593. *Isothiazoles. Part IV.*[1] *The Preparation of 3-Formyl- and 3-Acetyl-isothiazoles.*

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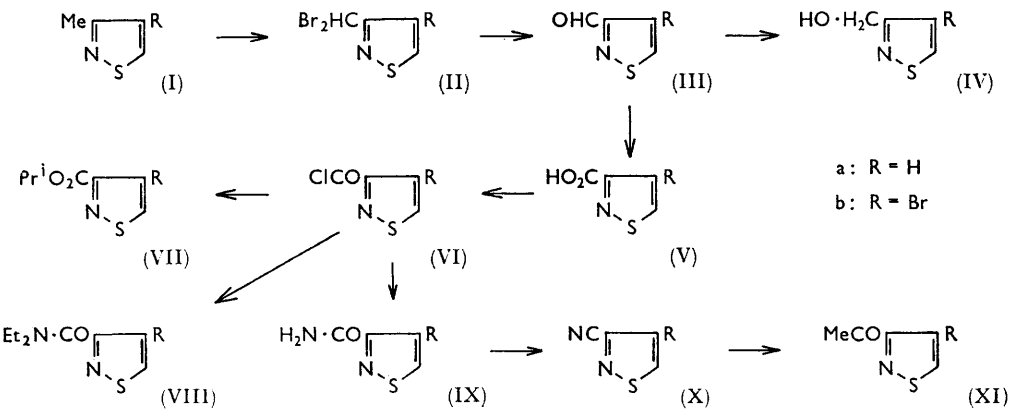
Syntheses of 3-formyl-, 3-acetyl-, 4-bromo-3-formyl-, and 3-acetyl-4-bromo-isothiazole are described, and the ultraviolet spectra of these and related compounds are recorded and correlated.

Many isothiazoles with functional substituents in the 4- or 5-positions have been described [1-4] but the corresponding 3-substituted compounds have received little attention.[5] Our interest in isothiazole carbonyl derivatives [1,3] led us to examine the possibility of obtaining 3-carbonyl compounds from the readily available 3-methylisothiazole (Ia).[3,6] This compound could not be oxidised with selenium dioxide, and it did not condense with benzaldehyde. Treatment with *N*-bromosuccinimide in trifluoroacetic acid [7] resulted in nuclear substitution, but in carbon tetrachloride in the presence of benzoyl peroxide side-chain halogenation occurred. Under suitable conditions either mono- [8] or di-bromomethylisothiazole (IIa) predominated. 4-Bromo-3-methylisothiazole,[1] gave analogous products.



With silver nitrate, (dibromomethyl)isothiazoles (II) gave the aldehydes (III), which were oxidised to the carboxylic acids (V) by silver oxide. The acid chlorides (VI) gave esters (VII) and amides (VIII and IX) by conventional methods. Dehydration of the amides (IX) with phosphorus oxychloride afforded the nitriles (X) which were converted into the ketones (XI) by treatment with methylmagnesium iodide.

The carbonyl compounds behave normally, and condense readily with carbonyl reagents. The aldehydes (III) undergo the Cannizzaro reaction, and give hydroxymethyl compounds (IV) on reduction with sodium borohydride.

Ultraviolet absorption data are given in the Table. As described previously [1,3] the influence of substituents on the higher-wavelength band of isothiazole is additive, and the increments for substituents in the 3-position can be calculated from the Table.

[1] Part III, Caton, Jones, Slack, and Wooldridge, *J.*, 1964, 446.
[2] Adams and Slack, *J.*, 1959, 3061.
[3] Buttimore, Jones, Slack, and Wooldridge, *J.*, 1963, 2032.
[4] Goerdeler and Pohland, *Chem. Ber.*, 1961, **94**, 2950; 1963, **96**, 526; Goerdeler and Horn, *ibid.*, p. 1551.
[5] Goerdeler and Mittler, *Chem. Ber.*, 1963, **96**, 944.
[6] Wille, Capeller, and Steiner, *Angew. Chem.* (*Internat. Edn.*), 1962, **1**, 335; Hübenett, Flock, and Hofmann, *ibid.*, 1962, **1**, 508.
[7] Cohen, Thom, and Bendlich, *J. Org. Chem.*, 1962, **27**, 3545.
[8] Caton and Renwick, unpublished work.

