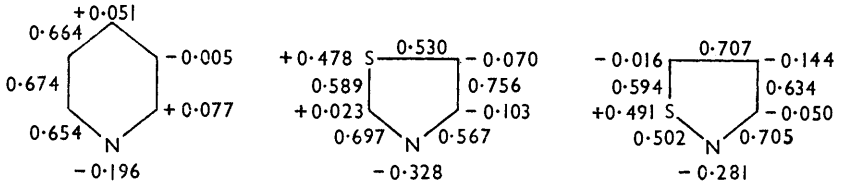
613. *Isothiazole: A New Mononuclear Heterocyclic System.*

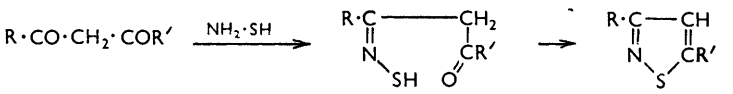
By A. Adams and R. Slack.

Many derivatives of isothiazole (1,2-thiazole), a hitherto unknown heterocyclic system, have been prepared, and the parent base and its 3-methyl derivative have been characterized.

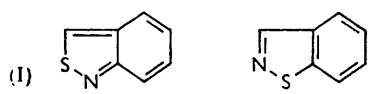
Mononuclear isothiazoles (1,2-thiazoles) have not hitherto been described, but a theoretical consideration of the properties of the parent led us to believe that it should be a reasonably stable molecule. Thus, the electronic similarity between –S– and –CH=CH– particularly in aromatic systems, has frequently been discussed (*e.g.*, by Longuet-Higgins [1]), and isothiazole might, therefore, be expected to resemble pyridine in many of its properties. A simplified calculation * of electron densities and mobile bond orders of the unsubstituted molecule emphasized its inherent stability, and its similarity to both pyridine and thiazole (cf. annexed diagram).



The unknown thiohydroxylamine would perhaps provide the most direct route to the system, but even this is doubtful since our experience of similar cyclizations suggests that



hydrogen sulphide is almost always lost in preference to water. The use of a thioketone would eliminate this difficulty but would introduce added complications. We therefore adopted two different methods of approach and have succeeded in preparing both isothiazole itself and a series of its derivatives.

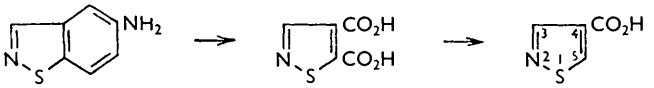


The first route [2] depended on disruptive oxidation of a substituted benzisothiazole. There are two series of benzisothiazoles, derived from benz[*c*]isothiazole (I) and benz[*d*]-isothiazole (II). The *o*-quinonoid system of the former made it likely that this compound would be completely ruptured by oxidation; and the latter, weakened in the *Bz*-ring by an anionoid substituent, appeared to be more suitable. 5-Aminobenz[*d*]isothiazole (III) was prepared by the known, but tedious route (*o*-chlorobenzaldehyde ⟶ 2-chloro-

* In these simplified calculations, overlap has been neglected. The following parameters were used for the Coulomb integrals. $\alpha_C = \alpha$; $\alpha_N = \alpha + 0{\cdot}5\beta$; $\alpha_S = \alpha + 1{\cdot}1\beta$. These were suggested by Professor C. A. Coulson (personal communication), the latter value being derived from that of α_O used by Orgel *et al.* (*Trans. Faraday Soc.*, 1951, **47**, 113) by a comparison of the electronegativities of oxygen and sulphur. A somewhat lower value for α_S might be more acceptable but would only slightly reduce the calculated charges without altering the relation between them. It is realized that our parameters, and therefore the calculated charges and bond orders, vary slightly from those used by Pullman and Metzger (*Bull. Soc. chim. France*, 1948, **15**, 1021) for thiazole calculations, but we believe that they are more soundly derived. The only difference between the two sets of results lies in the relative interchange of charge on the thiazole $C_{(4)}$ and $C_{(5)}$ atoms. The large difference between these charges and that on $C_{(2)}$, and the magnitude of the bond orders, remain virtually unaltered.

[1] Longuet-Higgins, *Trans. Faraday Soc.*, 1949, **45**, 173.
[2] Cf. Adams and Slack, *Chem. and Ind.*, 1956, 1232.

