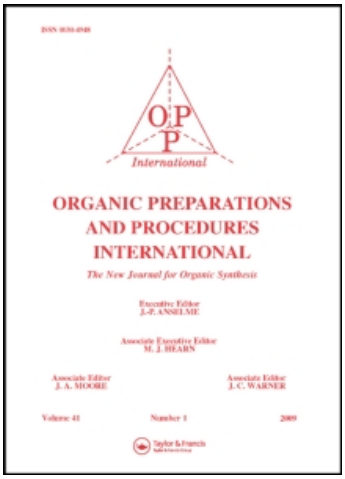

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1-METHYL-4-NITRO-5-IMIDAZOLYL SULFONES

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Anal. Calcd. for $C_6H_{11}N_5OS$: C, 35.81; H, 5.51; N, 34.80; S, 15.93

Found: C, 36.04; H, 5.54; N, 34.62; S, 16.00

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1-METHYL-4-NITRO-5-IMIDAZOLYL SULFONES

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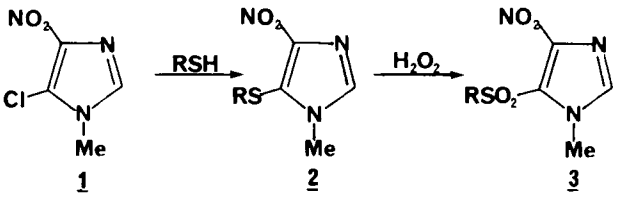
4-Nitroimidazoles substituted in the 5-position with sulfur-containing groups such as sulfide, sulfonamide, sulfone, and sulfonate have been reported as radiation sensitizers in Chinese hamster cells.[1] The sulfones, of which only a few are known, have been prepared by oxidation of the sulfides (2) or by nucleophilic displacement of halogen by a sodium arylsulfinate on 1-methyl-4-nitro-5-chloroimidazole.[2] We now report the synthesis of six new sulfones by the controlled oxidation of imidazole

sulfides (see Scheme). Several of these sulfones have been found to be ten to one hundred times more potent as radiosensitizers in radiation-induced toxicity of human colorectal tumor cells than the current standard, misonidazole.[3]



1 2 3

a) R = c-C_6H_{11} c) R = 4-t-BuC_6H_4 e) R = 4-BrC_6H_4

b) R = n-C_5H_{11} d) R = 4-$CH_3C_6H_4$ f) R = 4-ClC_6H_4

Careful control of time and temperature were required in the oxidation of the sulfides to obtain the yields quoted. The sulfones (3) displayed characteristic proton NMR signals (DMSO-d_6) for the C-2 imidazole hydrogen at δ 8.17 ± 0.03 ppm and for the N-methyl hydrogens at 4.00 ± 0.03 ppm.

EXPERIMENTAL SECTION

NMR spectra were recorded on a JEOL-FX90Q instrument with TMS internal standard. Elemental analyses were performed by the Robertson Microanalytical Laboratory, Florham Park, NJ.

1-Methyl-4-Nitro-5-imidazole Sulfides (2a-f).- An equimolar mixture of 1-methyl-4-nitro-5-chloroimidazole (1) and the requisite mercapto compound was prepared in anhydrous ethanol (20 ml of alcohol/gram of 1) and heated at 50°. This suspension was stirred vigorously while a stream of anhydrous ammonia was passed through the medium at a slow rate for 20 min. The mixture was then stirred at 50° for 5 hrs, evaporated in vacuo, and recrystallized from 3:1 ethanol:water. Yields, analyses, and physical properties are shown in Table 1.

1-Methyl-4-nitro-5-imidazole Sulfones (3a-f).- The sulfide to be oxidized was dissolved in glacial acetic acid (10 ml/gram sulfide), stirred

vigorously, and heated at 60° while 30% hydrogen peroxide (5 ml/1 mmole of sulfide) was added dropwise over 15 minutes. The temperature was held at 60° until the initial yellow color of the reaction mixture faded. This time varied from sample to sample but was usually 3-6 hrs. The temperature

TABLE 1. Physical Data on Sulfides (2)

Compd.		2a	2b	2c	2d	2e	2f
mp(°C)		137-139	73.5-75	104.5-106	110-111	146-150	126-127
Yield(%)		74	54	77	62	90	63
Anal. (Found)	C	49.77 (49.56)	47.15 (46.88)	57.75 (57.41)	53.01 (52.90)	38.23 (38.17)	44.53 (44.53)
	H	6.27 (6.21)	6.59 (6.70)	5.88 (6.00)	4.45 (4.30)	2.57 (2.63)	2.99 (3.10)
	N	17.41 (17.56)	18.32 (18.11)	14.42 (14.04)	16.86 (17.10)	13.38 (13.11)	15.58 (15.55)

TABLE 2. Physical Data on Sulfones (3)

Compd.		3a	3b	3c	3d	3e	3f
mp.(°C)		169-171	96-97.5	128-129	127-129	152-154	180-182
Yield(%)		87	80	79	63	81	69
Anal. (Found)	C	43.94 (43.92)	41.37 (41.40)	52.00 (51.89)	46.97 (47.09)	34.69 (34.43)	39.81 (39.82)
	H	5.53 (5.58)	5.59 (5.80)	5.30 (5.40)	3.94 (3.77)	2.33 (2.26)	2.67 (2.66)
	N	15.38 (15.28)	16.08 (16.05)	13.00 (12.84)	14.94 (14.83)	12.14 (11.92)	13.93 (14.01)

was raised to 80° for 1 hr; then the rection mixture was stirred at room temperature for 12 hrs to complete the oxidation. The mixture was diluted with water, the precipitate collected, washed on the filter with water and recrystallized from 95% ethanol (See Table 2).

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3. Biological results on the radiosensitizing effects of these compounds will be reported elsewhere.

A CONVENIENT SYNTHESIS OF PYRROLE-3-CARBOXALDEHYDE

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Pyrrole-3-carboxaldehyde (3) may become an important synthon[1] in the design of complex compounds derived from 3-substituted pyrroles.[2,3] Yet there exists no efficient synthesis of 3 on a reasonable scale. It has been obtained in low yields from 4-formylpyrrole-2-carboxylic acid[4] and S-ethyl 4-formylpyrrole-2-thiocarboxylate[5] by decarboxylation and catalytic