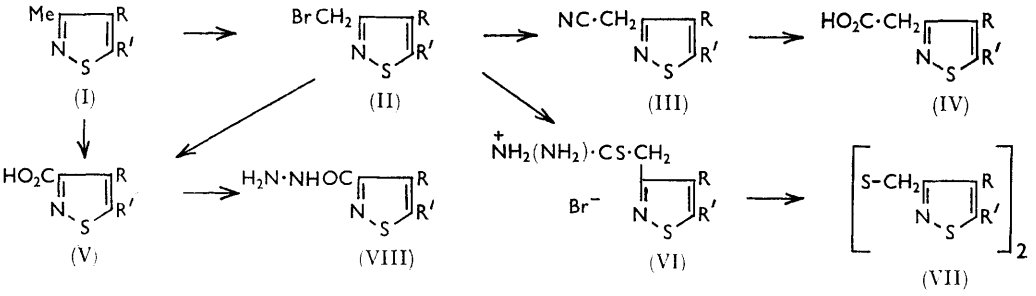
1336. *Isothiazoles. Part VIII.*[1] *Reactions of 3-Bromomethylisothiazoles*

By D. Buttimore, M. P. L. Caton, J. D. Renwick, and R. Slack

3-Methylisothiazoles (I) have been converted into 3-bromomethylisothiazoles (II), which have been oxidised to isothiazole-3-carboxylic acids (V). Some derivatives of these compounds are described.

The relatively inert character of the methyl group in 3-methylisothiazoles (I) [2,3] has limited the use of these readily available compounds for the preparation of 3-substituted isothiazoles. The 3-methyl group will, however, undergo halogenation [3] and this Paper describes their bromination with dibromodimethylhydantoin in the presence of benzoyl peroxide to give 3-bromomethylisothiazoles (II).

[1] Part VII, P. Chaplen, R. Slack, and K. R. H. Wooldridge, *J.*, 1965, 4577.
[2] D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1963, 2032.
[3] D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1964, 3114.



a: R = R′ = H; b: R = H, R′ = Br; c: R = Br, R′ = H; d: R = R′ = Br

With potassium permanganate the bromomethylisothiazoles were oxidised to isothiazole-3-carboxylic acids, in much better yields (37—60%) than those (<1—6%)* obtained from 3-methylisothiazoles. The carboxylic acids formed acid chlorides, methyl esters, amides, and hydrazides by normal methods. Decarboxylation of isothiazole-3-carboxylic acid (Va) to isothiazole [4] proceeded readily on heating, like the isothiazole-5-carboxylic acids but unlike the 4-carboxylic acids.[4]

The 3-bromomethylisothiazoles formed thiouronium salts (VI) which gave disulphides (VIIc,d) on hydrolysis. 3-Bromomethyl-4-bromoisothiazole with potassium cyanide in dimethylformamide gave the cyanomethyl compound (IIIc) which was hydrolysed to 4-bromoisothiazol-3-ylacetic acid (IVc).

Experimental

N.B. 3-Bromomethylisothiazoles are lachrymators and skin irritants.

3-Bromomethylisothiazole (IIa).—3-Methylisothiazole [4] (99 g., 1 mole), 1,3-dibromo-5,5-dimethylhydantoin (145 g., 0·51 mole), benzoyl peroxide (1 g.), and carbon tetrachloride (1 l.) were stirred under reflux for 24 hr. The hot mixture was filtered and the filtrate was distilled to give a fraction, b. p. 100—120°/30 mm. (71 g., 40%), mainly *3-bromomethylisothiazole*, which was used for subsequent experiments without further purification. A sample redistilled for analysis had b. p. 97—100°/15 mm. (Found: C, 26·7; H, 2·5; N, 7·4. C_4H_4BrNS requires C, 27·0; H, 2·3; N, 7·9%); *hexamethylenetetramine salt*, m. p. 149—150° (Found: N, 21·6; S, 9·8. $C_{10}H_{16}BrN_5S$ requires N, 22·0; S, 10·1%); *thiouronium salt* (VIa), m. p. 187—189° (Found: C, 23·9; H, 3·3; S, 25·2. $C_5H_8BrN_3S_2$ requires C, 23·6; H, 3·2; S, 25·2%). The compounds listed in Table 1 were prepared similarly.

Table 1

3-Bromomethylisothiazoles

Compound	Yield (%)	B. p./mm. or m. p.	Found (%) C	H	Br	N	S	Formula	Required (%) C	H	Br	N	S
(IIb)	35	120°/25	18·9	1·3	—	—	12·1	$C_4H_3Br_2NS$	18·7	1·2	—	—	12·5
(i)		158—160	—	—	—	17·6	7·7	$C_{10}H_{15}Br_2N_5S$	—	—	—	17·6	8·1
(ii)		155—157	—	—	47·6	12·7	19·0	$C_5H_7Br_2N_3S_2$	—	—	48·0	12·6	19·3
(IIc)	47	65—72/12	18·2	1·1	62·6	—	—	$C_4H_3Br_2NS$	18·7	1·2	62·2	—	—
(i)		166—168	—	—	—	17·3	7·7	$C_{10}H_{15}Br_2N_5S$	—	—	—	17·6	8·1
(ii)		174—176	18·4	2·2	—	—	18·8	$C_5H_7Br_2N_3S_2$	18·0	2·1	—	—	19·3
(IId)	32	170—172/23 *	14·7	0·8	—	—	9·35	$C_4H_2Br_3NS$	14·3	0·6	—	—	9·55
(i)		190—192	25·6	3·2	—	—	6·8	$C_{10}H_{14}Br_3N_5S$	25·2	3·0	—	—	6·7
(ii)		229—230	—	—	58·4	9·8	15·3	$C_5H_6Br_3N_3S_2$	—	—	58·2	10·2	15·6

(i) Hexamethylenetetramine salt; (ii) thiouronium salt. * M. p. 59—60°.

