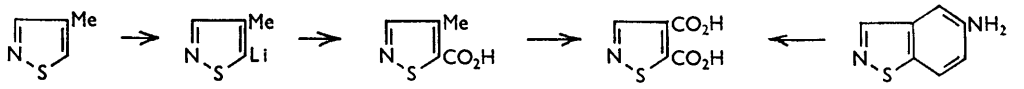
80. *Isothiazoles. Part III.*[1] *Reactions of Isothiazol-5-yl-lithium Compounds.*

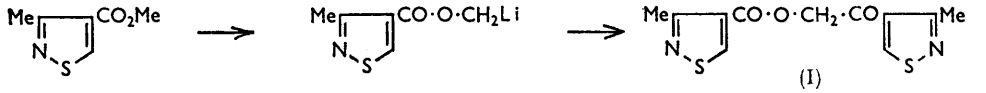
By M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge.

Isothiazoles with butyl-lithium at −70° readily form isothiazol-5-yl-lithium compounds. The lithium compounds react normally to give acids, aldehydes, and alkyl and halogeno-derivatives. The ultraviolet-absorption characteristics of these compounds are correlated.

Heterocyclic systems such as furan,[2] thiophen,[3] and thiazole [4] are lithiated by butyl- or phenyl-lithium. A similar reaction occurs with isothiazole and butyl-lithium at −70°, to give isothiazol-5-yl-lithium. The orientation was confirmed by treating the lithium compound with methyl iodide, which gave 5-methylisothiazole.[5] Again, carbonation of 4-methylisothiazol-5-yl-lithium, followed by oxidation, gave the dicarboxylic acid obtained by oxidation of 5-aminobenz[*d*]isothiazole.[6]

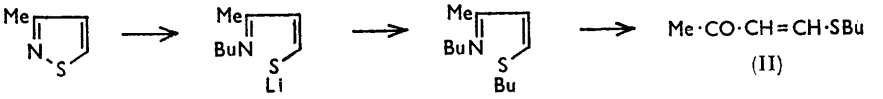


In general, 3- or 4-alkyl, halogeno-, or carboxy-substituents did not affect the ease of lithiation, as estimated by the yield of acid on carbonation. However, 3-methyl-4-nitro-isothiazole and butyl-lithium gave no carbonation product. Methyl 3-methylisothiazole-4-carboxylate gave a neutral compound, $C_{11}H_{10}N_2O_3S_2$. This appeared to be the keto-ester (I), as indicated by its infrared spectrum and conversion into 3-methylisothiazole-4-carboxylic acid on hydrolysis. Presumably methyl 3-methylisothiazole-4-carboxylate is lithiated preferentially on the methyl group of the ester and undergoes self-condensation.



(I)

During the preparation of the 5-aldehyde from 3-methylisothiazole, a by-product $C_8H_{14}OS$ was isolated. The infrared spectrum is consistent with structure (II) which could have resulted from ring-opening followed by reaction with butyl bromide; hydrolysis could occur during the isolation. Butyl bromide would be present in the reaction mixture since butyl-lithium was prepared from lithium and an excess of butyl bromide. Alternatively, butyl-lithium might add in the opposite sense, the postulated etherification of SLi then being unnecessary.

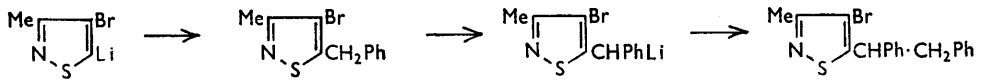


(II)

The isothiazol-5-yl-lithium compounds react normally with the appropriate reagents to give acids, aldehydes, alkyl, and halogeno-derivatives. The dialkyl-4-bromoisothiazoles were converted successively into the nitriles and acids. The reaction between 4-bromo-3-methylisothiazol-5-yl-lithium and benzyl bromide did not terminate with formation of the expected 5-benzyl-4-bromo-3-methylisothiazole (III) but gave in addition a compound

[1] Part II, Buttimore, Jones, Slack, and Wooldridge, *J.*, 1963, 2032.
[2] Ramanthan and Levine, *J. Org. Chem.*, 1962, **27**, 1216.
[3] Ramanthan and Levine, *J. Org. Chem.*, 1962, **27**, 1667.
[4] Erne and Erlenmeyer, *Helv. Chim. Acta*, 1948, **31**, 652; Beraud and Metzger, *Bull. Soc. chim. France*, 1962, 2072.
[5] Hübenett, Flock, and Hofmann, *Angew. Chem.*, 1962, **74**, 653.
[6] Adams and Slack, *J.*, 1959, 3061.

