376. *Isothiazoles. Part II.*[1] *Isothiazolealdehydes and Isothiazolyl Ketones.*

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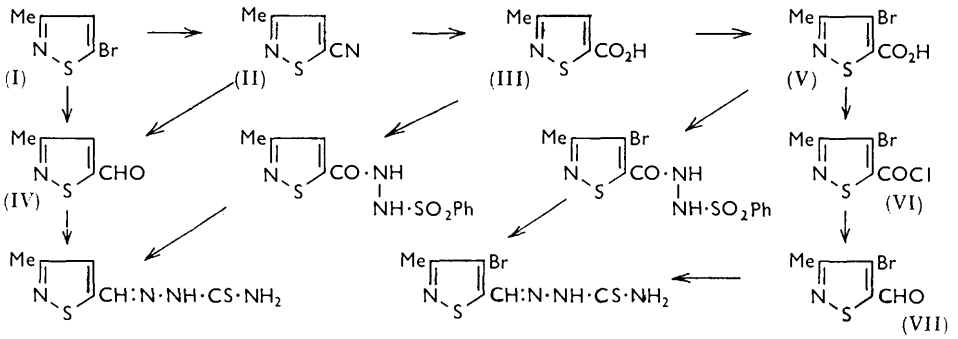
The synthesis of a number of substituted isothiazole-4- and -5-aldehydes and ketones is described, and ultraviolet absorption characteristics of isothiazoles are correlated.

Syntheses of isothiazole, its 3-methyl derivative and a number of related compounds were reported some years ago by Adams and Slack.[1,2] Since then, interest in this new monocyclic system has increased (cf. Goerdeler and Pohland [3]) and attractive new syntheses of the parent and its 3-methyl derivative have been reported.[4]

We have, meanwhile, been systematically examining the chemistry of the isothiazoles and the present paper is concerned with the synthesis and properties of the 4- and 5-aldehydes and ketones. The first paper [1] in the series described a convenient synthesis of 5-amino-3-methylisothiazole and the corresponding 5-bromo- (I), 5-cyano- (II), and 5-carboxy-compound (III).

5-Formyl-3-methylisothiazole (IV) was obtained by reduction of 5-cyano-3-methylisothiazole (II) with lithium trimethoxyaluminium hydride.[5] Reduction of the nitrile by Stephen's method [6] gave 5-aminomethyl-3-methylisothiazole as the only product, a reaction analogous to that observed in the corresponding isoxazole series.[7] The aldehyde was prepared in better yield from 5-lithio-3-methylisothiazole (from 5-bromo-3-methylisothiazole and butyl-lithium) and dimethylformamide at −70°.

Bromination of 3-methylisothiazole-5-carboxylic acid (III) gave the 4-bromo-acid (V), and reduction of the acid chloride (VI) with lithium tri-t-butoxyaluminium hydride [8] at −40° gave 4-bromo-5-formyl- (VII) and an equal amount of 4-bromo-5-hydroxymethyl-3-methylisothiazole. At −70° only the aldehyde was formed.



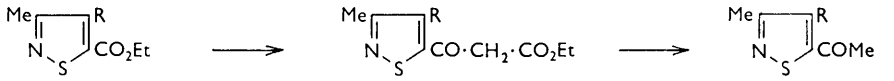
The thiosemicarbazones of these aldehydes are of chemotherapeutic interest [9] and were readily prepared from the benzenesulphonylcarboxyhydrazides by the McFadyen–Stevens [10] method carried out in the presence of thiosemicarbazide.

5-Acetyl-3-methylisothiazole (Xa) was obtained by the action of methylmagnesium iodide on 5-cyano-3-methylisothiazole (II) or by hydrolysis and decarboxylation of the

[1] The paper by Adams and Slack, *J.*, 1959, 3061, is considered as Part I.
[2] Adams and Slack, *Chem. and Ind.*, 1956, 1232.
[3] Goerdeler and Pohland, *Chem. Ber.*, 1961, **94**, 2950.
[4] Wille, Capeller, and Steiner, *Angew. Chem. (Internat. Edn.)*, 1962, **1**, 335.
[5] Cf. Brown, Shoaf, and Garg, *Tetrahedron Letters*, 1959, No. 3, 9.
[6] Stephen, *J.*, 1925, 1874.
[7] Quilico and Panizzi, *Gazzetta*, 1938, **68**, 411.
[8] Brown and Subba Rao, *J. Amer. Chem. Soc.*, 1958, **80**, 5377.
[9] McFadzean and Squires, unpublished results.
[10] McFadyen and Stevens, *J.*, 1936, 584; Newman and Cafiish, *J. Amer. Chem. Soc.*, 1958, **80**, 862.

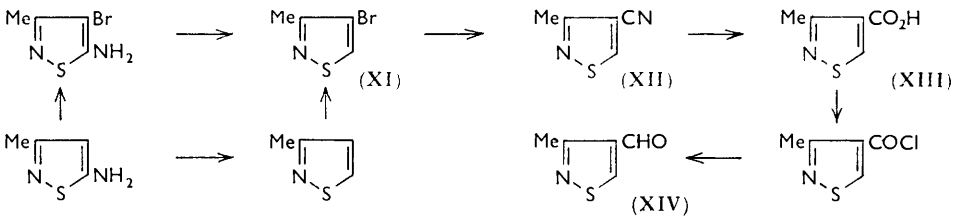
keto-ester (IXa), formed by condensation of ethyl 3-methylisothiazole-5-carboxylate (VIIIa) and ethyl acetate. 5-Acetyl-4-bromo-3-methylisothiazole (Xb) was prepared similarly from ethyl 4-bromo-3-methylisothiazole-5-carboxylate (VIIIb).