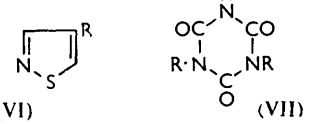
5-nitrobenzaldehyde ⟶ 2,2′-diformyl-4,4′-dinitrodiphenyl disulphide ⟶ 2-formyl-4-nitrosulphenyl bromide ⟶ 5-nitrobenz[*d*]isothiazole ⟶ 5-aminobenz[*d*]isothiazole) and its oxidation with alkaline potassium permanganate took place smoothly to give isothiazole-4,5-dicarboxylic acid (IV). Isolation of this acid was greatly simplified by the extreme insolubility of its monosodium salt which, surprisingly, recrystallized unchanged



(III) (IV) (V)

from 2N-sulphuric acid. Monodecarboxylation gave isothiazole-4-carboxylic acid (V) (cf. decarboxylation of 3-methylisothiazole-5-carboxylic acid, p. 3064), but many varied attempts at further decarboxylation were unsuccessful. The acid (V) was, therefore, degraded by the normal Curtius sequence to 4-aminoisothiazole. Hofmann's method from the amide (VIa) was unsuccessful. Methyl isothiazole-4-carboxylate (VIb) and isothiazole-4-carboxyhydrazide (VIc) and -4-carboxyazide (VId) were prepared by standard methods, and the corresponding benzylurethane (VIe) was smoothly hydrolysed to the amine (VIf) by hydrogen bromide in acetic acid.

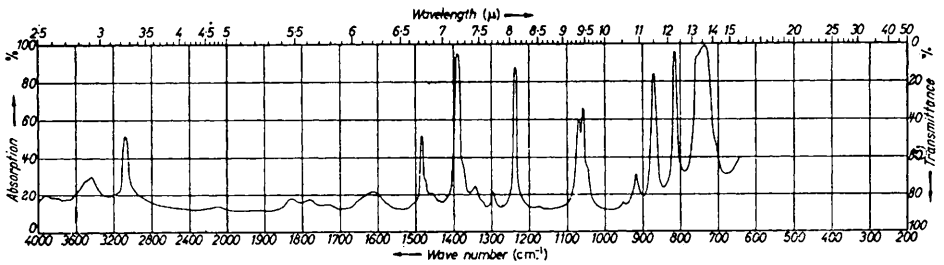
R	R
a, $CO{\cdot}NH_2$	f, NH_2
b, CO_2Me	g, $NH{\cdot}CO_2Et$
c, $CO{\cdot}NH{\cdot}NH_2$	h, $N(CO)_2C_6H_4$
d, CON_3	j, $NH{\cdot}SO_2{\cdot}C_6H_4{\cdot}NH_2$-*p*
e, $NH{\cdot}CO_2{\cdot}CH_2Ph$	k, H



(VI) (VII)

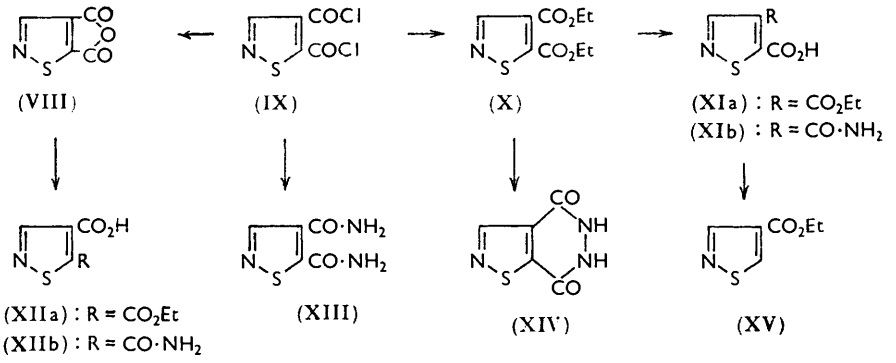
The ethylurethane (VIg) resisted hydrolysis, and 4-phthalimidoisothiazole (VIh) was obtained from the azide only in poor yield, the trimeric isocyanate (VII; R = isothiazolyl) being occasionally formed instead. The imide (VIh) could be hydrolysed to the amine, but again the overall yield from azide was low. 4-Aminoisothiazole was also converted into its acetyl and benzoyl derivatives and into the sulphonamide (VIj). Treatment of the diazotized amine with hypophosphorous acid gave isothiazole (VIk), a colourless, highly refractive, mobile liquid with an odour reminiscent of both pyridine and thiazole. Its infrared spectrum is shown in the Figure; ultraviolet data are given on p. 3067. It readily formed crystalline derivatives with mercuric chloride, chloroplatinic acid, and chloroauric acid.