$C_{18}H_{16}BrNS$. This is probably the diphenylethylisothiazole (IV) resulting from further lithiation of the product (III) followed by reaction with benzyl bromide.



(III) (IV)

Ultraviolet absorption maxima are given in Table 1. As described in Part II,[1] the influence of substituents on the higher-wavelength band of isothiazole is additive; some new increments are given in Table 2. The values given in Part II [1] for the increments

TABLE 1.

Ultraviolet spectra of isothiazoles (in ethanol).

Subst. at position					Subst. at position				
3	4	5	$\lambda_{max.}$ (mμ)	ε	3	4	5	$\lambda_{max.}$ (mμ)	ε
H	NO_2	H	272, 215	10,900, 11,700	H	I	CHO	265, 218, 204	5520, 2530, 3450
H	NH_2	H	286, 211	4570, 5390					
H	Br	H	256, 211	7580, 2480	Me	Cl	CHO	257, 217	4030, 6650
H	I	H	264	10,530	Me	I	CHO	266	7000
Me	Cl	H	255, 213	8430, 2530	H	Me	H	251, 208	6720, 3610
Me	I	H	264, 203	9850, 6025	H	H	Me	243, 213	8960, 4400
H	H	CO_2H	263, 229	5800, 9020	Me	H	Me	246, 216·5	8350, 5760
H	Me	CO_2H	271, 231	4940, 5750	Me	Br	Me	258, 220	8780, 3780
H	Cl	CO_2H	278, 233	6700, 6500	Me	Br	Et	258, 244	7710, 3870
H	Br	CO_2H	281, 233	6800, 6000	Me	Br	CH_2Ph	258, 207	8870, 5965
Me	Cl	CO_2H	279, 233	6200, 6400	H	H	Br	241	7220
Me	I	CO_2H	288, 248, 204	5710, 3690, 5830	Me	CO_2H	Br	258, 208	9350, 8000
					Me	CN	Me	257	3900
Me	CO_2H	CO_2H	278, 252	3600, 5400	Me	$CO·NH_2$	Me	254	6180
H	H	CHO	246, 214	6840, 4670	Me	CO_2H	Me	257	9720
H	Me	CHO	255, 217	7000, 2910	Me	$CO·NH_2$	Et	254	6380
H	Cl	CHO	256, 214	7700, 4500	Me	$CO·NH_2$	Pr	254	8340
H	Br	CHO	260, 217	6500, 3600	Me	CO_2H	CH_2Ph	256, 207	7240, 21,500

TABLE 2.

Average bathochromic displacements of the isothiazole upper band due to substituents.

Subst.	4-Me	5-Me	4-Cl	4-Br	4-I	4-CO_2H	5-CO_2H	4-$CO·NH_2$
Δλ (mμ) ...	7	−1	10	13	18	8	22	7

due to 4- and 5-carboxy- and 4-bromo-substituents have been revised slightly in the light of more examples and the new figures are also included in Table 2. In every case the predicted and observed maxima agree within ±3 mμ, and it is clear that the ultraviolet absorption of isothiazoles affords valuable information as to the nature and orientation of nuclear substituents.

EXPERIMENTAL

4-Nitroisothiazole.—Concentrated sulphuric acid (640 ml.) was added slowly to isothiazole [7] (100 g., 1·18 mole) below 30°. Fuming nitric acid (64 ml.) was then added cautiously and the stirred solution was heated at 116° in an oil-bath for 19 hr. After the solution had been poured on ice (*ca.* 2 kg.), the *4-nitroisothiazole* (149 g., 97%) was filtered off and afforded colourless plates (from aqueous ethanol), m. p. 86—87° (Found: N, 21·4; S, 24·4. $C_3H_2N_2O_2S$ requires N, 21·5; S, 24·7%).