As a starting point for the synthesis of 4-carbonyl compounds, 4-bromo-3-methylisothiazole (XI) was prepared by decarboxylation of the bromo-acid (V), as well as by bromination of 3-methylisothiazole and by deamination of 5-amino-4-bromo-3-methylisothiazole. The bromo-compound (XI) and cuprous cyanide gave the nitrile (XII), which



(VIIIa : R = H) (IXa : R = H) (Xa : R = H)
(VIIIb : R = Br) (IXb : R = Br) (Xb : R = Br)

was hydrolysed to the acid (XIII). In contrast to the results in the 5-series, the 4-nitrile was relatively unreactive and did not, for example, react with methylmagnesium iodide, lithium trimethoxyaluminium hydride,[5] or stannous chloride in ethereal hydrogen chloride.[6] However, hydrolysis of the Reissert compound [11] gave 4-formyl-3-methylisothiazole (XIV). McFadyen–Stevens conditions gave only a poor yield of the thiosemicarbazone,



in contrast to the result in the 5-series. Attempts at direct formylation of 3-methylisothiazole by treatment with dimethylformamide and phosphorus oxychloride, and acylation under Friedel–Crafts conditions, were unsuccessful.

4-Acetyl-3-methylisothiazole was obtained from the 4-acid chloride and methylmagnesium iodide at −20° in the presence of ferric chloride.[12] The route used in the 5-series was unsuccessful owing to the failure of methyl 3-methylisothiazole-4-carboxylate to undergo Claisen condensation.

Attempts to prepare an isothiazole-3-carbonyl compound from 3-methylisothiazole were unsuccessful because of the unreactivity of the 3-methyl group.

In general, the isothiazole carbonyl compounds behave normally and condense readily with carbonyl reagents. The aldehydes reduce ammoniacal silver nitrate and undergo the Cannizzaro reaction.

The reactions shown by the isothiazole derivatives described in this and the first paper of the series [1] are in general agreement with the electron-density pattern previously reported.[1] Thus, positions 3 and 5 are resistant to electrophilic attack; substitution by halogens and, less easily, by the nitro-group, occurs exclusively in the 4-position. On the other hand, nucleophilic attack, exemplified by metallation, occurs easily in the 5-position, and 5-substituents appear to be as reactive as, for example, those in the 2- or 4-position of pyridine. The 3-position seems relatively inert although as yet we have few experimental results.

Ultraviolet absorption maxima are given in Table 1. The position of the upper absorption maxima may be predicted to within ±3 mμ by adding the bathochromic shifts of the individual substituents to the wavelength maxima of isothioazole itself.[13] The

[11] Popp, Blount, and Soto, *Chem. and Ind.*, 1962, 1022.
[12] Cason and Kraus, *J. Org. Chem.*, 1961, **26**, 1768.
[13] Cf. Boarland and McOmie, *J.*, 1952, 3722; Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1954, **37**, 1298.

same does not appear to be true for the molecular extinction coefficients. The average wavelength increments are given in Table 2.

TABLE 1.

Ultraviolet absorption spectra of isothiazoles (in ethanol).

Subst. at posn.					Subst. at posn.				
3	4	5	$\lambda_{max.}$ (mμ)	ε	3	4	5	$\lambda_{max.}$ (mμ)	ε
H *	H	H	244	5210	Me	Br	CHO	260·5	7850
Me *	H	H	246·5	7050	Me	CHO	H	264, 213	8150, 8700
Me *	H	Br	247	7780	Me	H	Ac	284, 242	3190, 7200
Me	Br	H	259	7060	Me	Br	Ac	295, 250	5460, 4660
Me	Br	Br	261	6920	Me	Ac	H	262, 208	7400, 7630
Me *	H	CN	272, 232	5630, 6640	Me	H	CH_2·OH	249, 219	8700, 4700
Me	CN	H	258	8260	Me	Br	CH_2·OH	258, 223	7900, 3220
Me	Br	CN	287, 243	9960, 6400	Me	CH_2·OH	H	252, 214	8100, 2000
H *	CO_2H	H	250	7800	Me	H	CH_2·NH_2	248	7400
H *	CO_2H	CO_2H	271, 232	7430, 6100	Me *	H	NH_2	266, 234	8860, 3960
Me *	H	CO_2H	270, 230	5050, 7750	Me *	NH_2	H	286	5040
Me	CO_2H	H	256	5820	Me	Br	NH_2	271, 225	6960, 3480
Me	Br	CO_2H	282, 238	5970, 5390	Me *	H	NHAc	258	9050
Me *	NO_2	H	277·5	6940	Me *	NHAc	H	272	6950
Me *	NO_2	Br	270	7240	Me *	NO_2	NHAc	287	7430
Me	H	CHO	249	7400	Me *	NH_2	NHAc	297, 250	6680, 1900

* Described in ref. 1.

