Isothiazoles. Part XV.[1] 5-Nitroisothiazoles

By R. J. A. Walsh and K. R. H. Wooldridge,* The Research Laboratories, May & Baker Ltd., Dagenham, Essex RM10 7XS

3-Methyl-5-nitroisothiazole has been prepared from diazotised 5-amino-3-methylisothiazole and sodium nitrite. Oxidation gave the 3-carboxylic acid, which was converted into the amide, nitrile, aldehyde, and derivatives. Treatment of 3,5-dichloroisothiazole-4-carbonitrile with sodium nitrite gave 3-chloro-5-hydroxyisothiazole-4-carbonitrile.

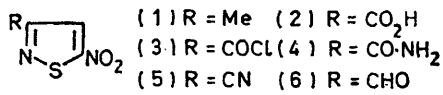
In view of the high chemotherapeutic activity of 2- and 5-nitroimidazoles and 2-nitrofurans, the synthesis of analogous 3- and 5-nitroisothiazoles was explored. 3-Methyl-5-nitroisothiazole (1) was readily obtained from the corresponding diazonium salt by treatment with sodium nitrite in the presence of copper(I)–copper(II) sulphite.[2] Oxidation with chromium trioxide[3] afforded 5-nitroisothiazole-3-carboxylic acid (2) in 39% yield. Unexpectedly, this acid could not be thermally decarboxylated, although the unsubstituted isothiazole-3-carboxylic acid is decarboxylated smoothly at the m.p.[3] The acid chloride (3) gave the amide (4), which was dehydrated to the nitrile (5) with phosphoryl chloride. Reduction of the acid chloride (3) with lithium tri-t-butoxyaluminium hydride afforded the aldehyde (6), which was converted into a number of hydrazone derivatives of potential chemotherapeutic interest. The thiosemicarbazone was oxidised with iron(III) chloride to an aminothiadiazole (7).

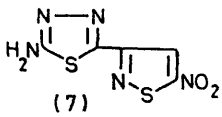
An alternative synthesis of a 5-nitroisothiazole by treatment of 3,5-dichloroisothiazole-4-carbonitrile with either sodium nitrite[4] or silver nitrite gave the 5-hydroxy-compound (8), presumably *via* an unstable nitrite ester. Assignment of the 5-hydroxy- rather than the 3-hydroxy-structure was made on the basis of the expected higher reactivity of the 5-halogen atom to nucleophilic displacement[5] and the characteristic i.r. spectrum of 5-hydroxyisothiazoles.[1]

Attempts to prepare 3-nitroisothiazoles from the 3-diazonium sulphate were unsuccessful. 3-Chloro-5-phenylisothiazole-4-carbonitrile and sodium nitrite gave the 3-hydroxy-compound (9), and oxidation of 3-amino-5-phenylisothiazole with persulphuric acid gave a

[1] Part XIV, I. D. H. Stocks, J. A. Waite, and K. R. H. Wooldridge, *J. Chem. Soc.* (*C*), 1971, 1314.
[2] H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, *J. Chem. Soc.*, 1947, 1392.
[3] D. Buttimore, M. P. L. Caton, J. D. Renwick, and R. Slack, *J. Chem. Soc.*, 1965, 7274.
[4] N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. E. Graham, *J. Amer. Chem. Soc.*, 1956, **78**, 1497.
[5] K. R. H. Wooldridge, 'Advances in Heterocyclic Chemistry,' 1972, vol. 15, p. 1.

compound formulated as an *S*-oxide (10) on the basis of a strong i.r. band at 1040 cm^{-1}.[6]

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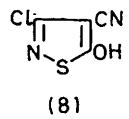
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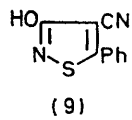
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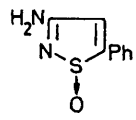
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Some of the 5-nitroisothiazoles possess antibacterial, antifungal, and antiprotozoal activity *in vitro* but no useful *in vivo* activity was observed.

EXPERIMENTAL

3-Methyl-5-nitroisothiazole (1).*—A solution of 5-amino-3-methylisothiazole [7] (11·4 g) in glacial acetic acid (50 ml) was added dropwise with vigorous stirring to a solution of nitrosylsulphuric acid [prepared by adding sodium nitrite (30 g) to conc. sulphuric acid (210 ml) and filtering from sodium sulphate] at 15—16°. The solution was stirred for 1·75 h at room temperature, then cooled to 0°, and treated dropwise with ether (250 ml) at 0—5°. The precipitated diazonium sulphate was separated by filtration. Sodium nitrite (62 g) in water (250 ml) was treated with copper(I)–copper(II) sulphite [prepared from copper(II) sulphate (31 g) by adding a solution of anhydrous sodium sulphite (31 g) in water (100 ml), filtering off the brown precipitate, and washing with water]. This suspension was stirred vigorously and treated in portions with the diazonium sulphate during 45 min, the temperature rising to 35°. The mixture was stirred for 5 h and then steam distilled. The yellow oil which separated from the distillate was extracted into ether (5 × 40 ml). The combined extracts were dried ($MgSO_4$) and distilled to give a yellow *oil* (6·40 g, 49%), b.p. 99° at 17 mmHg (Found: C, 33·7; H, 3·2; S, 22·0. $C_4H_4N_2O_2S$ requires C, 33·3; H, 2·8; S, 22·2%), $\nu_{max.}$ (KBr) 1530 and 1345 cm^{-1}.