4-Aminoisothiazole.—4-Nitroisothiazole (90 g., 0·7 mole) was added in small portions to a stirred solution of stannous chloride (480 g.) in concentrated hydrochloric acid (80 ml.) at 35—40°. The mixture was stirred for 15 min., and the pH was adjusted to 11 with 50% sodium hydroxide solution. Continuous ether-extraction for 20 hr. afforded 4-aminoisothiazole [6] (24 g., 35%), m. p. 42—43°, b. p. 83—85°/0·1 mm.

[7] Wille, Capeller, and Steiner, *Angew. Chem.* (*Internat. Edn.*), 1962, **1**, 335.

4-Bromoisothiazole.—4-Aminoisothiazole (12·0 g., 0·12 mole) in 50% w/v hydrobromic acid (75 ml.) was treated with a solution of sodium nitrite (9·0 g., 0·13 mole) in water (18 ml.) at 0°. The resulting diazonium solution was added slowly to a stirred solution of cuprous bromide (38 g., 0·13 mole) in hydrobromic acid (60 ml.) at <0°. The frothing mixture was stirred for 30 min. and the pH was adjusted to 11 with 50% sodium hydroxide solution. Steam-distillation afforded *4-bromoisothiazole* (13·1 g., 67%) as colourless plates, m. p. 31—33° (Found: N, 8·2; S, 19·2. C_3H_2BrNS requires N, 8·5; S, 19·5%). The product was extremely volatile and had to be dried in a desiccator over silica gel in a refrigerator.

4-Chloroisothiazole.—Similarly, adding the diazonium solution prepared from 4-aminoisothiazole (10·0 g., 0·1 mole) in 6N-hydrochloric acid to cuprous chloride (22·0 g., 0·11 mole) in 6N-hydrochloric acid, and adjusting the pH to 11, gave *4-chloroisothiazole* (4·9 g., 41%), b. p. 140—141° (Found: N, 11·9; S, 26·9. C_3H_2ClNS requires N, 11·7; S, 26·8%).

4-Chloro-3-methylisothiazole (75%), b. p. 156—160° (Found: Cl, 26·3; N, 10·1. C_4H_4ClNS requires Cl, 26·5; N, 10·5%), was prepared similarly.

4-Iodoisothiazole.—A solution of potassium iodide (15·8 g., 0·095 mole) in water (15 ml.) was added dropwise at 0° to the diazonium solution prepared from 4-aminoisothiazole (9·5 g., 0·095 mole) in 18N-sulphuric acid (60 ml.). The mixture was stirred 1 hr. at 0° and heated on the steam-bath for 30 min. The mixture was cooled and made alkaline by the addition of 2N-sodium hydroxide. Steam-distillation afforded *4-iodoisothiazole* (13·3 g., 67%) which crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 30—31° (Found: I, 59·8; S, 14·8. C_3H_2INS requires I, 60·1; S, 15·2%).

4-Iodo-3-methylisothiazole (62%) m. p. 31—33°, b. p. 100—103°/22 mm., (Found: N, 6·0; S, 13·9. C_4H_4INS requires N, 6·2; S, 14·2%), was prepared similarly.

Isothiazole-5-carboxylic Acid.—A solution [in dry ether [8] or 15% w/w in n-hexane (Foote Mineral Co., Johnsonville, Tenn.)] of n-butyl-lithium (0·125 mole) was added to one of isothiazole (8·5 g., 0·1 mole) in dry tetrahydrofuran (100 ml.) at −70° in an atmosphere of nitrogen at such a rate that the temperature did not rise above −65°. After a further 15 min. at −65°, the mixture was poured on to an excess of dry, powdered carbon dioxide. The mixture was allowed to warm to room temperature and acidified with 2N-hydrochloric acid. The organic layer was separated, the aqueous layer was extracted with ether (2 × 100 ml.), and the combined, dried ($MgSO_4$) extracts were evaporated under reduced pressure. Crystallisation of the residue from water gave *isothiazole-5-carboxylic acid* (6·3 g., 48%), m. p. 201—202° (decomp.) (Found: C, 37·6; H, 2·7; N, 10·7; S, 24·8. $C_4H_3NO_2S$ requires C, 37·2; H, 2·3; N, 10·9; S, 24·8%).