TABLE 2.

Average bathochromic displacements of the higher band due to substituents in isothiazole.

Subst.	Δλ (mμ)	Subst.	Δλ (mμ)	Subst.	Δλ (mμ)	Subst.	Δλ (mμ)
4-NHAc ...	26	5-NH_2	14	4-CN	11	4-CH_2·OH...	4
5-NHAc ...	11	4-Br	12	5-CN	27	5-CH_2·OH...	−1
4-Ac	16	5-Br	−1	4-CHO	18	3-Me	4
5-Ac	37	4-CO_2R * ...	6	5-CHO	2	4-NO_2	27
4-NH_2	39	5-CO_2R * ...	23				

* R = H or alkyl.

EXPERIMENTAL

5-Formyl-3-methylisothiazole (IV).—(*a*) Anhydrous methanol (19·2 g., 0·60 mole) was added during 20 min. to a suspension of lithium aluminium hydride (7·6 g., 0·20 mole) in ether (150 ml.) at 0° in an atmosphere of nitrogen. 5-Cyano-3-methylisothiazole [1] (20 g., 0·16 mole) was added during 1 hr. and the mixture was successively kept at 0° for a further 2 hr. and treated with water (40 ml.) and 2N-sulphuric acid (200 ml.). The ethereal layer afforded *5-formyl-3-methylisothiazole* (4·8 g., 23%), b. p. 105—107°/20 mm. (Found: C, 46·8; H, 3·8; N, 10·8. C_5H_5NOS requires C, 47·2; H, 3·9; N, 11·0%). The *2,4-dinitrophenylhydrazone* crystallised from dioxan in prisms, m. p. 270—272° (Found: N, 22·7; S, 10·4. $C_{11}H_9N_5O_4S$ requires N, 22·8; S, 10·4%). The *semicarbazone* crystallised from water in prisms, m. p. 218—220° (decomp.) (Found: C, 39·4; H, 4·6; N, 30·0; S, 17·4. $C_6H_8N_4OS$ requires C, 39·1; H, 4·4; N, 30·4; S, 17·4%).

(*b*) 5-Bromo-3-methylisothiazole [1] (8·9 g., 0·05 mole) in tetrahydrofuran (50 ml.) was added during 25 min. to a solution of butyl-lithium (3·55 g., 0·055 mole) in tetrahydrofuran (100 ml.) at −70° in nitrogen. After 5 min., dimethylformamide (4·0 g., 0·055 mole) in tetrahydrofuran (5 ml.) was added, and the mixture was allowed to attain room temperature. 2N-Hydrochloric acid (40 ml.) was added and the aldehyde (2·5 g., 29%) was extracted with ether. The m. p. of the 2,4-dinitrophenylhydrazone was undepressed on admixture with that obtained by method (*a*).

5-Aminomethyl-3-methylisothiazole.—Dry hydrogen chloride was passed into a suspension of stannous chloride (30 g.) in ether (250 ml.) until two layers were obtained (4 hr.). 5-Cyano-3-methylisothiazole (7·5 g.) was added and the mixture was shaken for 3 hr. It was cooled to

−10° and treated with 10N-sodium hydroxide (250 ml.). The ethereal layer was separated, dried ($MgSO_4$), and evaporated. The residual oil was distilled to give *5-aminomethyl-3-methylisothiazole* (4 g., 55%), b. p. 110°/10 mm. (Found: C, 46·8; H, 6·4; S, 24·6. $C_5H_8N_2S$ requires C, 46·8; H, 6·3; S, 25·0%). The *dibenzenesulphonyl derivative* crystallised from ethanol in plates, m. p. 165—167° (Found: C, 50·1; H, 4·2; N, 6·7; S, 23·6. $C_{17}H_{16}N_2O_4S_3$ requires C, 50·0; H, 4·0; N, 6·9; S, 23·6%).

3-Methylisothiazole-5-carboxy-(N'-benzenesulphonylhydrazide).—3-Methylisothiazole-5-carboxyhydrazide [1] (47 g., 0·30 mole) was suspended in dry pyridine (250 ml.) at −5° and benzenesulphonyl chloride (69 g., 0·39 mole) was added during 30 min. The mixture was allowed to attain room temperature, then poured on concentrated hydrochloric acid (300 ml.) and ice (*ca.* 1 kg.). The product was crystallised from water, to give the *benzenesulphonylhydrazide* (58 g., 65%), m. p. 185—189° (Found: C, 44·4; H, 3·6; N, 14·0; S, 21·8. $C_{11}H_{11}N_3O_3S_2$ requires C, 44·4; H, 3·7; N, 14·1; S, 21·6%).