Ultraviolet spectra of isothiazoles (in ethanol).

3-Substituent	R = H		R = Br	
	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
CHO	245, 205	7860, 3930	259	8100
CH_2·OH	248, 213	9090, 2960	258, 216	7630, 1350
CO_2H	256, 233	8300, 3400	267	6700
CO_2Pr^i	256, 225	8900, 5000	270, 205	10,000, 5300
CO·NH_2	256, 216	8800, 6900	271	5500
CN	256, 221	8330, 4700	273	7400
CO·Me	262, 238, 205	8640, 6100, 3560	279, 211	12,500, 5440

Experimental

3-Formylisothiazole (IIIa).—A mixture of 3-methylisothiazole [3] (25·0 g., 0·25 mole), *N*-bromosuccinimide (97 g., 0·51 mole), benzyl peroxide (*ca.* 0·5 g.), and dry carbon tetrachloride (300 ml.) was refluxed with stirring for 48 hr. and then left at room temperature overnight. The mixture was filtered, and the filtrate was fractionated under reduced pressure. The fraction, b. p. 115—132°/22 mm. (32·0 g.), consisting mainly of 3-dibromomethylisothiazole, was dissolved in ethanol (250 ml.), treated with silver nitrate (46·0 g., 0·26 mole) in water (60 ml.), refluxed for 5 min., and filtered. The filtrate was concentrated to *ca.* 75 ml., treated with water (100 ml.), and extracted with methylene chloride (3 × 100 ml.). Evaporation of the dried ($MgSO_4$) extracts, and two fractional distillations, afforded *3-formylisothiazole* (6·5 g., 23%), b. p. 62—65°/9 mm., which partially crystallised, m. p. 28—29° (Found: C, 42·7; H, 3·1; N, 12·4. C_4H_3NOS requires C, 42·5; H, 2·7; N, 12·4%); *thiosemicarbazone*, prisms from ethanol, m. p. 176—178° (decomp.) (Found: C, 32·3; H, 3·4; S, 34·6. $C_5H_6N_4S_2$ requires C, 32·2; H, 3·4; S, 34·4%); *2,4-dinitrophenylhydrazone*, yellow needles, from benzene, m. p. 225—227° (Found: N, 24·2; S, 11·1. $C_{10}H_7N_5O_4S$ requires N, 23·9; S, 10·9%).

4-Bromo-3-dibromomethylisothiazole (IIb).—A mixture of 4-bromo-3-methylisothiazole [3] (200 g., 1·125 moles), *N*-bromosuccinimide (445 g., 2·5 moles), benzoyl peroxide (*ca.* 0·75 g.), and dry carbon tetrachloride (1700 ml.) was refluxed with stirring for 40 hr. and left at room temperature for 3 days. The mixture was filtered, and fractionation of the filtrate afforded *4-bromo-3-dibromomethylisothiazole* (336 g., 89%), b. p. 87—88°/0·3 mm., m. p. 43—44° (Found: Br, 71·0; S, 9·6. $C_4H_2Br_3NS$ requires Br, 71·4; S, 9·5%).

4-Bromo-3-formylisothiazole (IIIb).—As for the compound (IIIa), treatment of (IIb) with silver nitrate gave *4-bromo-3-formylisothiazole* (130 g., 69%), b. p. 150—152°/35 mm., m. p. 52—54°. A portion was recrystallised from light petroleum (b. p. 60—80°), to give pale yellow needles, m. p. 55—56° (Found: N, 7·2; S, 16·7. C_4H_2BrNOS requires N, 7·3; S, 16·7%); *thiosemicarbazone*, prisms from aqueous dimethylformamide, m. p. 225—226° (decomp.) (Found: N, 21·3; S, 24·0. $C_5H_5BrN_4S_2$ requires N, 21·1; S, 24·2%); *2,4-dinitrophenylhydrazone*, needles from benzene, m. p. 235—236° (Found: N, 18·4; S, 8·6. $C_{10}H_6BrN_5O_4S$ requires N, 18·4; S, 8·6%).