Infrared spectrum of isothiazole.

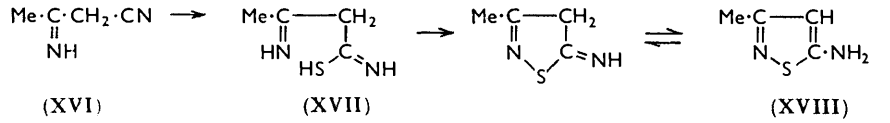


Attempts to remove selectively the 4-substituent of the diacid (IV) were unsuccessful. Thus, this acid was converted by standard methods into the dichloride (IX), the diethyl ester (X), and the diamide (XIII). Partial hydrolysis of the diester gave the 4-ethyl monoester (XIa) which on decarboxylation gave ethyl isothiazole-4-carboxylate (XV), converted by hydrazine hydrate into its hydrazide (VIc). The monoester was also converted into the amide-acid (XIb), which gave isothiazole-4-carboxyamide when heated. The monoester (XIa) was also prepared from the monosilver salt of the diacid (IV) and ethyl iodide. The diester (X) with hydrazine hydrate gave the cyclic hydrazide (XIV).

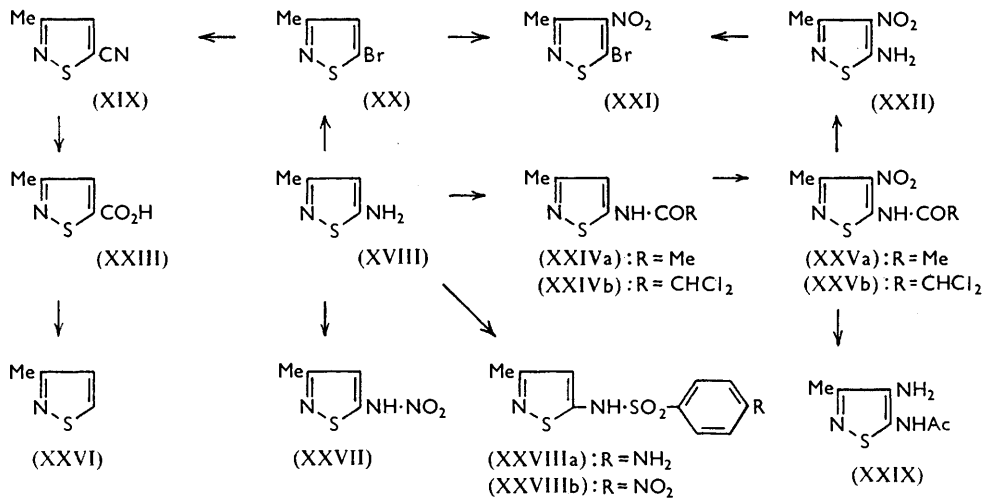
The anhydride (VIII) was prepared from the dichloride and yellow mercuric oxide and was converted into the 5-monoester (XIIa) and the related amide-acid (XIIb), but neither of these could be decarboxylated.



These failures to prepare 5-monosubstituted isothiazoles made us seek a more direct synthesis of this series. β-Iminothiobutyramide (XVII) was prepared from the known nitrile (XVI) and was converted by chloramine into 5-amino-3-methylisothiazole (XVIII). This conversion, at first believed to take place by successive elimination of ammonia and hydrogen chloride, can, however, be performed more conveniently by the action of hydrogen



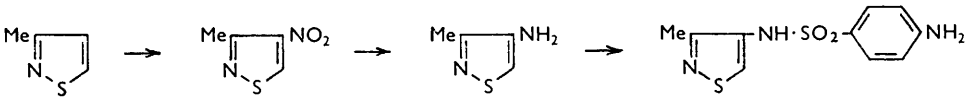
peroxide or persulphates and resembles that of amidinothioureas.[3] The amine (XVIII) was a useful intermediate for the preparation of many derivatives. Direct nitration gave the nitramine (XXVII), but the acetyl (XXIVa) and the dichloroacetyl (XXIVb) derivative under similar conditions gave the 4-nitro-compounds (XXVa) and (XXVb). Each



of these gave 5-amino-3-methyl-4-nitroisothiazole (XXII) on hydrolysis. This was converted by the Sandmeyer reaction into 5-bromo-3-methyl-4-nitroisothiazole (XXI),

[3] Kurzer, *J.*, 1955, 2288; *J.*, 1956, 2345.

