Synthesis and Properties of Alkylated Imidazoles (1)

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Alkylation of 4(5)-nitroimidazole-5(4)-sulfonamide with benzyl bromide occurred on both ring nitrogens. The structures of the products could be assigned by comparison of the chemical shifts of the sulfonamide hydrogens in the nmr spectra with those of the isomeric methyl derivatives, which were prepared by differing routes. Uv and nmr spectral data are reported for a number of bromo-, nitro-, mercapto-, sulfamyl- and amino- substituted imidazoles as well as for both of the isomeric methylated derivatives of the series.

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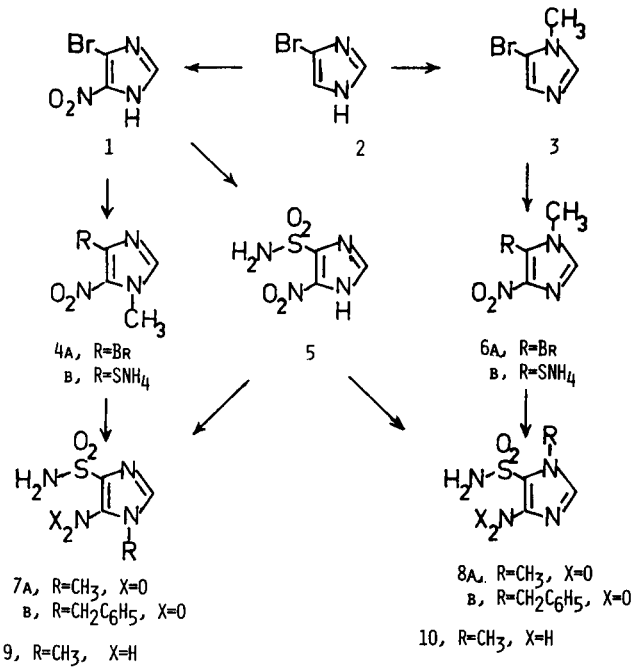
Studies on the synthesis of imidazo[4,5-*e*]-1,2,4-thiadiazine 1,1-dioxides (2) required an *N*-benzyl derivative of 4(5)-nitroimidazole-5(4)-sulfonamide (**5**) (Scheme 1) as an intermediate. Alkylation of **5** with benzyl bromide and sodium bicarbonate in DMF afforded two products with nmr and uv spectral properties appropriate for the previously unreported benzyl substituted imidazoles **7b** and **8b**. Assignment of structure of the products by comparison of spectral data for the corresponding alkyl derivatives, such as **7a** and **8a**, was not possible, however, because such data had not been reported for both compounds. To assign the structures of **7b** and **8b**, the 1-methyl-5,4-nitroimidazole-4,5-sulfonamides **7a** and **8a** were prepared by known procedures (3-7) (Scheme 1). In the course of that work it became evident that little nmr (8-10) and no uv spectral data had been reported for the imidazoles under study. We now report spectral data for the complete series of methyl substituted imidazoles as well as for the nonmethylated compounds (Table I) and assign the structures of the benzyl derivatives **7b** and **8b** by reference to it.

The two methyl substituted imidazoles **7a** and **8a** exhibited different uv absorption in neutral and in basic solution, indicating that the sulfonamide amino group was ionizable when the imidazole ring was alkylated, but the differences between the spectra of the two compounds were slight and insufficient to provide a means to characterize the benzyl derivatives **7b** and **8b**. However, **7a** and **8a** were readily distinguishable by the differences in the position of the exchangeable sulfonamide hydrogen signals in the nmr spectra. The signal of the sulfonamide hydrogen in 1-methyl-4-nitroimidazole-5-sulfonamide (**8a**) was significantly further downfield (δ 8.14) than that of 1-methyl-5-nitroimidazole-4-sulfonamide (**7a**) (δ 7.69). The differing electronic environments of the sulfonamide hydrogens in **7a** and **8a** reflected in the nmr spectra was also evident in the pK_a values for those groups in the two compounds. The pK_a of **8a** (8.1), the compound with the sulfonamide signal further downfield, was lower than the pK_a of the isomeric **7a** (8.7).

SCHEME 1



The two benzyl derivatives **7b** and **8b** exhibited a relationship of the sulfonamide amino hydrogen signals in the nmr comparable to that of the methyl derivatives **7a** and **8a**, which provided a basis for assignment of structure for the former. The higher melting benzyl derivative can be assigned as 1-benzyl-4-nitroimidazole-5-sulfonamide (**8b**) by the similarity of the sulfonamide (NH_2) signal (δ 8.21) to that of **8a** (δ 8.14), while the lower melting benzyl derivative can be assigned as 1-benzyl-5-nitroimidazole-4-sulfonamide (**7b**) by the close correspondence of its sulfonamide (NH_2) signal (δ 7.74) to that of **7a** (δ 7.69). In contrast to the small uv spectral differences between the two methyl derivatives, the anion of the 1-benzyl-4-nitro derivative (**8b**) absorbed at slightly longer wavelength (315 nm) than that of the 1-benzyl-5-nitro derivative (**7b**) (310 nm).