The following *isothiazole-5-carboxylic acids* were prepared similarly: 3-methyl- (50%), m. p. 206° (decomp.), which did not depress the m. p. of an authentic specimen; [6] *4-methyl-* (40%), m. p. 175—178° (decomp.) (Found: C, 42·2; H, 3·9; N, 9·5; S, 22·1. $C_5H_5NO_2S$ requires C, 42·0; H, 3·5; N, 9·8; S, 22·4%) (4-methylisothiazole for this preparation was kindly supplied by Dr. Hübenett [5]); *4-chloro-3-methyl-* (75%), m. p. 193—195° (decomp.) (Found: C, 34·0; H, 2·5; N, 8·3; S, 18·0. $C_5H_4ClNO_2S$ requires C, 33·8; H, 2·3; N, 7·9; S, 18·1%); 4-bromo-3-methyl- [1] (56%), m. p. 202—203° (decomp.); *4-iodo-3-methyl-* (58%), m. p. 196—198° (decomp.) (Found: C, 22·6; H, 1·8; N, 5·0; S, 11·7. $C_5H_4INO_2S$ requires C, 22·3; H, 1·5; N, 5·2; S, 11·9%); *4-chloro-* (68%), m. p. 167—168° (decomp.) (Found: C, 29·8; H, 1·1; S, 19·7. $C_4H_2ClNO_2S$ requires C, 29·4; H, 1·2; S, 19·6%); *4-bromo-* (70%), m. p. 180—181° (decomp.) (Found: N, 6·6; S, 15·5. $C_4H_2BrNO_2S$ requires N, 6·7; S, 15·4%); and isothiazole-4,5-dicarboxylic acid (15%) (isolated as the sodium salt, [6] m. p. 271—273°); and *3-methylisothiazole-4,5-dicarboxylic acid* (29%), m. p. 160° (decomp.) (Found: C, 38·1; H, 2·6; S, 17·4. $C_6H_5NO_4S$ requires C, 38·5; H, 2·7; S, 17·1%).

3-Methylisothiazole-4-carbonylmethyl 3-Methylisothiazole-4-carboxylate (I).—Attempted carbonation of the lithium compound from methyl 3-methylisothiazole-4-carboxylate [1] (10·0 g., 0·064 mole) gave a residue which slowly crystallised. Recrystallisation from ethanol afforded *3-methylisothiazole-4-carbonylmethyl 3-methylisothiazole-4-carboxylate* (4·9 g., 42%), prisms, m. p. 103—105° (Found: C, 46·6; H, 3·8; N, 9·8; S, 22·8. $C_{11}H_{10}N_2O_3S_2$ requires C, 46·8; H, 3·6; N, 9·9; S, 22·7%), $\nu_{max.}$ (in CCl_4) 1659s (C=O ester stretching) and 1718s cm.$^{-1}$ (C=O ketone stretching).

A portion (1·0 g.) was refluxed with 2N-sodium hydroxide for 1 hr. Acidification gave 3-methylisothiazole-4-carboxylic acid, m. p. 236—238°, undepressed on admixture with an authentic specimen.[1]

[8] Jones and Gilman, *Org. Reactions*, 1951, **6**, 352.

5-Formylisothiazole.—Dry dimethylformamide (8·0 g., 0·11 mole) was added in one portion to a solution of isothiazol-5-yl-lithium (from 8·5 g., 0·1 mole, of isothiazole) in dry tetrahydrofuran (100 ml.) at −60° in an atmosphere of nitrogen. The mixture was stirred for 30 min. and added to an excess of cold 2N-hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether (2 × 100 ml.), to give *5-formylisothiazole* (8·5 g., 75%), b. p. 95—98°/32 mm. (Found: C, 42·0; H, 3·0; N, 12·4. C_4H_3NOS requires C, 42·5; H, 2·7; N, 12·4%) [*thiosemicarbazone*, m. p. 192—194° (decomp.) (Found: N, 29·8; S, 34·3. $C_5H_6N_4S_2$ requires N, 30·1; S, 34·4%)].