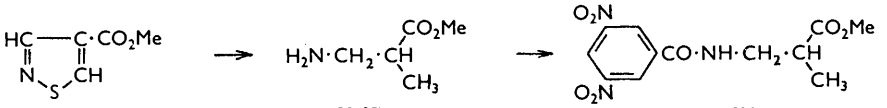
which was also prepared by nitration of 5-bromo-3-methylisothiazole (XX). Treatment of the bromo-compound (XXI) with sodium iodide and acetic acid (reagents used by Blatt and Tristram [4] for the elimination of chlorine from picryl chloride) gave only 5-iodo-3-methyl-4-nitroisothiazole. The bromo-compound (XX) was also degraded, through the nitrile (XIX) and acid (XXIII), to 3-methylisothiazole (XXVI), a substance which closely resembles the parent base in physical properties. The nitrile (XIX) was converted into the corresponding thioamide, and the methyl ester of the acid (XXIII) into the hydrazide. 5-Acetamido-4-amino-3-methylisothiazole (XXIX) and the sulphonamides (XXVIIIa * and b) were also prepared. Nitration of 3-methylisothiazole gave the 4-nitro-derivative (XXX) which was reduced by ferrous sulphate and ammonia to 4-amino-3-methylisothiazole (XXXI), derivatives of which differed from those of the corresponding 5-amino-compound. Catalytic reduction was unsuccessful. The amine (XXXI) was converted into the sulphonamide (XXXII), a position isomer of (XXVIIIa).



(XXVI) (XXX) (XXXI) (XXXII)

We regard the smooth decarboxylation of the 5-acid (XXIII) as compelling evidence for the loss of the 5-carboxy-group from the dicarboxylic acid (IV). Contributory evidence is provided by the following facts:

(a) Reductive desulphurization of the monomethyl ester (VIb) gave an amino-ester (XXXIII), which was converted into a 3,5-dinitrobenzoyl derivative [presumably (XXXIV)]. Kuhn–Roth analysis gave a *C*-methyl figure supporting this structure, whereas desulphurization of methyl isothiazole-5-carboxylate would have given an amino-ester containing no *C*-methyl group.



(VIb) (XXXIII) (XXXIV)

(b) 4-Aminoisothiazole exhibits the expected aromatic properties and was converted into isothiazole by reductive diazotization. 5-Amino-3-methylisothiazole, on the other hand, gave the bromo- and the chloro-compound under normal Sandmeyer conditions, but could not be converted by diazotization into the nitrile or into 3-methylisothiazole. 3-Amino- and 2(or 4)-aminopyridines behave similarly.

Experimental

5-Aminobenz[d]*isothiazole.*—2-Chloro-5-nitrobenzaldehyde was prepared by nitration of *o*-chlorobenzaldehyde.[5] Treatment with ethanolic sodium disulphide gave di-(2-formyl-4-nitrophenyl) disulphide [6] and this was converted into 2-formyl-4-nitrophenylsulphenyl bromide by warming with bromine in carbon tetrachloride.[7] The sulphenyl bromide gave 5-nitrobenz-[*d*]isothiazole when boiled with concentrated aqueous ammonia and benzene,[8] and reduction

* 5-*p*-Aminobenzenesulphonamido-3-methylisothiazole (XXVIIIa) is of considerable interest as an antibacterial agent. It is the subject of B.P. Applns. Nos. 32,801/56, 32,259/57, and 21,628—32,802/56.

[4] Cf. Blatt and Tristram, *J. Amer. Chem. Soc.*, 1952, **74**, 6273.
[5] Erdmann, *Annalen*, 1893, **272**, 153.
[6] Fries and Brothuhn, *Ber.*, 1923, **56**, 1630.
[7] Fries, Eishold, and Vahlberg, *Annalen*, 1927, **454**, 272.
[8] *Idem*, *ibid.*, p. 279.

with ferrous sulphate in ethanol and aqueous ammonia gave 5-aminobenz[d]isothiazole.[8] The overall yield was about 25%.