5-Nitroisothiazole-3-carboxylic Acid (2).—Chromium trioxide (26·0 g) was added in portions to a stirred solution of 3-methyl-5-nitroisothiazole (12·2 g) in conc. sulphuric acid (80 ml) during 3 h, the temperature being kept at 20—30° by cooling in a water-bath. The mixture was kept at room temperature for 2 days and then poured into iced water (220 ml). The precipitated white solid (6·2 g) was filtered off and dried. A further quantity (1·5 g) was isolated from the filtrate by continuous extraction with ether for 24 h. The combined solids gave *crystals* (5·8 g, 39%), m.p. 175—177° [from ethyl acetate–light petroleum (b.p. 60—80°)] (Found: C, 27·8; H, 1·0; S, 18·5. $C_4H_2N_2O_4S$ requires C, 27·6; H, 1·2; S, 18·4%), $\nu_{max.}$ (KBr) 2900—2400, 1730, 1540, and 1345 cm^{-1}.

5-Nitroisothiazole-3-carbonyl Chloride (3).—A suspension of 5-nitroisothiazole-3-carboxylic acid (14·4 g) in thionyl chloride (144 ml) was refluxed for 3 h, during which time the solid dissolved. The solution was distilled to give a pale yellow *liquid*, b.p. 131—132° at 16 mmHg (14·5 g, 91%) (Found: C, 25·3; H, 0·4; S, 16·6. $C_4HClN_2O_3S$ requires C, 25·0; H, 0·5; S, 16·7%).

5-Nitroisothiazole-3-carboxamide (4).—5-Nitroisothiazole-3-carbonyl chloride (15·7 g) was added dropwise to stirred aqueous ammonia (*d* 0·88; 250 ml) at 15—20°. The precipitated solid gave pale yellow *crystals* (10·7 g, 75%), m.p. 145—148° (from ethanol) (Found: C, 27·8; H, 1·7; N, 24·3. $C_4H_3N_3O_3S$ requires C, 27·7; H, 1·8; N, 24·3%).

5-Nitroisothiazole-3-carbonitrile (5).—A suspension of 5-nitroisothiazole-3-carboxamide (2·6 g) in phosphoryl chloride (5·5 ml) was heated on a steam-bath for 1 h. The excess of phosphoryl chloride was removed by distillation under reduced pressure and the residual liquid was poured on ice (60 g). The precipitated solid was dried and extracted with ether (75 ml) and the extract was evaporated. The residual solid gave *crystals* (0·9 g, 37%), m.p. 49—51° (from cyclohexane) (Found: C, 31·0; H, 0·9; N, 27·3. $C_4HN_3O_2S$ requires C, 31·0; H, 0·7; N, 27·1%), $\nu_{max.}$ (KBr) 2250, 1545, and 1355 cm^{-1}.

5-Nitroisothiazole-3-carbaldehyde (6).—A stirred solution of 5-nitroisothiazole-3-carbonyl chloride (14·1 g) in dry bis-(2-methoxyethyl) ether (43 ml) was cooled to −70° and treated dropwise at this temperature with a solution of lithium tri-t-butoxyaluminium hydride (19·2 g) in dry bis-(2-methoxyethyl) ether (57 ml) during 1 h. The solution was stirred for 1 h while warming to room temperature and then poured into iced water (600 ml). The solution was filtered from inorganic material and extracted with ether (3 × 200 ml), and the extracts were washed with 2N-sodium carbonate solution (100 ml) and dried ($MgSO_4$). Distillation gave a pale yellow liquid (5·6 g, 48%), b.p. 123—125° at 16 mmHg, which crystallised on cooling; m.p. 54—56° [from light petroleum (b.p. 40—60°)] (Found: C, 29·6; H, 1·4; N, 17·3. $C_4H_2N_2O_3S$ requires C, 30·4; H, 1·3; N, 17·7%), $\nu_{max.}$ (KBr) 1705, 1550, and 1350 cm^{-1}.

5-Nitroisothiazole-3-carbaldehyde Derivatives (*Table*).—These were prepared by standard procedures.