5-Formyl-3-methylisothiazole Thiosemicarbazone.—A ground mixture of the preceding benzenesulphonylhydrazide (100 g., 0·34 mole), anhydrous sodium carbonate (20 g., 0·19 mole), and thiosemicarbazide (35 g., 0·38 mole) was added during 15 min. to a stirred suspension of powdered soda-glass (150 g.) in glycerol (500 ml.) at 140—145°. The mixture was stirred at 140—145° for a further 10 min., cooled to 75°, and filtered, and the residue was washed with ethanol (500 ml.). The filtrate was diluted to 3 l. with water, to give the *thiosemicarbazone* (33·4 g., 51%), m. p. 191—196°. Crystallisation from ethanol (charcoal) gave yellow prisms, m. p. 196—200° (Found: C, 36·2; H, 3·7; N, 28·1; S, 32·0. $C_6H_8N_4S_2$ requires C, 36·0; H, 4·0; N, 28·0; S, 32·0%).

4-Bromo-3-methylisothiazole-5-carboxylic Acid (V).—3-Methylisothiazole-5-carboxylic acid [1] (454 g., 3·18 moles) was dissolved in a solution of sodium hydrogen carbonate (538 g., 6·40 moles) in water (4·5 l.). Bromine (564 g., 3·53 moles) was added during 90 min. to the stirred solution, and the mixture was stirred for a further 4 hr. and kept overnight at room temperature. The mixture was brought to pH 10 by the addition of 50% w/v sodium hydroxide and filtered. The filtrate was acidified with concentrated hydrochloric acid (*ca.* 70 ml.), to give the *carboxylic acid* (534 g., 76%), m. p. 202—203° (decomp.). Crystallisation from water gave colourless needles, m. p. 202·5—203·5° (decomp.) (Found: C, 27·4; H, 1·8; Br, 36·2; N, 6·3; S, 14·1. $C_5H_4BrNO_2S$ requires C, 27·0: H, 1·8; Br, 36·0; N, 6·3; S, 14·4%).

4-Bromo-3-methylisothiazole-5-carbonyl Chloride (VI).—A mixture of 4-bromo-3-methylisothiazole-5-carboxylic acid (534 g., 2·4 moles) and thionyl chloride (1 l.) was heated under reflux for 2 hr. The mixture was fractionally distilled to give the *5-carbonyl chloride* (549 g., 95%), b. p. 113—116°/12 mm., m. p. 31—33° (Found: N, 5·9; S, 13·3. $C_5H_3BrClNOS$ requires N, 5·8; S, 13·3%).

4-Bromo-5-formyl-3-methylisothiazole (VII).—(i) Lithium tri-t-butoxyaluminium hydride (19·0 g., 0·075 mole) in ether (200 ml.) and diethylene glycol dimethyl ether (150 ml.) was added during 90 min. to a solution of 4-bromo-3-methylisothiazole-5-carbonyl chloride (12 g., 0·05 mole) in the glycol ether (30 ml.) at −40° under nitrogen. After a further 5 min. the mixture was poured on ice (600 g.) and extracted with ether. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and concentrated to *ca.* 20 ml. *4-Bromo-5-hydroxymethyl-3-methylisothiazole* (2·2 g., 21%), m. p. 95—96°, was collected and crystallised from water (Found: N, 6·7; S, 15·2. C_5H_6BrNOS requires N, 6·8; S, 15·4%). Evaporation of the ethereal mother-liquors and crystallisation of the residue from light petroleum (b. p. 40—60°) gave colourless prisms of *4-bromo-5-formyl-3-methylisothiazole* (2·5 g., 24%), m. p. 62–64° (Found: C, 29·1; H, 1·9; N, 7·0; S, 15·6. C_5H_4BrNOS requires C, 29·1; H, 2·0; N, 6·8; S, 15·6%).

(ii) In a similar experiment at −70°, the only product was the aldehyde (4·4 g., 44%).

Methyl 4-Bromo-3-methylisothiazole-5-carboxylate.—4-Bromo-3-methylisothiazole-5-carbonyl chloride (62 g., 0·258 mole) was added during 30 min. to boiling anhydrous methanol (200 ml.). The excess of methanol was distilled off, leaving a residue of the *methyl ester* (56 g., 92%), m. p. 76—78° (Found: C, 30·5; H, 2·7; Br, 33·8; N, 5·5; S, 13·7. $C_6H_6BrNO_2S$ requires C, 30·5; H, 2·6; Br, 33·9; N, 5·9; S, 13·6%). The *ethyl ester*, b. p. 137—138°/15 mm. (Found: C, 33·3; H, 3·2; Br, 32·1; N, 5·5; S, 12·8. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; Br, 32·0; N, 5·6; S, 12·8%), was prepared similarly.

4-Bromo-3-methylisothiazole-5-carboxyhydrazide.—Hydrazine hydrate (16 g., 0·25 mole) was added during 10 min. to methyl 4-bromo-3-methylisothiazole-5-carboxylate (56 g., 0·237 mole)

in methanol (600 ml.). The mixture was refluxed for 10 min. and then cooled in ice, to give the *hydrazide* (41 g., 73%), m. p. 163—165°. Crystallisation from aqueous methanol gave colourless prisms, m. p. 166—168° (Found: C, 25·5; H, 2·8; Br, 34·1; N, 17·6; S, 13·7. $C_5H_6BrN_3OS$ requires C, 25·4; H, 2·6; Br, 33·9; N, 17·8; S, 13·6%).