Isothiazole-4,5-dicarboxylic Acid (IV).—To a suspension of finely powdered 5-aminobenz[*d*]-isothiazole (47·4 g.) in stirred, boiling water (1260 c.c.) and potassium carbonate (630 g.) was slowly added a solution of potassium permanganate (300 g.) in hot water (3150 c.c.). Decolorization was immediate at the beginning of the addition but slowed considerably towards the end. Boiling was continued for 2 hr. and the mixture was then cooled and filtered. The filtrate and aqueous washings were treated with concentrated hydrochloric acid to pH 1 and were continuously extracted with ether (1 l.) for 48 hr. Evaporation of the dried ($MgSO_4$) extracts gave the crude dicarboxylic acid (41·0 g.). This was dissolved in water (100 c.c.), and the solution was filtered from a little sticky residue and treated with 2N-sodium hydroxide to pH 4. After several hours, the *monosodium salt* was collected and the filtrate saturated with sodium chloride [total yield, 31·5 g.; m. p. 262° (decomp.)]. Recrystallization from water gave colourless hydrated needles, m. p. 275° (decomp.) (Found: N, 6·4; S, 15·2; Na, 10·8; loss in wt. at 100°, 8·6. $C_5H_2O_4NSNa,H_2O$ requires N, 6·6; S, 15·0; Na, 10·8; loss at 100°, 8·45%).

The free acid could not be obtained by acidification of an aqueous solution of the sodium salt, nor by boiling it with 2N-sulphuric acid; in each case it was recovered unchanged. The salt (31 g.) was dissolved in 2N-sulphuric acid (800 c.c.), and the solution was continuously extracted with ether (500 c.c.) overnight. Evaporation of the dried ($MgSO_4$) extracts gave *isothiazole-4,5-dicarboxylic acid* (23·8 g.), m. p. 144° (decomp.). Crystallization from benzene gave colourless prisms, m. p. 145° (decomp.) (Found: C, 35·0; H, 2·0; N, 8·0; S, 18·7. $C_5H_3O_4NS$ requires C, 34·7; H, 1·7; N, 8·1; S, 18·5%).

Isothiazole-4-carboxylic Acid (V).—Isothiazole-4,5-dicarboxylic acid (40·8 g.) was boiled under reflux with mesitylene (400 c.c.) for 2 hr. The hot solution was filtered from a little tar and cooled. *Isothiazole-4-carboxylic acid* (26·1 g.; m. p. 161—162°) was collected, washed with benzene, and dried. Recrystallization from water gave colourless needles, m. p. 162° (Found: C, 37·5; H, 2·2; N, 10·8; S, 24·75. $C_4H_3O_2NS$ requires C, 37·2; H, 2·3; N, 10·85; S, 24·8%).

Methyl Isothiazole-4-carboxylate (VIb).—Isothiazole-4-carboxylic acid (26·1 g.) was slowly added to an ethereal (750 c.c.) solution of diazomethane prepared from methylnitrosourea (75 g.). After 12 hr., evaporation gave the *methyl ester* (28·6 g.), which solidified. Recrystallization from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 55° (Found: C, 42·0; H, 3·8; N, 10·0. $C_5H_5O_2NS$ requires C, 41·95; H, 3·5; N, 9·8%).

Isothiazole-4-carboxyhydrazide (VIc).—Hydrazine hydrate (100%; 13 c.c.) was added to methyl isothiazole-4-carboxylate (13 g.) in ethanol (60 c.c.), and the mixture was heated on the steam-bath for 30 min. before being cooled overnight. The *isothiazole-4-carboxyhydrazide* (11·5 g., m. p. 173—175°) recrystallized from water in straw-coloured prisms, m. p. 176° (decomp.) (Found: C, 33·6; H, 3·4; N, 29·5; S, 22·85. $C_4H_5ON_3S$ requires C, 33·6; H, 3·5; N, 29·4; S, 22·4%).