3-Hydroxymethylisothiazole (IVa).—A solution of 3-formylisothiazole (8·5 g., 0·075 mole) in methanol (40 ml.) was added dropwise during 15 min. to a stirred solution of potassium borohydride (1·4 g., 0·025 mole) in 0·2N-sodium hydroxide (15 ml.) and methanol (40 ml.) at 10—15°. The solution was kept overnight and the methanol was distilled off. The residue was extracted with ether (3 × 75 ml.), and distillation of the dried ($MgSO_4$) extracts gave *3-hydroxymethylisothiazole* (5·2 g., 61%), b. p. 119—121°/19 mm. (Found: C, 41·9; H, 4·6; S, 27·6. C_4H_5NOS requires C, 41·7; H, 4·4; S, 27·9%); *p-nitrobenzoate*, prisms from ethanol, m. p. 104—106° (Found: C, 49·9; H, 3·5; S, 12·3. $C_{11}H_8N_2O_4S$ requires C, 50·0; H, 3·0; S, 12·1%).

4-Bromo-3-hydroxymethylisothiazole (IVb).—Similarly, 4-bromo-3-formylisothiazole (15 g., 0·078 mole) gave *4-bromo-3-hydroxymethylisothiazole* (10·1 g., 67%), b. p. 78°/0·1 mm. (Found: N, 7·4; S, 16·4. C_4H_4BrNOS requires N, 7·2; S, 16·5%); *p-nitrobenzoate*, plates from ethanol, m. p. 137—139° (Found: N, 8·0; S, 9·1. $C_{11}H_7BrN_2O_4S$ requires N, 8·2; S, 9·3%).

4-Bromoisothiazole-3-carboxylic Acid (Vb).—4-Bromo-3-formylisothiazole (57 g., 0·3 mole) was added all at once to a stirred suspension of freshly prepared silver oxide [from silver nitrate (51 g., 0·3 mole) and sodium hydroxide (12 g., 0·3 mole) as 25% solutions] in a solution of sodium hydroxide (60 g., 1·5 mole) in water (500 ml.).[9] The temperature rose to 50° and the

[9] Cf. Pearl, *J. Org. Chem.*, 1947, **12**, 85.

mixture was stirred at room temperature for 3 hr. The mixture was filtered and the filtrate acidified with 2N-sulphuric acid, to give the *acid* (49·2 g., 79%), needles, m. p. 175—176° (decomp.) (from water) (Found: C, 22·7; H, 1·5; N, 6·6; S, 15·3. $C_4H_2BrNO_2S$ requires C, 23·1; H, 1·0; N, 6·7; S, 15·4%).

Isothiazole-3-carboxylic Acid (Va).—In a similar manner, 3-formylisothiazole (20·0 g., 0·018 mole) gave *isothiazole-3-carboxylic acid* (10·0 g., 44%), needles from water, m. p. 135—137° (Found: C, 37·1; H, 2·3; S, 24·9. $C_4H_3NO_2S$ requires C, 37·2; H, 2·3; S, 24·8%).

Reaction of 3-Formyl- and 4-Bromo-3-formyl-isothiazole with Potassium Hydroxide (Cannizzaro Reaction).—A mixture of 4-bromo-3-formylisothiazole (2 g.) and N-potassium hydroxide (12 ml.) was kept at room temperature for 36 hr. Extraction with ether afforded 4-bromo-3-hydroxymethylisothiazole. Acidification of the aqueous layer gave 4-bromoisothiazole-3-carboxylic acid, m. p. and mixed m. p. 175—176° (decomp.).