4-Bromo-3-methylisothiazole-5-carboxyamide.—The 5-carbonyl chloride (60·0 g.) in dry acetone (60 ml.) gave, with aqueous ammonia (*d* 0·88; 500 ml.), the *amide* (51 g., 92%), crystallising from water in prisms, m. p. 188° (Found: C, 27·6; H, 2·2; N, 12·5. $C_5H_5BrN_2OS$ requires C, 27·2; H, 2·3; N, 12·7%).

4-Bromo-5-cyano-3-methylisothiazole.—4-Bromo-3-methylisothiazole-5-carboxyamide (4·5 g., 0·020 mole) and phosphorus oxychloride (11·5 g., 0·075 mole) were heated at 100° for 1 hr. The excess of oxychloride was distilled off and the residue poured on ice. Extraction with ether gave *4-bromo-5-cyanoiso-3-methylthiazole* (2·3 g., 55%) which crystallised from light petroleum (b. p. 60—80°) in colourless prisms (Found: C, 29·9; H, 1·2; S, 16·1. $C_5H_3BrN_2S$ requires C, 29·6; H, 1·5; S, 15·8%).

4-Bromo-3-methylisothiazole-5-carboxy-(N'-benzenesulphonylhydrazide).—(*a*) Benzenesulphonyl chloride (35·3 g., 0·2 mole) was added during 30 min. to a suspension of 4-bromo-3-methylisothiazole-5-carboxyhydrazide (35 g., 0·148 mole) in pyridine (150 ml.) at 0°. The mixture was stirred for 2 hr. at room temperature and then poured on concentrated hydrochloric acid (200 ml.) and ice (*ca.* 750 g.). The product was collected and crystallised from ethanol, to give the *benzenesulphonylhydrazide* (44 g., 79%), m. p. 162—163° (Found: Br, 21·1; N, 11·4; S, 17·2. $C_{11}H_{10}BrN_3O_3S_2$ requires Br, 21·2; N, 11·2; S, 17·0%).

(*b*) 4-Bromo-3-methylisothiazole-5-carbonyl chloride (549 g., 2·28 moles) in chloroform (750 ml.) was added during 1 hr. to a boiling, stirred solution of benzenesulphonylhydrazide (414 g., 2·4 moles) in chloroform (4000 ml.). The mixture was refluxed for 4 hr. and then cooled to give the preceding product (720 g., 84%). Concentration of the mother-liquors gave a second crop (65 g., 7·5%).

4-Bromo-5-formyl-3-methylisothiazole Thiosemicarbazone.—A ground mixture of the preceding hydrazide (200 g., 0·532 mole), anhydrous sodium carbonate (56·5 g., 0·532 mole), and thiosemicarbazide (48·5 g., 0·532 mole) was added during 15 min. to a stirred suspension of powdered glass (200 g.) in glycerol (1 l.) at 148—150°. The mixture was stirred for a further 5 min., then cooled to 40—50°, and N-sodium hydroxide (2 l.) was added. The mixture was filtered and the filtrate acidified with 5N-hydrochloric acid, to give the *thiosemicarbazone* (89 g., 60%), m. p. 205—210° (decomp.). Crystallisation from ethanol (charcoal) gave pale yellow prisms, m. p. 225—228° (Found: C, 25·6; H, 2·7; Br, 28·5; N, 19·8; S, 22·6. $C_6H_7BrN_4S_2$ requires C, 25·8; H, 2·5; Br, 28·6; N, 20·1; S, 23·0%).

3-Methylisothiazole-5-carbonyl Chloride.—3-Methylisothiazole-5-carboxylic acid and thionyl chloride gave the *acid chloride* (77%), b. p. 92—92·5°/18 mm. (Found: C, 37·3; H, 2·5; N, 8·3. C_5H_4ClNOS requires C, 37·2; H, 2·5; N, 8·7%).

Ethyl 3-Methylisothiazole-5-carboxylate (VIIIa).—3-Methylisothiazole-5-carbonyl chloride and ethanol gave the *ethyl ester* (93%), b. p. 100°/9 mm. (Found: C, 49·3; H, 5·4; N, 8·0; S, 18·3. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; N, 8·2; S, 18·7%).

5-Acetyl-3-methylisothiazole (Xa).—(*a*) A mixture of ethyl 3-methylisothiazole-5-carboxylate (48 g., 0·28 mole) and ethyl acetate (63 g., 0·72 mole) was added to a hot suspension of sodium ethoxide (31·7 g., 0·466 mole) in dry toluene (150 ml.). The mixture was refluxed with stirring for 6 hr. and then evaporated under reduced pressure. The residue was treated with 2N-acetic acid (300 ml.) and extracted with ether. The dried ($MgSO_4$) extract gave *ethyl β-(3-methyl-5-isothiazolyl)-β-oxopropionate* (IXa) (43·5 g., 73%), b. p. 170—172°/16 mm., m. p. 49—50° (Found: C, 50·5; H, 5·4; N, 6·3; S, 15·2. $C_9H_{11}NO_3S$ requires C, 50·7; H, 5·2; N, 6·6; S, 15·0%). This keto-ester (43·5 g., 0·22 mole), concentrated hydrochloric acid (260 ml.), and dioxan (260 ml.) were refluxed for 2 hr. The mixture was then cooled and poured on ice. Extraction with ether afforded *5-acetyl-3-methylisothiazole* (21·4 g., 74%), b. p. 109—110°/15 mm. (Found: C, 50·7; H, 5·2; N, 9·9; S, 22·6. C_6H_7NOS requires C, 51·0; H, 5·0; N, 9·9; S, 22·7%). The *thiosemicarbazone* crystallised from ethanol in prisms, m. p. 215—219° (Found: C, 39·1; H, 4·5; N, 26·0; S, 29·5. $C_7H_{10}N_4S_2$ requires C, 39·2; H, 4·7; N, 26·1; S, 29·9%).