The following were prepared similarly: 5-formyl-3-methylisothiazole [1] (50%), b. p. 66—68°/1 mm.; *5-formyl-4-methylisothiazole* (55%), m. p. 26—28°, b. p. 85—91°/16 mm. (Found: C, 46·9; H, 4·2; N, 10·7. C_5H_5NOS requires C, 47·2; H, 4·0; N, 11·0%) [*thiosemicarbazone*, m. p. 215—218° (decomp.) (Found: N, 28·0; S, 31·7. $C_6H_8N_4S$ requires N, 28·0; S, 32·0%)]; *4-chloro-5-formyl-3-methylisothiazole* (47%), m. p. 48—50°, b. p. 76—77°/1 mm. (Found: C, 37·3; H, 3·5; Cl, 21·7; S, 19·7. C_5H_4ClNOS requires C, 37·2; H, 2·5; Cl, 21·9; S, 19·8%) [*thiosemicarbazone*, m. p. 231—233° (decomp.) (Found: N, 23·5; S, 27·2. $C_6H_7ClN_4S_2$ requires N, 23·9; S, 27·4%)]; 4-bromo-5-formyl-3-methylisothiazole [1] (51%), m. p. 65—67°; *5-formyl-4-iodo-3-methylisothiazole* (68%), m. p. 90—92° (Found: C, 23·6; H, 1·6; N, 5·4; S, 12·3. C_5H_4INOS requires C, 23·7; H, 1·6; N, 5·5; S, 12·7%) [*thiosemicarbazone*, m. p. 233—235° (decomp.) (Found: N, 17·6; S, 19·7. $C_6H_7IN_4S_2$ requires N, 17·2; S, 19·7%); *4-chloro-5-formylisothiazole* (65%), m. p. 38—39° (Found: C, 32·7; H, 1·7; N, 9·4; S, 21·8. C_4H_2ClNOS requires C, 32·6; H, 1·4; N, 9·5; S, 21·7%) [*thiosemicarbazone*, m. p. 215—216° (decomp.) (Found: N, 25·3; S, 29·2. $C_5H_5ClN_4S_2$ requires N, 25·4; S, 29·1%)]; *4-bromo-5-formylisothiazole* (73%), m. p. 73—74° (Found: C, 24·9; H, 1·2; Br, 41·6; N, 7·2. C_4H_2BrNOS requires C, 25·0; H, 1·1; Br, 41·6; N, 7·3%) [*thiosemicarbazone*, m. p. 220—221° (decomp.) (Found: N, 21·4; S, 24·0. $C_5H_5BrN_4S_2$ requires N, 21·1; S, 24·2%)]; *5-formyl-4-iodoisothiazole* (33%), m. p. 88—89° (Found: N, 5·8; S, 13·8. C_4H_2INOS requires N, 5·9; S, 13·4%) [*thiosemicarbazone*, m. p. 206—207° (decomp.) (Found: N, 17·6; S, 20·7. $C_5H_5IN_4S_2$ requires N, 17·9; S, 20·6%)]; 5-formyl-3-methylisothiazole-4-carboxylic acid (25%), m. p. 190—200° (analytical figures were bad) [*thiosemicarbazone*, m. p. 256° (decomp.) (Found: C, 34·7; H, 3·7; S, 26·3. $C_7H_8N_4O_2S_2$ requires C, 34·4; H, 3·3; S, 26·2%)].

4-Butylthiobuten-2-one (II).—From the preparation of 5-formyl-3-methylisothiazole, a higher-boiling *compound* (II) was obtained (11%); b. p. 87—88°/0·4 mm. (Found: C, 60·7; H, 8·5; S, 20·2. $C_8H_{14}OS$ requires C, 60·7; H, 8·9; S, 20·3%), $\nu_{max.}$ (capillary film) 1667 (C:C·C=O stretching), 1642sh (C:C·C=C stretching), and 1252 cm.$^{-1}$ (C:C·S).