4,5-Dibromoisothiazole-3-carboxylic Acid (Vd).—4,5-Dibromo-3-bromomethylisothiazole (8·95 g., 0·027 mole) and anhydrous sodium carbonate (3·1 g., 0·029 mole) in water (220 ml.) were

* 3-Methylisothiazoles, however, are oxidised by chromic acid to isothiazole-3-carboxylic acids in good yields (see A. Holland, R. Slack, T. Warren, and D. Buttimore; forthcoming publication).

[4] A. Adams and R. Slack, *J.*, 1959, 3061.

vigorously stirred and refluxed. Potassium permanganate was added (5·64 g., 0·036 mole), in small portions over 0·75 hr. Heating was continued for 0·5 hr. and the hot suspension filtered. The cold filtrate was then extracted with ether and the extract discarded. The aqueous layer, brought to pH 2 with hydrochloric acid and extracted continuously with ether, gave 4,5-*dibromoisothiazole*-3-*carboxylic acid* (4·19 g., 55%), m. p. 153—155° (from water) (Found: C, 17·0; H, 0·6; S, 10·9. $C_4HBr_2NO_2S$ requires C, 16·7; H, 0·35; S, 11·2%). In a similar manner, 4,5-dibromo-3-methylisothiazole gave this acid in <1% yield. Yields of other isothiazole-3-carboxylic acids are given in Table 2.

TABLE 2

Yields of carboxylic acids from bromomethyl- and methylisothiazoles

Compound	Ref.	Yield from (I) (%)	Yield from (II) (%)	M. p.
(Vc)	3	2	60	177—178°
(Vb)	New cpd.[a]	6	37	179—182
(Va)	3	2	47	135—138

[a] Found: C, 22·8; H, 1·0; S, 15·4. $C_4H_2BrNO_2S$ requires C, 23·1; H, 1·0; S, 15·4%.

TABLE 3

Compounds prepared by standard methods from 3-bromomethylisothiazoles or their derivatives

			Found (%)					Required (%)			
Compound	M. p.	Solvent	C	H	Br	N	Formula	C	H	Br	N
(VIIc)[a]	77—80°	Pr^i_2O	23·4	1·5	—	6·7	$C_8H_6Br_2N_2S_4$	23·0	1·45	—	6·7
(VIId)[b]	107—109	PhH	18·8	0·7	—	5·7	$C_8H_4Br_4N_2S_4$	18·8	0·8	—	5·5
(IIIc)	—[c]	—	—	—	39·4	13·9	$C_5H_3BrN_2S$	—	—	39·4	13·8
(IVc)	100—102	Pr^i_2O[d]	27·0	1·8	—	6·2	$C_5H_4BrNOS_2$	27·0	1·8	—	6·3
—[e]	90—92	Pr^i_2O[d]	—	—	38·6	—	$C_{13}H_9Br_2NO_3S$	—	—	38·1	—

[a] Found: *M*, 401. Required *M*, 418. [b] Found: *M*, 519. Required *M*, 512. [c] B. p. 170—190° (bath)/0·5 mm.; $n_D^{23} = 1·5795$. [d] Diluted with light petroleum (b. p. 40—60°) and cooled to −60°. [e] 4-Bromophenacyl ester of (IVc) (Found: S, 7·6. Required S, 7·65%).

TABLE 4

Hydrazides

		Found (%)				Required (%)		
Hydrazide	M. p.	C	H	N	Formula	C	H	N
(VIIIa)	130—133°	33·6	3·7	28·5	$C_4H_5N_3OS$	33·55	3·5	29·3
(VIIIb)	177—180	21·4	1·8	19·0	$C_4H_4BrN_3OS$	21·6	1·8	18·9
(VIIIc)	148—152	21·7	1·6	18·5	$C_4H_4BrN_3OS$	21·6	1·8	18·9

5-*Bromoisothiazole*-3-*carbonyl chloride*.—5-Bromoisothiazole-3-carboxylic acid with thionyl chloride gave the *acid chloride*, m. p. 95—99° (from light petroleum) (Found: C, 20·7; H, 0·5; S, 14·0. $C_4HBrClNOS$ requires C, 21·2; H, 0·45; S, 14·2%). With methanol the acid chloride gave the *methyl ester* (m. p. 36—39°) (Found: N, 6·3; S, 14·6. $C_5H_4BrNO_2S$ requires N, 6·3; S, 14·4%). This ester with hydrazine hydrate gave the hydrazide (VIIIb, Table 4); other hydrazides were prepared similarly from the acid chlorides without isolation of the intermediate esters.

5-Bromoisothiazole-3-carbonyl chloride with concentrated aqueous ammonia in acetone gave the *amide*, m. p. 165—167° (Found: C, 23·1; H, 1·6; N, 13·4. $C_4H_3BrN_2OS$ requires C, 23·2; H, 1·5; N, 13·5%).

Decarboxylation of isothiazole-3-*carboxylic Acid*.—Isothiazole-3-carboxylic acid (5 g.) was gently heated over a free flame. The product distilled at 100—120°. Redistillation gave isothiazole (1 g.), b. p. 112—114° (lit.,[4] 113°/770 mm.).

The authors are indebted to Mr. S. Bance, B.Sc., F.R.I.C., for the analyses and to Mr. M. J. Parnell, L.R.I.C. for preparative assistance.

THE RESEARCH LABORATORIES, MAY & BAKER LTD.,
DAGENHAM, ESSEX.

[*Received, April 5th*, 1965.]