Isothiazole-4-carboxyazide (VId).—A suspension of the hydrazide (17·0 g.) in concentrated hydrochloric acid (85 c.c.) and water (85 c.c.) was covered with ether (265 c.c.) and stirred vigorously at −5° to 0° while being treated with sodium nitrite (14·4 g.) in water (58 c.c.). The ethereal layer was separated after 2—3 hr. and the aqueous layer was re-extracted with ether (2 × 200 c.c.). The combined ethereal liquors were washed with aqueous sodium hydrogen carbonate and with water, dried ($CaSO_4$), and evaporated. The residual *azide* (15·4 g.) crystallized from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 32° (Found: C, 31·2; H, 1·5; N, 36·5. $C_4H_2ON_4S$ requires C, 31·2; H, 1·3; N, 36·3%).

4-Phthalimidoisothiazole (VIh).—Isothiazole-4-carboxyazide (8·3 g.) and phthalic anhydride (8·0 g.) were heated on the steam-bath with dry pyridine (60 c.c.) for 3 hr. The solvent was removed under reduced pressure and the solid residue dissolved in the minimum quantity of boiling ethanol. *4-Phthalimidoisothiazole* separated on cooling (5·1 g.; m. p. 155—156°) and recrystallized from light petroleum (b. p. 80—100°) as needles, m. p. 157° (Found: C, 57·05; H, 3·0; N, 11·9. $C_{11}H_6O_2N_2S$ requires C, 57·4; H, 2·6; N, 12·2%). Occasionally the product was mixed with an ethanol-insoluble compound which crystallized from pyridine in colourless prisms, m. p. 294—295°. This was probably *4-isothiazolyl isocyanate trimer* (Found: C, 37·95; H, 1·2; N, 21·95; S, 24·8%; *M*, 370. $C_{12}H_6O_3N_6S_3$ requires C, 38·1; H, 1·6; N, 22·2; S, 25·4%; *M*, 378).

4-Ethoxycarbonylaminoisothiazole (VIg).—A solution of isothiazole-4-carboxyazide (4·2 g.) in dry ethanol (120 c.c.) was boiled under reflux for 3 hr. The solvent was removed under

reduced pressure to give 4-*ethoxycarbonylaminoisothiazole* (4·0 g.; m. p. 72—74°), in colourless prisms, m. p. 78° [from light petroleum (b. p. 60—80°)] (Found: C, 41·7; H, 5·1; N, 16·1. $C_6H_8O_2N_2S$ requires C, 41·9; H, 4·7; N, 16·3%).

4-*Benzyloxycarbonylaminoisothiazole* (VIe).—Isothiazole-4-carboxyazide (39·0 g.) was heated with benzyl alcohol (500 c.c.) for 1 hr. at 150°. The solvent was removed under reduced pressure to give oily 4-*benzyloxycarbonylaminoisothiazole* which solidified (54·3 g.; m. p. 99—100°) after trituration with light petroleum (b. p. 80—100°). Recrystallization from light petroleum (b. p. 80—100°) gave colourless needles, m. p. 101° (Found: C, 56·7; H, 4·5; N, 12·1. $C_{11}H_{10}O_2N_2S$ requires C, 56·4; H, 4·3; N, 12·0%).

4-*Aminoisothiazole* (VIf).—*Method* I. Hydrazine hydrate (100%; 2·6 g., 2 mol.) in a little ethanol was added to a stirred suspension of finely powdered 4-phthalimidoisothiazole (6·0 g.) in ethanol (100 c.c.). After 18 hr., the white flocculent precipitate [5·0 g.; m. p. 165° (decomp.)] was collected, washed with a little ethanol, and dried. The powdered product was stirred with 2N-hydrochloric acid (100 c.c.), and the solution filtered from phthalhydrazide [3·0 g.; m. p 340° (decomp.)]. The filtrate was evaporated to small bulk, made alkaline with 2N-sodium hydroxide, and continuously extracted with ether for 18 hr. Evaporation of the dried ($MgSO_4$) extracts gave an oil (1·2 g.) which solidified. Crystallization from light petroleum (b. p. 40—60°) gave 4-aminoisothiazole in colourless needles, m. p. 45°. The m. p. was not depressed on admixture with a specimen prepared by Method II.