(*b*) To a solution of methylmagnesium iodide in ether (from 5·7 g. of magnesium, 31·9 g. of methyl iodide, and 250 ml. of ether) 5-cyano-3-methylisothiazole (12·4 g.) in ether (50 ml.) was added during 30 min. The mixture was refluxed for 4 hr., then poured on ice (*ca.* 250 g.) and

2N-sulphuric acid (250 ml.) and steam-distilled. The distillate was extracted with ether. Evaporation of the dried ($MgSO_4$) extract and distillation gave 5-acetyl-3-methylisothiazole (3·4 g., 24%). The m. p. of the thiosemicarbazone was undepressed on admixture with that obtained by method (*a*).

5-*Acetyl*-4-*bromo*-3-*methylisothiazole* (Xb).—By a procedure similar to the preceding method (*a*), ethyl 4-bromo-3-methylisothiazole-5-carboxylate (28·5 g., 0·14 mole) gave *ethyl* β-(4-*bromo*-3-*methyl*-5-*isothiazolyl*)-β-*oxopropionate* (IXb) (26·5 g., 80%), m. p. 63—66° (Found: Br, 27·5; N, 4·7; S, 10·9. $C_9H_{10}BrNO_3S$ requires Br, 27·4; N, 4·8; S, 11·0%). Acid-hydrolysis gave 5-*acetyl*-4-*bromo*-3-*methylisothiazole* (11·8 g., 59%), b. p. 134—137°/16 mm. (Found: N, 6·3; S, 14·3. C_6H_6BrNOS requires N, 6·4; S, 14·6%) [*thiosemicarbazone*, prisms (from aqueous ethanol), m. p. 209—212° (Found: C, 29·0; H, 3·3; Br, 27·3; N, 18·7. $C_7H_9BrN_4S_2$ requires C, 28·7; H, 3·1; Br, 27·3; N, 19·1%)].

3-*Methylisothiazole*.—5-Amino-3-methylisothiazole [1] (28·5 g., 0·25 mole) was added portionwise during 45 min. to a solution of sodium nitrite (19·0 g., 0·275 mole) in concentrated sulphuric acid (135 ml.) at 0—2°. After being stirred for a further 60 min. at 0—2°, the mixture was added during 30 min. to a stirred mixture of 30% hypophosphorous acid (450 ml.) and cuprous oxide (1 g.) at −10°. The mixture was allowed to attain room temperature and then brought to pH 9 by addition of 25% sodium hydroxide solution and steam-distilled. The distillate (*ca.* 1 l.) was extracted with ether (3 × 100 ml.), the dried ($MgSO_4$) extracts were concentrated, and the residual liquid was distilled, to give 3-methylisothiazole (13 g., 53%), b. p. 135—136° (Adams and Slack [1] give b. p. 133°/751 mm.).

5-*Amino*-4-*bromo*-3-*methylisothiazole*.—Bromine (480 g., 3 moles) was added during 2·5 hr. to a mixture of 5-amino-3-methylisothiazole (342 g., 3 moles), glacial acetic acid (250 ml.), and benzene (2·5 l.) kept at 10—12° by cooling. After 30 min. 5-amino-4-bromo-3-methylisothiazole hydrobromide, m. p. 140—145° (decomp.), was filtered off and washed with ether. The hydrobromide was stirred with 2N-sodium carbonate (3 l.) for 2 hr., to give 5-*amino*-4-*bromo*-3-*methylisothiazole* (500 g., 87%), m. p. 101—105° (Found: Br, 41·5; N, 14·2; S, 16·2. $C_4H_5BrN_2S$ requires Br, 41·4; N, 14·5; S, 16·6%).

4,5-*Dibromo*-3-*methylisothiazole*.—Sodium nitrite (10·3 g., 0·15 mole) in water (33 ml.) was added during 30 min. to a solution of 5-amino-4-bromo-3-methylisothiazole (24·3 g., 0·125 mole) in 86% phosphoric acid (50 ml.) and concentrated nitric acid (25 ml.) at 0—2°. After 2 hr. at 0—2°, the mixture was added during 1 hr. to a solution of cuprous bromide (from 39·1 g. of cupric sulphate, 18 g. of sodium bromide, and 8 g. of sodium metabisulphite) in 48—50% hydrobromic acid (60 ml.) at 0—5°. After 1 hr. the mixture was brought to pH 10 with 50% aqueous sodium hydroxide and steam-distilled. The distillate (*ca.* 1 l.) deposited 4,5-*dibromo*-3-*methylisothiazole* (18·8 g., 58%), m. p. 52—56°. Sublimation gave colourless prisms, m. p. 54—55° (Found: C, 18·7; H, 1·1; Br, 61·8; S, 12·6. $C_4H_3Br_2NS$ requires C, 18·7; H, 1·2; Br, 62·2; S, 12·5%).

