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Aryl 5-Nitro-2-thiazolyl Sulphides, Sulphones and Ethers as Potential Antibacterials

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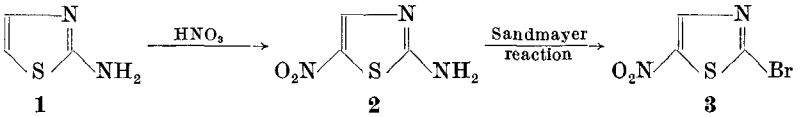
The antibacterial activity of 5-nitrofurfural thiosemicarbazone and related compounds [1] encouraged the synthesis of a large number of nitrofuryl compounds [2]. In majority of these compounds a nitro group at position 5 is necessary and a conjugated C=N-moiety in position 2 is desirable for antibacterial activity [3]. The search for antimicrobial agents with nitrofuran moiety replaced by nitropyrrol [4], nitrothiophene [5], nitropyrazole [6], nitroisooxazole [6], 1-methyl-5-nitro-imidazole [7], nitrobenzothiazole [8], nitrochromone [8], 2- or 5-nitro-thiazole [3], 5-nitro-1,3,4-thiadiazole [9] has been reported in literature. In all these cases the authors have restricted their work on thiosemicarbazones and related compounds of nitroheterocyclic aldehydes. In general the activity of these compounds is inferior to that of nitrofurans.

The antibacterial activity of 5-nitrothiazole derivatives has been studied by a few authors. 2-Amino-5-nitrothiazole has been shown to possess activity against various experimental viruses [10]. 2-Phenoxy- [12], 2-phenylthio- and 2-phenylsulphonyl-5-nitrothiazoles [13] are found to be agricultural antifungal compounds.

We have undertaken the synthesis of aryl 5-nitro-2-thiazolyl sulphides, sulphones and ethers and tested them against Mycobacterium tuberculosis var. hominis $H_{37}Rv$ in vitro.



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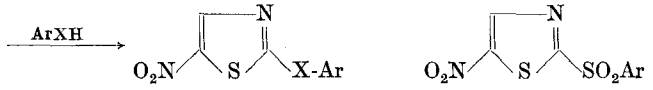

4a – n 5a – g

X = O, S

5a 6

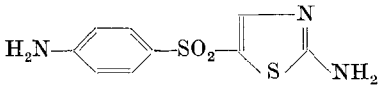

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Table 1 2-Arylthio(aryloxy)-5-nitrothiazoles **4a—n** and 2-Arylsulphonyl-5-nitrothiazoles **5a—g**

No.	R	X	M.p. °C	Molecular formula	Activity μg per ml	Analysis Calculated C	H	N	Found C	H	N
4a	Phenyl	O	106[a])	$C_9H_6N_2O_3S$	1	49.02	2.721	12.65	48.76	2.702	12.61
4b	4-Chlorophenyl	O	84[a])	$C_9H_5ClN_2O_3S$	10	41.90	1.862	10.52	41.97	1.961	10.98
4c	4-Methylphenyl	S	78[b])	$C_{10}H_8N_2O_2S_2$	0.1	47.70	3.20	11.20	47.62	3.20	11.11
4d	4-Chlorophenyl	S	87[b])	$C_9H_5ClN_2O_2S_2$	0.1	40.00	1.90	10.40	39.65	1.84	10.28
4e	2,5-Dichlorophenyl	S	135	$C_9H_4Cl_2N_2O_2S_2$	1	30.40	1.50	9.00	30.20	1.31	9.12
4f	2,4-Dichlorophenyl	S	95	$C_9H_4Cl_2N_2O_2S_2$	1	30.40	1.50	9.00	30.50	1.40	9.30
4g	2-Chlorophenyl	S	140	$C_9H_5ClN_2O_2S_2$	0.1	40.00	1.90	10.40	39.65	1.84	10.28
4h	4-t-Butylphenyl	S	89	$C_{13}H_{14}N_2O_2S_2$	10	53.15	4.85	9.50	53.06	4.80	9.52
4i	4-Hydroxyphenyl	S	170	$C_9H_6N_2O_3S_2$	0.1	48.70	2.70	12.70	48.75	2.703	12.65
4j	2-Methoxyphenyl	S	121	$C_{10}H_8N_2O_3S_2$	1	44.90	3.10	10.60	44.78	3.01	10.45
4k	4-Aminophenyl	S	170	$C_9H_7N_3O_2S_2$	1	40.00	2.83	16.72	39.82	2.767	16.59
4l	4-Acetaminophenyl	S	145	$C_{10}H_9N_3O_3S_2$	1	44.80	3.00	14.25	44.75	3.051	14.23
4m	4-Nitrophenyl	S	115	$C_9H_5N_3O_4S_2$	10	38.20	1.800	15.01	38.87	1.767	14.63
4n	2-Methylphenyl	S	128	$C_{10}H_8N_2O_2S_2$	0.1	47.70	3.20	11.20	47.62	3.20	11.11
5a	4-Nitrophenyl	SO_2	120	$C_9H_5N_3O_6S_2$	1	34.40	1.60	13.90	34.29	1.588	13.33
5b	2,4-Dichlorophenyl	SO_2	143	$C_9H_4Cl_2N_2O_4S_2$	10	31.60	1.20	8.50	31.88	1.19	8.26
5c	4-t-Butylphenyl	SO_2	135	$C_{13}H_{14}N_2O_4S_2$	1	47.90	4.40	8.70	47.85	4.33	8.59
5d	2-Methylphenyl	SO_2	101	$C_{10}H_8N_2O_4S_2$	10	40.45	3.00	9.55	40.01	2.69	9.33
5e	4-Chlorophenyl	SO_2	168[b])	$C_9H_5ClN_2O_4S_2$	10	35.49	1.620	9.50	35.65	1.657	9.24
5f	2-Chlorophenyl	SO_2	191	$C_9H_5ClN_2O_4S_2$	10	35.49	1.620	9.50	35.40	1.630	9.25
5g	4-Methylphenyl	SO_2	135[b])	$C_{10}H_8N_2O_4S_2$	0.1	40.45	3.00	9.55	40.20	3.20	9.60