Similarly, 3-formylisothiazole gave 3-hydroxymethylisothiazole and isothiazole-3-carboxylic acid, m. p. and mixed m. p. 136—137°.

Isothiazole-3-carbonyl Chloride (VIa).—A mixture of isothiazole-3-carboxylic acid (40 g., 0·31 mole) and thionyl chloride (120 ml.) was refluxed for 1 hr. The excess of thionyl chloride was distilled off, and distillation of the residue afforded *isothiazole-3-carbonyl chloride* (27·8 g., 61%), b. p. 123—124°/19 mm., m. p. 34—36° (Found: C, 32·6; H, 1·5; Cl, 23·9. C_4H_2ClNOS requires C, 32·6; H, 1·4; Cl, 24·0%).

4-Bromoisothiazole-3-carbonyl Chloride (VIb).—Similarly, 4-bromoisothiazole-3-carboxylic acid (52 g., 0·25 mole) gave the *acid chloride* (30 g., 54%), b. p. 148—152°/25 mm., needles, m. p. 72° [from light petroleum (b. p. 60—80°)] (Found: N, 5·9; S, 14·25. $C_4HBrClNOS$ requires N, 6·2; S, 14·2%).

Isopropyl Isothiazole-3-carboxylate (VIIa).—A mixture of propan-2-ol (50 ml.) and isothiazole-3-carbonyl chloride (7·5 g., 0·051 mole) was refluxed for 2 hr. The excess of propan-2-ol was distilled off, the residue was dissolved in ether (75 ml.), and the solution was washed with saturated sodium hydrogen carbonate solution and water. Evaporation of the dried ($MgSO_4$) extracts afforded *isopropyl isothiazole-3-carboxylate* (6·1 g., 70%), b. p. 123—124°/16 mm. (Found: C, 49·3; H, 5·6; S, 18·7. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; S, 18·7%).

Isopropyl 4-Bromoisothiazole-3-carboxylate (VIIb).—In a similar manner, 4-bromoisothiazole-3-carbonyl chloride (11·3 g., 0·05 mole) gave the *isopropyl ester* (8·3 g., 67%), b. p. 97—99°/0·5 mm. (Found: C, 33·8; H, 3·2; Br, 32·4. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; Br, 32·0%).

4-Bromo-3-NN-diethylcarbamoylisothiazole (VIIIb).—4-Bromoisothiazole-3-carbonyl chloride (5·0 g., 0·022 mole) in dry benzene (10 ml.) was added dropwise to a stirred, refluxing solution of diethylamine (3·5 g., 0·048 mole) in dry benzene (25 ml.). The solution was refluxed for 2 hr., cooled, and washed with 2N-hydrochloric acid, water, 2N-sodium carbonate, and water. Evaporation of the dried ($MgSO_4$) extract afforded *4-bromo-3-NN-diethylcarbamoylisothiazole* (2·3 g., 40%), needles from light petroleum (b. p. 60—80°), m. p. 40—41° (Found: C, 36·4; H, 4·6; S, 12·2. $C_8H_{11}BrN_2OS$ requires C, 36·5; H, 4·2; S, 12·2%).

The following were prepared similarly: *3-NN-diethylcarbamoylisothiazole* (VIIIa) (48%), m. p. 46—47° (Found: C, 52·5; H, 6·4; N, 14·8. $C_8H_{12}N_2OS$ requires C, 52·1; H, 6·6; N, 15·2%), and *4-bromo-3-NN-diphenylcarbamoylisothiazole* (60%), needles, m. p. 118—120° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 54·0; H, 3·4; S, 8·9. $C_{16}H_{11}BrN_2OS$ requires C, 53·5; H, 3·1; S, 8·9%).