4-*Bromo*-3-*methylisothiazole* (XI).—(*a*) 4-Bromo-3-methylisothiazole-5-carboxylic acid (200 g.) was heated at 200—210° until gas evolution ceased. Distillation gave 4-*bromo*-3-*methylisothiazole* (130 g., 81%), b. p. 67—71°/12 mm. (Found: C, 27·1; H, 2·2; Br, 44·9; N, 7·5; S, 17·8. C_4H_4BrNS requires C, 27·0; H, 2·3; Br, 44·9; N, 7·9; S, 18·0%).

(*b*) Sodium nitrite (51 g., 0·74 mole) in water (250 ml.) was added during 15 min. to a solution of 5-amino-4-bromo-3-methylisothiazole (129 g., 0·67 mole) in concentrated sulphuric acid (150 ml.) and phosphoric acid (150 ml.) at 0—5°. After 30 min., the mixture was added during 45 min. to a stirred mixture of 30% hypophosphorous acid (750 ml.) and cuprous oxide (2 g.) at 30°. When gas evolution moderated during the addition, further small quantities of cuprous oxide (4 × 2 g.) were added. The mixture was stirred for a further 15 min. at 30° and then brought to pH 9 by the addition of 50% sodium hydroxide solution and steam-distilled. The distillate (*ca.* 2 l.) was extracted with ether (3 × 350 ml.), and the dried ($MgSO_4$) extracts were fractionally distilled, to give 4-bromo-3-methylisothiazole (78·2 g., 65·5%), b. p. 75—76°/13 mm., n_D^{23} 1·5800.

(*c*) Bromine (160 g., 1 mole) was added during 90 min. to a solution of 3-methylisothiazole (49·5 g., 0·50 mole) in glacial acetic acid at 100°. The mixture was heated at 100° for a further 6 hr., then cooled and poured on ice and extracted with ether. Fractional distillation of the extract gave the bromo-compound (61 g., 69%), b. p. 67—70°/13 mm.

4-*Cyano*-3-*methylisothiazole* (XII).—4-Bromo-3-methylisothiazole (184 g., 1·03 moles) and cuprous cyanide (130 g., 1·45 moles) were heated together. At 185°, a vigorous reaction

occurred and the temperature rose to *ca.* 230°. After 20 min., distillation gave 4-*cyano*-3-*methylisothiazole* (116 g., 90%), b. p. 81—83°/10 mm. (Found: S, 25·8. $C_5H_4N_2S$ requires S, 25·6%).

3-*Methylisothiazole*-4-*carboxylic Acid* (XIII).—4-Cyano-3-methylisothiazole (116 g., 0·93 mole) was refluxed with 2N-sodium hydroxide (700 ml.) until dissolution was complete. The solution was cooled and acidified with concentrated hydrochloric acid, to give 3-*methylisothiazole*-4-*carboxylic acid* (122 g., 92%), m. p. 230—231°. Crystallisation from ethanol gave colourless needles, m. p. 231—233° (Found: C, 42·1; H, 3·6; N, 9·8; S, 22·8. $C_5H_5NO_2S$ requires C, 42·0; H, 3·5; N, 9·8; S, 22·4%).

3-*Methylisothiazole*-4-*carbonyl Chloride*.—3-Methylisothiazole-4-carboxylic acid and thionyl chloride gave the *acid chloride* (89%), b. p. 94—95°/11 mm. (Found: N, 8·6; S, 19·9. C_5H_4ClNOS requires N, 8·7; S, 19·8%).

Methyl 3-*Methylisothiazole*-4-*carboxylate*.—The last-mentioned chloride and methanol gave the *methyl ester* (90%), b. p. 101—102°/14 mm., m. p. 50—52° (Found: C, 46·2; H, 4·4; N, 8·9; S, 20·1. $C_6H_7NO_2S$ requires C, 45·4; H, 4·5; N, 8·9; S, 20·4%).

The *ethyl ester* (65%), b. p. 102—103°/8 mm. (Found: C, 48·8; H, 5·1; N, 8·0; S, 18·8. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; N, 8·2; S, 18·7%), was prepared similarly.

3-*Methylisothiazole*-4-*carboxyhydrazide*.—By the method described above for the 4-bromo-compound, 3-methylisothiazole-4-carboxylate (48 g.) gave the *hydrazide* (28 g., 58%), m. p. 154—157° (Found: C, 38·6; H, 4·45; N, 28·6; S, 20·1. $C_5H_7N_3OS$ requires C, 38·2; H, 4·5; N, 26·7; S, 20·4%).

This (27 g.) gave its N′-*benzenesulphonyl derivative* (50 g., 98%) as colourless needles, m. p. 192—193° (Found: C, 44·4; H, 3·8; N, 14·2; S, 21·7. $C_{11}H_{11}N_3O_3S_2$ requires C, 44·4; H, 3·7; N, 14·1; S, 21·6%).