5-Methylisothiazole.—Methyl iodide (15·6 g., 0·11 mole) was added in one portion to a solution of isothiazol-5-yl-lithium (from 8·5 g., 0·1 mole, of isothiazole) in dry tetrahydrofuran (100 ml.) and stirred for 30 min. at −60°. The mixture was allowed to warm to room temperature and acidified with 2N-hydrochloric acid. The organic layer was separated, and the aqueous layer extracted with ether (2 × 100 ml.). Evaporation of the dried ($MgSO_4$) extracts afforded *5-methylisothiazole* (4·0 g., 40%), b. p. 44—46°/18 mm. (Found: C, 48·0; H, 5·2; N, 13·9. C_4H_5NS requires C, 48·4; H, 5·1; N, 14·1%).

Similarly, 3-methylisothiazole [6] and methyl iodide gave a crude product, b. p. 152—158°. Purification by gas–liquid chromatography gave *3,5-dimethylisothiazole*, b. p. 157° (Found: C, 53·1; H, 6·2; N, 12·4; S, 28·3. C_5H_7NS requires C, 53·1; H, 6·2; N, 12·4; S, 28·4%). 4-Bromo-3-methylisothiazole [1] and the appropriate alkyl halide gave: *4-bromo-3,5-dimethylisothiazole* (40%), b. p. 94—97°/28 mm. (Found: C, 31·6; H, 3·2; N, 7·5, C_5H_6BrNS requires C, 31·3; H, 3·1; N, 7·3%); *4-bromo-5-ethyl-3-methylisothiazole* (34%). b. p. 100—105°/18 mm. (Found: C, 34·9; H, 3·8; N, 6·7. C_6H_8BrNS requires C, 35·0; H, 3·9; N, 6·8%); *4-bromo-3-methyl-5-n-propylisothiazole* (28%), b. p. 108—130°/17 mm. (Found: N, 6·1; S, 14·4. $C_7H_{10}BrNS$ requires N, 6·4; S, 14·6%); and *5-benzyl-4-bromo-3-methylisothiazole* (III) (13%), b. p. 123—125°/0·2 mm. (Found: C, 49·2; H, 4·1; N, 5·1. $C_{11}H_{10}BrNS$ requires C, 49·2; H, 3·8; N, 5·2%). Extraction of the distillation residue from the preparation of 5-benzyl-4-bromo-3-methylisothiazole with boiling light petroleum (b. p. 40—60°) afforded *4-bromo-3-methyl-5-(1,2-diphenylethyl)isothiazole* (IV) (10%), m. p. 54—57° (Found: N, 4·0; S, 9·4. $C_{18}H_{16}BrNS$ requires N, 3·9; S, 8·9%).

5-Bromoisothiazole.—Bromine (32·0 g., 0·2 mole) was added during 15 min. to a solution of isothiazol-5-yl-lithium (from 8·5 g., 0·1 mole, of isothiazole) in dry tetrahydrofuran (100 ml.) at −65°. The mixture was allowed to warm to room temperature and added to an excess of

cold 2N-hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether (2 × 100 ml.). The combined extracts were washed with sodium dithionite solution and dried ($MgSO_4$). Distillation afforded *5-bromoisothiazole* (5·6 g., 34%), b. p. 55—56°/23 mm., n_D^{20} 1·5825 (Found: C, 21·5; H, 1·3; Br, 48·4; N, 8·4; S, 19·5. C_3H_2BrNS requires C, 22·0; H, 1·2; Br, 48·7; N, 8·5; S, 19·5%).