[a]) Reported in ref. [12]; [b]) Reported in ref. [13]

Commercially available, inexpensive 2-aminothiazole **1** has been nitrated to yield 2-amino-5-nitrothiazole **2** which on diazotization and SANDMAYER reaction in situ gave 2-bromo-5-nitrothiazole **3** in good yield. Compound **3** underwent reaction with arylthiols and phenols to yield aryl 5-nitro-2-thiazolyl sulphides and ethers **4a—n**. Nucleophilic replacement of the bromine atom in **3** by phenyl thiol is reported in [13].

Some of the sulphides **4** have been oxidised to the corresponding sulphones **5a—g**.

The attempt to reduce **5a** by various methods to give **6** was unsuccessful. Compound **6** is a position isomer of promizole **7** which is a well known antibacterial.

The IR spectra of compounds **4** and **5** showed characteristic bands of nitro and sulphide (sulphone) linkages.

Results of bacterial screening

Out of twenty one compounds six compounds have the activity equivalent to INH, viz. compounds **4c, d, g, i, n** and **5g** (cf. Table 1).

Experimental

The physical properties of the compounds prepared are collected in Table 1. M.p. are uncorrected. IR spectra were recorded in Nujol on a Perkin-Elmer spectrophotometer model No. 427.

The phenyl thiols were prepared by literature procedures.

2-Bromo-5-nitrothiazole **3** [14]

2-Aminothiazole (20 g) was added to sulphuric acid (50 ml) below 15°C followed by fuming nitric acid (10 ml) and left overnight. Then it was poured on a mixture of sodium bromide (100 g), copper sulphate (100 g) and water (375 ml). The mixture was cooled and diazotised by sodium nitrite (25 g). It was extracted with ether, and the ether layer was concentrated to give 2-bromo-5-nitrothiazole **3** which was purified by steam distillation. Yield 15 g, m.p. 91°C.

2-Arylthio-5-nitrothiazoles **4c—n**

To a mixture of aryl thiol (0.01 mole) and 2-bromo-5-nitrothiazole (0.01 mole) in acetone (25 ml) was added pyridine (5 ml) dropwise with occasional shaking. The flask was stoppered and kept overnight at room temperature. Excess of acetone was evaporated and the solid thus obtained was treated with water, filtered and washed with water till free from pyridine. The products were recrystallised from ethanol or acetic acid.

2-Arylsulphonyl-5-nitrothiazoles **5a—g**

2-Arylthio-5-nitrothiazole (1 g) was dissolved in acetic acid (50 ml), and hydrogen peroxide (30%, 10 ml) was added. The turbidity so obtained was made clear by heating and the solution kept for three days at room temperature. The solid precipitated was filtered and washed with water till free from acetic acid. Compounds **5a—g** were recrystallised from ethanol.

2-Aryloxy-5-nitrothiazoles **4a, b**

0.01 mole of **3** was added to a well cooled solution of 0.01 mole of phenol in 50% aqueous acetone containing caustic soda (0.02 mole). The mixture was stirred and poured on water after 4 hours. The precipitate was collected by filtration and recrystallised from ethanol.

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