2-Amino-5-(5-nitroisothiazol-3-yl)-1,3,4-thiadiazole (7).—A solution of iron(III) chloride hexahydrate (2·7 g) in water (14 ml) and methanol (5 ml) was refluxed and treated in portions during 10 min with 5-nitroisothiazole-3-carbaldehyde thiosemicarbazone (1·2 g). The suspension was refluxed for 30 min, cooled, and filtered. After washing with water and ethanol there remained a yellow *solid* (1·1 g, 80%), m.p. 222—224° (decomp.) (Found: C, 25·8; H, 1·4; N, 30·3. $C_5H_3N_5O_2S_2$ requires C, 26·2; H, 1·3; N, 30·6%).

3-Chloro-5-hydroxyisothiazole-4-carbonitrile (8).—A stirred solution of 3,5-dichloroisothiazole-4-carbonitrile [8] (5·4 g) in dimethylformamide (50 ml) and water (2·5 ml) was treated with sodium nitrite (7·0 g) during 30 min, the temperature rising to 40°. After stirring and heating on a steam-bath for 1 h, the solution was filtered from inorganic material and evaporated to dryness under reduced pressure; the residue was triturated with benzene to give the sodium salt of 3-chloro-5-hydroxyisothiazole-4-carbonitrile as a

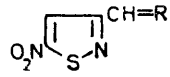
* Preliminary experiments were performed by Mr. D. Buttimore.

[6] A. Bruno and G. Purrello, *Gazzetta*, 1966, **96**, 1009.
[7] A. Adams and R. Slack, *J. Chem. Soc.*, 1959, 3061.
[8] W. R. Hatchard, *J. Org. Chem.* 1963, **28**, 2163.

pale yellow *solid* (4·9 g), m.p. >300° (Found: C, 26·0; Cl, 19·3; N, 15·4. C_4ClN_2NaOS requires C, 26·3; Cl, 19·4; N, 15·4%). The free hydroxy-compound was liberated by dissolving the sodium salt in 2N-hydrochloric acid (50 ml). Continuous extraction with ether for 24 h afforded a fawn *solid* (2·1 g, 43%), m.p. 150—152° (decomp.) (Found: C, 30·1; H, 0·9; N, 17·9. C_4HClN_2OS requires C, 29·9; H, 0·6; N, 17·5%), $\nu_{max.}$ (KBr) 3000—2500 and 2250 cm^{-1}.

solution of 30% hydrogen peroxide (25 ml) in conc. sulphuric acid (10 ml) and 25% oleum (50 ml) was treated in portions with 3-amino-5-phenylisothiazole [10] (4·9 g) at 10—20°. The solution was stirred at room temperature for a further 2 h and then poured on ice (300 g). Neutralisation with 50% sodium hydroxide solution at 20—25° precipitated a solid which gave fawn *crystals* (3·2 g, 60%), m.p. 242—244° (decomp.) (from methanol) (Found: C, 55·9; H, 4·1; N

5-Nitroisothiazole-3-carbaldehyde derivatives



R	M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N
=N·NH·CO·NH$_2$	234—236 *	$C_5H_5N_5O_3S$	28·3	2·5	32·8	27·9	2·3	32·6
=N·NH·CS·NH$_2$	211—213 *	$C_5H_5N_5O_2S_2$	26·1	2·2	30·4	26·0	2·2	30·3
=N·NHAc	200—202	$C_6H_6N_4O_3S$	33·7	2·8	26·4	33·6	2·8	26·2
=N·N·CO·O·CH$_2$·CH$_2$	194—196	$C_7H_6N_4O_4S$	34·9	2·6	23·4	34·7	2·5	23·1
=N·NH·C(:NH)·NH$_2$,HCl	261—263 *	$C_5H_6N_6O_2S$,HCl	24·1	2·8	33·1	24·0	2·8	33·5
=N·NH·C(:NH)·NH·N:CHR′,HI (R′ = 5-nitroisothiazol-3-yl)	223—225 *	$C_9H_7N_9O_4S_2$,HI	21·8	1·8	25·1	21·8	1·6	25·4

* Decomp.

3-Hydroxy-5-phenylisothiazole-4-carbonitrile (9).—Sodium nitrite (8·4 g) was added to a solution of 3-chloro-5-phenylisothiazole-4-carbonitrile [9] (6·4 g) in dimethylformamide (90 ml). The stirred mixture was refluxed for 24 h, cooled, and filtered, and the filtrate was evaporated under reduced pressure. The residual solid was dissolved in water (150 ml) and acidified with 2N-hydrochloric acid to give a white *solid* (4·3 g, 74%), m.p. 235—236° (Found: C, 59·1; H, 3·1; N, 13·5. $C_{10}H_6N_2OS$ requires C, 59·4; H, 3·0; N, 13·9%), $\nu_{max.}$ (KBr) 2900—2600 and 2250 cm^{-1}.

3-Amino-5-phenylisothiazole S-Oxide (10).—A stirred

14·5; S, 16·8. $C_9H_8N_2OS$ requires C, 56·2; H, 4·2; N, 14·6; S, 16·7%), $\nu_{max.}$ (KBr) 3300, 3275, and 1040 cm^{-1} (SO).

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[1/2476 *Received*, 29*th December*, 1971]

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