5-Bromo-3-methylisothiazole-4-carboxylic Acid.—Butyl-lithium in hexane (64 g. of a 15% w/w solution, 0·15 mole) was added during 15 min. to 3-methylisothiazole-4-carboxylic acid [1] (10 g., 0·07 mole) in dry tetrahydrofuran (300 ml.) at −70° in an atmosphere of nitrogen. The mixture was stirred for 15 min. and bromine (21·6 g., 0·14 mole) was added during 10 min. The mixture was allowed to warm to −20° and added to an excess of cold 2N-hydrochloric acid. The mixture was evaporated *in vacuo* and the residue dissolved in 2N-sodium hydroxide solution (150 ml.). Acidification and crystallisation from ethanolic dimethylformamide gave *5-bromo-3-methylisothiazole-4-carboxylic acid* (8·0 g., 52%), prisms, m. p. 223—225° (Found: C, 27·2; H, 2·1; Br, 35·8; S, 14·4. $C_5H_4BrNO_2S$ requires C, 27·1; H, 1·8; Br, 36·0; S, 14·4%).

Oxidation of 4-Methylisothiazole-5-carboxylic Acid.—Potassium permanganate (6·0 g., 0·037 mole) was added in small portions to a refluxing solution of 4-methylisothiazole-5-carboxylic acid (1·5 g., 0·0105 mole) and sodium carbonate (0·75 g.) in water (120 ml.). The mixture was refluxed for a further 2 hr., then filtered hot, and the cooled filtrate was acidified with concentrated sulphuric acid. Continuous ether-extraction afforded isothiazole-4,5-dicarboxylic acid (0·34 g., 19%), m. p. 136—137° (decomp.), undepressed on admixture with an authentic specimen.[6]

4-Chloro-3-methylisothiazole-5-carbonyl Chloride.—4-Chloro-3-methylisothiazole-5-carboxylic acid (21·9 g., 0·123 mole) with thionyl chloride (100 ml.) gave *4-chloro-3-methylisothiazole-5-carbonyl chloride* (21·1 g., 92%), b. p. 114—115°/18 mm. (Found: Cl, 35·8; N, 7·0. $C_5H_3Cl_2NOS$ requires Cl, 36·2; N, 7·1%).

Methyl 4-chloro-3-methylisothiazole-5-carboxylate.—4-Chloro-3-methylisothiazole-5-carbonyl chloride (21·1 g., 0·108 mole) and dry methanol (100 ml.) gave the *methyl ester* (20 g., 97%) in needles (from methanol), m. p. 51—52° (Found: N, 7·0; S, 17·0. $C_6H_6ClNO_2S$ requires N, 7·3; S, 16·8%).

4-Chloro-3-methylisothiazole-5-carboxyhydrazide.—Methyl 4-chloro-3-methylisothiazole-5-carboxylate (9·0 g., 0·047 mole) and 100% w/w hydrazine hydrate (2·6 g., 0·052 mole) were refluxed in ethanol (50 ml.) for 30 min. The mixture was cooled and the *hydrazide* (6·2 g., 69%) filtered off. A portion was recrystallised from water to give colourless prisms, m. p. 174—176° (Found: Cl, 18·8; N, 21·9. $C_5H_6ClN_3OS$ requires Cl, 18·5; N, 21·9%).

The following were prepared in a similar way without isolation of the intermediate acid chlorides and esters; *isothiazole-5-carboxyhydrazide*, m. p. 158—160° (Found: N, 29·0; S, 22·4. $C_4H_5NO_3S$ requires N, 29·4; S, 22·4%); *4-methylisothiazole-5-carboxyhydrazide*, m. p. 131—133° (Found: N, 26·3; S, 20·0. $C_5H_7NO_3S$ requires N, 26·7; S, 20·4%); and *4-iodo-3-methylisothiazole-5-carboxyhydrazide*, m. p. 145—147° (Found: N, 14·5; S, 11·5. $C_5H_6INO_3S$ requires N, 14·8; S, 11·3%).

4-Cyano-3,5-dimethylisothiazole.—A mixture of 4-bromo-3,5-dimethylisothiazole (5·76 g., 0·03 mole) and cuprous cyanide (4·0 g., 0·045 mole) was heated to 190°. A vigorous reaction occurred and the temperature rose to *ca.* 235°. After the reaction had moderated, the temperature was kept at 210—215° for 10 min. Distillation *in vacuo* and crystallisation of the distillate from light petroleum (b. p. 40—60°) afforded *4-cyano-3,5-dimethylisothiazole* (3·63 g., 88%), m. p. 50—54° (Found: C, 52·0; H, 4·7; N, 19·9. $C_6H_6N_2S$ requires C, 52·1; H, 4·4; N, 20·3%).

