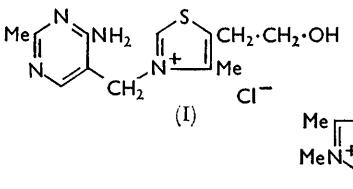
843. *Isothiazoles. Part VII.*[1] *Quaternary Isothiazoles*

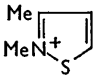
By P. Chaplen, R. Slack, and K. R. H. Wooldridge

Possible thiamine antagonists have been prepared by quaternisation of 3-methylisothiazole with selected aromatic and heterocylic halogenomethyl compounds, in an attempt to discover agents active against *Coccidia* and *Salmonella* of veterinary importance. None of these compounds had any useful anticoccidial or antibacterial activity.

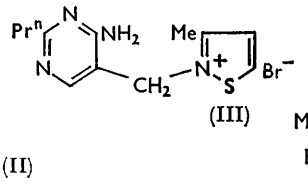
In continuation of our studies on isothiazole analogues of compounds of biological interest,[2] we considered the introduction of the isothiazole nucleus into a number of compounds related to thiamine (I). It was hoped that this might lead to agents active against *Coccidia* or *Salmonella* since it is known that thiamine is an essential growth requirement of *Salmonella gallinarum*,[3] and that the prophylactic activity against protozoal coccidiosis of certain pyridinium, thiazolium, and imidazolium salts occurs by a thiamine-reversible inhibitory mechanism.[4a,b]



(I)



(II)



(III)

(IV)

3-Methylisothiazole reacted rapidly with methyl toluene-*p*-sulphonate at 130° to give 2,3-dimethylisothiazolium toluene-*p*-sulphonate in good yield; anion exchange with sodium iodide in acetone afforded the iodide (II). Simple alkyl iodides and isothiazoles when kept for prolonged periods gave isothiazolium iodides directly. Heating led to gross decomposition and the reaction was very slow in the presence of solvents.

An isothiazole analogue (III) of amprolium [4a] was prepared readily from the appropriate bromide and 3-methylisothiazole at 130°. Other isothiazolium compounds (see Table) were prepared similarly, the more reactive bromide in general being preferred to the chloride. Chemical or catalytic reduction of the *o*-nitrobenzyl derivative to give an analogue of the carp thiamine inhibitor, 3-(*o*-aminobenzyl)-4-methylthiazolium chloride [5] was unsuccessful, only unidentified sulphur-free compounds being isolated.

Experimental

Published procedures were used to prepare isothiazole,[6] 3-methylisothiazole,[7] 4-methylisothiazole,[8] 5-methylisothiazole,[9] *o*-nitrobenzyl bromide,[10] *p*-nitrobenzyl bromide,[11] 4-chloromethylimidazole hydrochloride,[12] 4-amino-5-bromomethyl-2-methylpyrimidine,[13] and 4-amino-5-bromomethyl-2-n-propylpyrimidine.[4b] Benzyl bromide, *m*-nitrobenzyl bromide, and methyl toluene-*p*-sulphonate were obtained commercially and purified appropriately.

2-Bromomethylimidazole Hydrobromide.—2-Hydroxymethylimidazole hydrochloride [14] (5 g.)

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[4] (*a*) E. F. Rogers, R. L. Clark, A. A. Pessolano, H. J. Becker, W. J. Leanza, L. H. Sarett, A. C. Cuckler, E. McManus, M. Garzillo, C. Malanga, W. H. Ott, A. M. Dickinson, and A. Van Iderstine, *J. Amer. Chem. Soc.*, 1960, **82**, 2974; (*b*) E. F. Rogers and R. L. Clark, U.S.P. 3,030,364.
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and hydrogen bromide in glacial acetic acid (36% w/v; 100 ml.) were heated together at 100° for 4 hr. Evaporation gave a residue which was crystallised from acetonitrile to give colourless prisms of 2-*bromomethylimidazole hydrobromide* (8·1 g., 90%), m. p. 159—160° (Found: C, 19·8; H, 2·5; Br, 65·7. $C_4H_6Br_2N_2$ requires C, 19·9; H, 2·5; Br, 66·1%).

