - O), 125 [M - C(OH)CH_2OCH_3]. Anal. ($C_7H_9N_3O_4$) C, H, N.

The lower fraction was obtained as an oil and assigned structure **2d**, which was crystallized (ethyl ether) to yield 106 mg (14%): mp 71-72 °C; IR (KBr) 3500 (OH), 1536 and 1326 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.08 (s, C_5 H), 4.63 (m, CHO), 4.00 (m, NCH_2), 3.48 (d, CH_2O), 3.33 (s, CH_3); MS, *m/e* 246 (M^+), 200 (M - NO_2), 183 [M - (NO_2 + OH)], 154 (M - 2NO_2). Anal. ($C_7H_{10}N_4O_6$) C, H, N.

Reaction of 2,4(5)-Dinitroimidazole (1) with 1,2-Epoxy-3-hydroxypropane. A suspension of 1 (0.5 g, 3.2 mmol) in 5 mL of 1,2-epoxy-3-hydroxypropane was stirred at room temperature for 60 h (1 went into solution after 4 h); the reaction was followed by TLC (EtOAc); the excess oxirane appeared polymerized during the reaction. After the reaction was completed, the mixture was deposited on a silica gel column (60 g) and eluted first with chloroform (250 mL) and then followed by ethyl acetate (2.5 L); 25-mL fractions were collected. The fractions as monitored by TLC (EtOAc) were indicative of only a single component. The appropriate fractions were combined and concentrated to afford crystalline product **3e**, which was recrystallized (EtOAc) to yield 180 mg (31%): mp 167-168 °C dec; IR (KBr) 3336 (OH), 1516 and 1310 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.35 (s, C_5 H), 5.44 (m, CHO), 4.31 (m, NCH_2), 3.77 (dd, CH_2O); MS, *m/e* 185 (M^+), 169 (M - O). Anal. ($C_6H_7N_3O_4$) C, H, N.

General Procedure for Cyclization of 1-(2-Hydroxyalkyl)-2,4-dinitroimidazoles 2b-d into 6-Nitro-2,3-dihydroimidazo[2,1-*b*]oxazoles 3b-d. In a typical experiment a solution of 100 mg of **2b** in 10 mL of absolute ethanol and 10 mL of propylene oxide was refluxed for 48 h at 40 °C. The solvent was evaporated under reduced pressure and the residue was characterized by NMR and MS as **3b**, which was recrystallized (absolute ethanol) to yield 47 mg (60%): mp 156-157 °C; IR (KBr) 1500 and 1315 cm^{-1} (NO_2); NMR (Me_2SO-d_6) δ 8.39 (s, C_5 H), 5.64 (m, CHO), 4.27 (m, NCH_2), 1.41 (d, CH_3); MS, *m/e* 169 (M^+), 153 (M - O), 123 (M - NO_2). Anal. ($C_6H_7N_3O_3$) C, H, N. Compounds **3c** and **3d** were obtained similarly in 75 and 78% yield, respectively.

1-(2-Hydroxy3-methoxypropyl)-2,4-dinitroimidazole (2d). This compound was synthesized by the following modified procedure to obtain a higher yield than described above under the reaction of 1 with 1,2-epoxy-3-methoxypropane. To 1.2 g (7.6 mmol) of 1 was added 25 mL of 1,2-epoxy-3-methoxypropane, and the mixture was stirred at room temperature for 48 h. The excess of oxirane was removed under vacuum, and the residual oil was purified by column chromatography (silica gel), initially employing chloroform as eluant and then followed by chloroform-methanol (5:1). The UV-absorbing fractions were collected and crystallized (ethyl ether) to yield 0.56 g of **2d**. The filtrate consisted of a mixture of **2d**, **3d**, and **4d**, which were separated by preparative TLC (silica gel) using chloroform as eluant. The material corresponding to **2d** was collected and crystallized to yield an additional 0.32 g, mp 71-72 °C. The total yield by this procedure was 48%.

Radiosensitization Studies. The radiosensitization studies were carried out by employing asynchronous monolayer cultures of Chinese hamster cells (V-79). The techniques used for culturing and handling this cell line have been reported earlier.[15] The cells were grown as monolayers in 25-cm^2 plastic culture flasks (Falcon) in Eagles minimum essential medium (MEM) with 15% fetal calf serum.

For toxicity tests, approximately 200 cells were placed in permanox petri dishes (60 × 15 mm, Lux Scientific Corp.) containing 3 mL of media and were allowed to attach for 2 h. The medium was then removed by aspiration and replaced by the medium containing the nitro compound under study. The cells were exposed to a range of concentrations of each drug for 2 h at 37 °C in air or in hypoxia. The plated cultures were rendered hypoxic in sealed containers capable of holding seven petri dishes, by purging with 95% nitrogen/5% CO_2 for 90 min. At the end of a 2-h period, 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.

Irradiation was carried out at room temperature by using a cobalt-60 source at a dose rate of approximately 280 rad/min. The petri dishes in the sealed containers were directly irradiated under aerobic and hypoxic conditions. Complete survival curves were obtained for each compound at the radiation doses of 400 to 3000 rad. The D_0 value was calculated for each compound and the ratio of the D_0 value for the hypoxic control cells to the D_0 value of hypoxic drug-treated cells provided the sensitizer enhancement ratio of the corresponding agent.

Effect of Structural Change on Acute Toxicity and Antiinflammatory Activity in a Series of Imidazothiazoles and Thiazolobenzimidazoles[1]

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The effect of structural change on the biological activity of a series of imidazothiazoles and thiazolobenzimidazoles is described. It was found that compounds with polar substituents at the 2 or 3 position of the ring system are less acutely toxic while maintaining antiinflammatory activity. Other structural changes, such as the incorporation of a *gem*-dimethyl substituent in the 6 position, increase acute toxicity and eliminate antiinflammatory activity. The compound with the best activity/toxicity ratio contains an alkyl sulfonyl substituent on the thiazole ring. The thiazolobenzimidazole analogues are more potent than the imidazole analogues.

In the course of compound screening as part of a search for novel antiinflammatory compounds, it was observed that a series of dihydroimidazothiazoles caused a reduction in carrageenin-induced edema.[2] Evaluation of the antiinflammatory activity of this initial series of compounds indicated that edema reduction in the carrageenin assay was observed for most of the analogues. Unfortunately,

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