4-*Formyl*-3-*methylisothiazole Thiosemicarbazone*.—By the procedure described for the 5-isomer, the benzenesulphonylhydrazide (20 g.) gave this *thiosemicarbazone* (2 g., 15%), m. p. 190—193°. Crystallisation from ethanol (charcoal) afforded pale yellow prisms, m. p. 198—201° (Found: C, 36·4; H, 4·2; N, 27·8; S, 32·2. $C_6H_8N_4S_2$ requires C, 36·0; H, 4·0; N, 28·0; S, 32·0%).

4-*Formyl*-3-*methylisothiazole* (XIV).—3-Methylisothiazole-4-carbonyl chloride (10·0 g., 0·062 mole) was added during 20 min. to a stirred mixture of quinoline (7·8 g., 0·062 mole), potassium cyanide (6·2 g., 0·095 mole), methylene chloride (40 ml.), and water (16 ml.). The mixture was stirred at room temperature for 3·5 hr. and the methylene chloride layer was separated. It was washed successively with water, 2N-hydrochloric acid, water, 2N-sodium carbonate, and water. Concentration of the dried ($MgSO_4$) extract gave 2-*cyano*-1,2-*dihydro*-1-(3-*methylisothiazole*-4-*carbonyl*)*quinoline*, which crystallised from ethanol in colourless needles (3·2 g., 18·4%), m. p. 183—185° (Found: N, 14·8; S, 11·4. $C_{15}H_{11}N_3OS$ requires N, 14·95; S, 11·4%).

This compound (3·2 g., 0·0114 mole) was refluxed with 25% sulphuric acid (50 ml.) for 30 min. Extraction with ether gave 4-*formyl*-3-*methylisothiazole* (1·33 g., 92%), b. p. 58—60°/0·04 mm. (Found: C, 47·5; H, 4·25; N, 10·7. C_5H_5NOS requires C, 47·3; H, 4·0; N, 11·0%). The 2,4-*dinitrophenylhydrazone* crystallised from dimethylformamide in red prisms, m. p. 306—308° (Found: N, 23·2; S, 10·2. $C_{11}H_9N_5O_4S$ requires N, 22·8; S, 10·4%), and the thiosemicarbazone crystallised from aqueous ethanol as yellow prisms, m. p. 203—205° undepressed on admixture with the product obtained as above.

4-*Acetyl*-3-*methylisothiazole*.—A solution of methylmagnesium iodide in ether, prepared from magnesium (4·38 g., 0·180 mole), methyl iodide (25·4 g., 0·180 mole), and ether (100 ml.), was added during 45 min. to a mixture of 3-methylisothiazole-4-carbonyl chloride (21·5 g., 0·133 mole), anhydrous ferric chloride (0·5 g.), toluene (75 ml.), and ether (75 ml.) at −20° in nitrogen. The mixture was stirred for 1 hr. and the temperature allowed to rise to 0°. Water (50 ml.) was added and the mixture acidified with 2N-hydrochloric acid. The organic layer was separated and washed successively with saturated aqueous sodium hydrogen carbonate, water, N-sodium thiosulphate, and water. The dried ($MgSO_4$) extract was fractionally distilled, to give 4-*acetyl*-3-*methylisothiazole* (11·0 g., 59%), b. p. 56—57°/0·25 mm. (Found: N, 9·6; S, 22·5. C_6H_7NOS requires N, 9·9; S, 22·7%). The *thiosemicarbazone*, m. p. 232—234° (decomp.), crystallised from methanol in colourless prisms (Found: C, 39·2; H, 5·0; N, 26·0; S, 30·1. $C_7H_{10}N_4S_2$ requires C, 39·2; H, 4·7; N, 26·1; S, 29·9%).

Reactions of Formyl-3-*methylisothiazoles with Potassium Hydroxide* (*Cannizzaro Reaction*).—

A mixture of 4-bromo-5-formyl-3-methylisothiazole (0·5 g.), potassium hydroxide (1·0 g.), and water (2 ml.) was shaken and kept at room temperature for 36 hr. The resulting oil was extracted in ether and dried ($MgSO_4$). Acidification of the aqueous layer with concentrated hydrochloric acid gave a colourless solid, m. p. 196—198° (decomp.), which did not depress the m. p. of 4-bromo-3-methylisothiazole-5-carboxylic acid. Evaporation of the ethereal extract gave an oil which crystallised on trituration with light petroleum (b. p. 40—60°) as colourless needles, m. p. 93—94°. This compound did not depress the m. p. of 4-bromo-5-hydroxymethyl-3-methylisothiazole obtained as a by-product in the preparation of 4-bromo-5-formyl-3-methylisothiazole.

Similarly, 5-formyl-3-methylisothiazole gave 3-methylisothiazole-5-carboxylic acid, m. p. 206—208° (decomp.), and *5-hydroxymethyl-3-methylisothiazole*, b. p. 108—110°/0·1 mm., m. p. 35—37° (Found: N, 10·7; S, 25·1. C_5H_7NOS requires N, 10·9; S, 24·8%); and 4-formyl-3-methylisothiazole gave 3-methylisothiazole-4-carboxylic acid, m. p. 233—234°, and *4-hydroxymethyl-3-methylisothiazole*, b. p. 104—106°/0·5 mm. (Found: C, 46·4; H, 5·4. C_5H_7NOS requires C, 46·5; H, 5·5%).

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