Similarly were prepared 4-cyano-3-methyl-5-ethyl-, -5-n-propyl-, -5-benzyl-, and -5-(1,2-diphenylethyl)-isothiazole. No attempt was made to purify the products and the crude nitriles were hydrolysed directly.

Hydrolysis of 4-Cyano-3,5-dimethylisothiazole.—4-Cyano-3,5-dimethylisothiazole (2·0 g., 0·0145 mole) was refluxed with 2N-sodium hydroxide (12 ml.) for 2 hr. On cooling and dilution with water, *3,5-dimethylisothiazole-4-carboxamide* (0·55 g., 24%) separated. Crystallisation from ethanol–light petroleum (b. p. 80—100°) afforded needles, m. p. 164—166° (Found: C, 46·2; H, 5·3; N, 17·8. $C_6H_8N_2OS$ requires C, 46·1; H, 5·2; N, 17·9%). Acidification of the filtrate with concentrated hydrochloric acid gave *3,5-dimethylisothiazole-4-carboxylic acid* (0·97 g., 43%) which crystallised from water in prisms, m. p. 184—189° (Found: C, 46·2; H, 4·3; N, 8·9. $C_6H_7NO_2S$ requires C, 45·9; H, 4·5; N, 8·9%).

In a similar manner, crude 4-cyano-5-ethyl-3-methylisothiazole gave *5-ethyl-3-methylisothiazole-4-carboxamide* (23%), m. p. 156—158° (Found: C, 49·6; H, 6·1; S, 19·2. $C_7H_{10}N_2OS$ requires C, 49·4; H, 5·9; S, 18·8%), and *5-ethyl-3-methylisothiazole-4-carboxylic acid* (50%, m. p. 136—138° (Found: C, 49·1; H, 5·4; N, 8·0; S, 18·8. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; N, 8·2; S, 18·7%). Crude 4-cyano-3-methyl-5-n-propylisothiazole gave only *3-methyl-5-n-propylisothiazole-4-carboxamide* (9%), m. p. 131—132° (Found: N, 14·8. $C_8H_{12}N_2OS$ requires N, 15·2%).

3-Methyl-5-n-propylisothiazole-4-carboxylic Acid.—A mixture of 3-methyl-5-n-propylisothiazole-4-carboxamide (0·3 g.), potassium hydroxide (0·2 g.), water (0·5 ml.), and ethylene glycol (2·5 ml.) was refluxed for 24 hr. The mixture was cooled, filtered, and extracted with ether (25 ml.). Acidification of the aqueous layer with concentrated hydrochloric acid gave *3-methyl-5-n-propylisothiazole-4-carboxylic acid* (0·17 g., 56%), which crystallised from water in prisms, m. p. 91—93° (Found: N, 7·3; S, 17·7. $C_8H_{11}NO_2S$ requires N, 7·6; S, 17·3%).

In similar conditions the following *acids* were prepared by hydrolysis of the crude nitriles: *5-Benzyl-3-methylisothiazole-4-carboxylic* (7%), prisms (from benzene), m. p. 212—218° (Found: N, 5·7. $C_{12}H_{11}NO_2S$ requires N, 6·0%), and *3-methyl-5-(1,2-diphenylethyl)-isothiazole-4-carboxylic* (47%), needles (from aqueous ethanol), m. p. 172—176° (Found: C, 70·2; H, 5·3; N, 4·3. $C_{19}H_{17}NO_2S$ requires C, 70·5· H, 5·3; N, 4·3%).

The authors are indebted to Mr. S. Bance, B.Sc., F.R.I.C., and his staff for analyses, Mr. T. L. Threlfall, B.Sc., for spectra, Mr. P. Atkinson, A.R.I.C., for gas–liquid chromatography, and Messrs. D. Gell, D. C. Mills, M. J. Parnell, and R. J. A. Walsh for preparative assistance.

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

[*Received, July 9th,* 1963.]