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Table I

Imidazole	Uv (a) λ Max (ε × 10^{-3}) Nm *p*H 1	*p*H 13	Nmr (δ) C_2-*H*	N*H*	Other (b,c,d,e)
4-Bromo- (**2**)	215 (5.0)	[213] (3.8)	7.64 (7.73) (9)	12.52	7.26 (7.30) (b) (9)
4(5)-Bromo-5(4)-nitro-(**1**)	218 (5.3)	275 (2.8)	7.99	12.13	
	312 (7.1)	354 (9.7)			
4(5)-Mercapto-5(4)-nitro-	230 (11.5)	237 (12.1)	7.15 (7.33) (10)	12.32	7.29 (8.31) (c) (10)
(ammonium salt)	[265] (3.8)	318 (8.2)			
	410 (10.2)	442 (8.9)			
4(5)-Nitro-5(4)-sulfonamide (**5**)	225 (4.5)	227 (3.1)	7.93 (8.00) (10)	14.28 (14.03) (10)	8.00 (8.10) (d) (10)
	297 (5.4)	283 (2.9)			
		357 (7.8)			
1-Methylimidazole				NC*H*$_3$	
4-Bromo-			7.58	3.65	7.27 (b)
4-Bromo-5-nitro- (**4a**)	240 (3.8) (f)		7.51 (g)	4.03 (g)	
	307 (7.3) (f)				
4-Mercapto-5-nitro- (**4b**)	[224] (10.1)	227 (10.0)	7.56	3.68	7.06 (c)
(ammonium salt)	[234] (9.9)	293 (5.4)			
	407 (7.5)	434 (7.4)			
5-Nitro-4-sulfonamide (**7a**)	235 (3.9)	235 (3.4)	8.10	3.93	7.69 (d)
	303 (6.3)	317 (5.2)			
5-Amino-4-sulfonamide (**9**)			7.19	3.39	5.35 (e)
					6.84 (d)
5-Bromo- (**3**)			7.81 (7.49) (g) (8)	3.60 (3.53) (g) (8)	7.00 (6.97) (b,g) (8)
5-Bromo-4-nitro- (**6a**)	223 (5.7) (f)		7.57 (7.58) (g) (8)	3.75 (3.69) (g) (8)	
	299 (7.1) (f)				
5-Mercapto-4-nitro- (**6b**)	[221] (5.8)	237 (10.2)	7.36 (7.43) (10)	3.35 (3.38) (10)	7.15 (7.26) (c) (10)
(ammonium salt)	238 (7.3)	285 (2.6)			
	[267] (2.1)	420 (6.6)			
	410 (5.9)				
4-Nitro-5-sulfonamide (**8a**)	[230] (4.7)	317 (4.6)	8.00 (8.00) (10)	3.87 (3.92) (10)	8.14 (8.06) (d) (10)
	300 (5.5)				
4-Amino-5-sulfonamide (**10**)			7.40	3.62	5.05 (e)
					7.25 (d)

(a) Brackets indicate a shoulder. (b) $C_{4,5}$-*H*. (c) Ammonium salt. (d) SO_2NH_2. (e) NH_2. (f) Determined in methanol. (g) Determined in deuteriochloroform.

EXPERIMENTAL

Nmr spectra were determined in DMSO-d_6 using TMS as an internal standard with a JOEL PFT-100 NMR Spectrometer, and uv spectra were determined with a Cary 15 Recording Spectrophotometer. Melting points were determined with a Mel-Temp Apparatus and were uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. The pK_a values were determined potentiometrically at 23° in 0.001*M* solutions with a Beckman Research Model *p*H meter. The pK_a of 4(5)-nitroimidazole-5(4)-sulfonamide (**5**) was 5.29 ± 0.07, that of 1-methyl-5-nitroimidazole-4-sulfonamide was 8.7 ± 0.1, and the pk_a of 1-methyl-4-nitroimidazole-5-sulfonamide was 8.1 ± 0.1.

1-Benzyl-(4 and 5)nitroimidazole-(5 and 4)sulfonamides (**8b**) and (**7b**).

A mixture of 5.76 g. (30 mmoles) of 4(5)-nitroimidazole-5-(4)-sulfonamide (7) (**5**), 5.70 g. (33 mmoles) of benzyl bromide, 3.03 g. (36 mmoles) of finely ground sodium bicarbonate and 20 ml. of DMF was stirred at 20° overnight and then filtered. The filtrate was evaporated to dryness *in vacuo* and the residue was washed with 150 ml. of dichloromethane to afford 8.40 g. of tan solid containing **7b** and **8b**. The mixture was separated by chromatography over silica gel (ethyl acetate). 1-Benzyl-4-nitroimidazole-5-sulfonamide (**8b**) was eluted first, 3.68 g. (43%), m.p. 210-212° dec; uv λ max (ε) (*p*H 1): 231 sh (4700), 297 nm (5400); (*p*H 13): 255 sh (3400), 315 nm (4600); nmr (DMSO-d_6): δ 8.21 (2H, s, exchangeable, NH_2), 8.15 (1H, s, CH), 7.22-7.41 (5H, m, C_6H_5), 5.60 (2H, s, CH_2); ms: (EI) m/e (RA) 282 (19, M^+), 106 (36), 91 (100, $C_6H_5CH_2^+$), 65 (10).

Anal. Calcd. for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85; S, 11.36. Found: C, 42.53; H, 3.55; N, 19.77; S, 11.35.

Continued elution of the column with ethyl acetate gave 3.51 g. (41%) of 1-benzyl-5-nitroimidazole-4-sulfonamide (**7b**), m.p. 184-185°; uv: λ max (ε) (methanol) 235 nm (4900), 297 (6200); (*p*H 13): 310 nm (5600): nmr (DMSO-d_6): 8.35 (1H, S, CH), 7.74 (2H, S, exchangeable, NH_2), 7.16-7.42 (m, 5, C_6H_5), 5.58 (s, 2, CH_2); ms: (CI) m/e 283 $(M + 1)^+$.

An analytical sample recrystallized from methanol-water to give colorless needles was dried (phosphorus pentoxide) for 20 hours at 70°.

Anal. Calcd. as above. Found: C, 42.58; H, 3.56; N, 19.84; S, 11.35.

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