Isothiazole-3-carboxyamide (IXa).—Isothiazole-3-carbonyl chloride (20·0 g., 0·135 mole) in dry acetone (50 ml.) was added dropwise with stirring to concentrated ammonium hydroxide (250 ml.; *d* 0·9). The mixture was stirred for 1 hr., concentrated to *ca.* 75 ml., cooled, and filtered. Crystallisation of the residual solid from water afforded *isothiazole-3-carboxyamide* (16·1 g., 93%), needles, m. p. 154—155° (Found: C, 37·3; H, 3·3; S, 24·8. $C_4H_4N_2OS$ requires C, 37·5; H, 3·1; S, 25·0%).

4-Bromoisothiazole-3-carboxyamide (IXb).—Similarly, 4-bromoisothiazole-3-carbonyl chloride (10 g., 0·044 mole) gave *4-bromoisothiazole-3-carboxyamide* (6·1 g., 67%), needles from water, m. p. 152—154° (Found: C, 23·2; H, 1·5; S, 15·8. $C_4H_3BrN_2OS$ requires C, 23·2; H, 1·5; S, 15·5%).

3-Cyanoisothiazole (Xa).—Isothiazole-3-carboxyamide (16·1 g., 0·125 mole) was heated on a steam-bath with phosphorus oxychloride (75 g., 0·5 mole) for 1 hr. The excess of phosphorus oxychloride was distilled off under reduced pressure and the residue was poured on to

ice (*ca.* 200 g.). Extraction with ether (3 × 125 ml.) afforded **3-*cyanoisothiazole*** (9·5 g., 69%,) prisms from light petroleum (b. p. 60—80°), m. p. 60—61° (Found: C, 43·7; H, 2·1; S, 29·2. $C_4H_2N_2S$ requires C, 43·6; H, 1·8; S, 29·1%).

4-*Bromo*-3-*cyanoisothiazole* (Xb).—Similarly, 4-bromoisothiazole-3-carboxyamide (10·0 g., 0·05 mole) gave **4-*bromo*-3-*cyanoisothiazole*** (7·0 g., 73%), needles from light petroleum (b. p. 60—80°), m. p. 49—50° (Found: N, 14·5; S, 16·9. C_4HBrN_2S requires N, 14·8; S, 17·0%).

3-*Acetylisothiazole* (XIa)—3-Cyanoisothiazole (9·5 g., 0·087 mole) in dry ether (50 ml.) was added dropwise during 15 min. to a stirred solution of methylmagnesium iodide (0·214 mole) (from 5·15 g. of magnesium and 30·4 g. of methyl iodide in 175 ml. of dry ether). The mixture was refluxed for 4 hr., cooled, and cautiously poured on to ice (*ca.* 120 g.) and 2N-sulphuric acid (135 ml.). The ether was evaporated off, and steam-distillation afforded **3-*acetylisothiazole*** (7·15 g., 65%), m. p. 32—34° (Found: C, 46·9; H, 3·8; S, 24·9. C_5H_5NOS requires C, 47·2; H, 4·0; S, 25·2%); *thiosemicarbazone*, plates from ethanol, m. p. 163—164° (decomp.) (Found: C, 36·2; H, 4·2; S, 31·8. $C_6H_8N_4S_2$ requires C, 36·0; H, 4·0; S, 32·0%).

3-*Acetyl*-4-*bromoisothiazole* (XIb).—Similarly, 4-bromo-3-cyanoisothiazole (6·5 g., 0·035 mole) gave **3-*acetyl*-4-*bromoisothiazole*** (3·33 g., 47%), m. p. 37—39° (Found: C, 29·1; H, 1·9; S, 15·7. C_5H_4BrNOS requires C, 29·1; H, 2·0; S, 15·6%); *thiosemicarbazone*, pale yellow needles from ethanol, m. p. 193—195° (decomp.) (Found: C, 26·1; H, 2·8; Br, 28·7. $C_6H_7BrN_4S_2$ requires C, 25·8; H, 2·5; Br, 28·6%); *2,4-dinitrophenylhydrazone*, prisms from benzene, m. p. 231—233° (Found: C, 34·6; H, 2·2; N, 18·3. $C_{11}H_8BrN_5O_4S$ requires C, 34·2; H, 2·1; N, 18·1%).

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