2,3-*Dimethylisothiazolium Salts* (*see Table*).—A mixture of 3-methylisothiazole (1·0 g., 0·01 mole) and methyl toluene-*p*-sulphonate (1·86 g., 0·01 mole) was refluxed for 5 min. The reaction mixture was cooled, and diluted with anhydrous ether (30 ml.) to give a solid (2·3 g.), m. p. 149—152°, which on crystallisation from ethanol–ether (1 : 1) and then anhydrous acetone afforded colourless plates of 2,3-*dimethylisothiazolium toluene*-p-*sulphonate*. A solution of 2,3-dimethylisothiazolium toluene-*p*-sulphonate (0·57 g., 0·002 mole) in the minimum volume of hot anhydrous acetone was mixed with a solution of sodium iodide (0·3 g., 0·002 mole) in hot anhydrous acetone (10 ml.). After 30 min., colourless needles (0·36 g.), m. p. >360°, were filtered off, and the mother liquor was concentrated to a small volume and cooled. A solid separated which on crystallisation from anhydrous acetone gave colourless needles of 2,3-*dimethylisothiazolium iodide* (0·22 g., 46%), m. p. 175—176° (decomp.). The iodide [41%, m. p. 171—173° (decomp.)] was also obtained directly when 3-methylisothiazole (50 g.) and methyl iodide (75 g.) were allowed to stand at room temperature for 20 days. 2-*Methylisothiazolium iodide* (43%), m. p. 147—149° (decomp.) (Found: C, 21·1; H, 2·6; I, 55·9; S, 14·1. C_4H_6INS requires C, 21·2; H, 2·6; I, 55·9; S, 14·1%), 2,4-*dimethylisothiazolium iodide* (31%), m. p. 110—112° (Found: C, 25·3; H, 3·7; S, 13·5. C_5H_8INS requires C, 24·9; H, 3·4; S, 13·3%), and 2,5-*dimethylisothiazolium iodide* (23%), m.p. 119—124° (decomp.) (Found: C, 25·0; H, 3·0; S, 13·5. C_5H_8INS requires C, 24·9; H, 3·4; S, 13·3%) were also prepared directly from the isothiazole and methyl iodide on standing at room temperature for prolonged periods.

Quaternary isothiazoles (IV)

No.	R	X	HX	M. p.	Yield (%)	Formula
1	Methyl-	Ts *	—	156—157°	60	$C_{12}H_{15}NO_3S_2$
2	Methyl-	I	—	175—176	46	C_5H_8INS
3	Benzyl-	Br	—	174—175	52	$C_{11}H_{12}BrNS$
4	*o*-Nitrobenzyl-	Br	—	189—190	33	$C_{11}H_{11}BrN_2O_2S$
5	*m*-Nitrobenzyl-	Br	—	204—205	35	$C_{11}H_{11}BrN_2O_2S$
6	*p*-Nitrobenzyl-	Br	—	180—181	33	$C_{11}H_{11}BrN_2O_2S$
7	Imidazol-4-ylmethyl-	Cl	HCl	236—238	26	$C_8H_{11}Cl_2N_3S$
8	Imidazol-2-ylmethyl-	Br	HBr	198—200	27	$C_8H_{11}Br_2N_3S$
9	4-Amino-2-methylpyrimidyl-5-methyl-	Br	HBr	239—240	62	$C_{10}H_{14}Br_2N_4S$
10	4-Amino-2-n-propylpyrimidyl-5-methyl	Br	HBr	219—220	69	$C_{12}H_{18}Br_2N_4S$

	Found (%)					Required (%)				
No.	C	H	Hal	N	S	C	H	Hal	N	S
1	50·6	5·5			22·1	50·5	5·3			22·5
2	25·1	3·5	52·4		13·5	24·9	3·4	52·7		13·3
3	49·0	4·6	29·6			48·9	4·5	29·6		
4			25·1	8·8	10·4			25·4	8·9	10·2
5			24·8	8·7	10·0			25·4	8·9	10·2
6			25·2	8·5	10·05			25·4	8·9	10·2
7			27·9	16·4	12·6			28·1	16·7	12·7
8			47·0	12·1	9·5			46·9	12·3	9·4
9			41·8	14·3	8·5			41·8	14·7	8·4
10			38·75	13·1	7·8			39·0	13·7	7·8

* Ts = Toluene-*p*-sulphonate.

The general procedure for the preparation of the remaining compounds in the Table is illustrated by the following example:

2-*Benzyl*-3-*methylisothiazolium Bromide*.—3-Methylisothiazole (14·35 g., 0·15 mole) and benzyl bromide (18 ml., 0·15 mole) were heated under reflux until the separation of an oily lower phase appeared complete. The reaction mixture was diluted with anhydrous ether, and the resulting solid was twice crystallised from ethanol–ether (1 : 1) to give colourless leaflets of 2-*benzyl*-3-*methylisothiazolium bromide* (21·5 g., 52%), m. p. 174—175° (decomp.).

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