Method II. 4-Benzyloxycarbonylaminoisothiazole (52·0 g.) was treated with 36% w/w hydrogen bromide in acetic acid (500 c.c.) and set aside at room temperature for 1 hr. After 1 hr. on the steam-bath the product (54·7 g.), consisting mainly of the amine dihydrobromide, was collected, washed with acetic acid, and dried. This salt was dissolved in water (60 c.c.), and the solution made alkaline with sodium carbonate and continuously extracted with ether (75 c.c.) for 18 hr. Evaporation of the dried extracts gave 4-*aminoisothiazole* (22·2 g.) as pale yellow needles, m. p. 35—40°. Recrystallization from light petroleum (b. p. 40—60°) gave colourless needles, m. p. and mixed m. p. 45° (Found: C, 36·2; H, 4·0; N, 27·7. $C_3H_4N_2S$ requires C, 36·0; H, 4·0; N, 28·0%).

The *acetyl* derivative crystallized from water in colourless prisms, m. p. 127—128° (Found: C, 42·05; H, 4·4; N, 19·7. $C_5H_6ON_2S$ requires C, 42·2; H, 4·25; N, 19·7%). The *benzoyl* derivative crystallized from aqueous ethanol in colourless needles, m. p. 137° (Found: C, 58·8; H, 3·9. $C_{10}H_8ON_2S$ requires C, 58·8; H, 3·95%).

4-p-*Acetamidobenzenesulphonamidoisothiazole.*—To an ice-cooled solution of 4-aminoisothiazole (12·5 g.) in dry pyridine (125 c.c.) was slowly added, below 10°, *p*-acetamidobenzenesulphonyl chloride (32·0 g.). After 18 hr. at room temperature, the solution was stirred into water (4 l.), and the solid product was filtered off, washed with water, and dried (37·0 g.; m. p. 257—258°). Recrystallization from ethanol gave 4-p-*acetamidobenzenesulphonamidoisothiazole* in fawn needles, m. p. 261—262° (Found: C, 44·8; H, 4·0; N, 14·4; S, 21·15. $C_{11}H_{11}O_3N_3S_2$ requires C, 44·3; H, 3·7; N, 14·1; S, 21·6%).

4-p-*Aminobenzenesulphonamidoisothiazole* (VIj).—A solution of 4-*p*-acetamidobenzenesulphonamidoisothiazole (37·5 g.) in 2N-sodium hydroxide (300 c.c.) was boiled for 2 hr., and for a further 5 min. after the addition of decolorizing charcoal (1 g.). The cold, filtered solution was treated with concentrated hydrochloric acid to pH 6, 4-p-*aminobenzenesulphonamidoisothiazole* (30·1 g.; m. p. 195—200°) being collected, washed with water, and dried. Recrystallization from ethanol gave colourless needles, m. p. 203—204° (Found: C, 42·25; H, 3·7; N, 16·2; S, 25·2. $C_9H_9O_2N_3S$ requires C, 42·35; H, 3·55; N, 16·5; S, 25·1%). The same compound was obtained in 89% yield by hydrolysis of the acetyl derivative with 2N-hydrochloric acid.

Isothiazole (1,2-*Thiazole*) (VIk).—A solution of 4-aminoisothiazole (10·0 g.) in concentrated hydrochloric acid (40 c.c.) and water (40 c.c.) was treated at 0—5° with an ice-cooled solution of sodium nitrite (8·1 g.) in water (40 c.c.). Ice-cooled 30—32% w/w hypophosphorous acid (260 c.c.) was added, and the mixture was stirred at 0° for 30 min. and then set aside at 0° for 36 hr. The solution was then made alkaline with 50% sodium hydroxide solution and filtered, and the filtrate steam-distilled into ether (100 c.c.) until the distillate no longer gave a crystalline precipitate with mercuric chloride solution. The ether layer was separated and the aqueous layer extracted with ether (5 × 100 c.c.). Evaporation of the dried ($CaSO_4$) combined ethereal liquors gave *isothiazole* (4·4 g.). Distillation gave a colourless liquid (2·9 g.), b.p. 113°/770 mm. (Found: C, 42·3; H, 3·7; N, 16·55; S, 37·8. C_3H_3NS requires C, 42·3; H, 3·55; N, 16·5;

S, 37·7%). Isothiazole is a colourless, highly refractive (n_D^{20} 1·5320), mobile liquid with a pyridine- and thiazole-like odour and $\lambda_{max.}$ 242 mμ (log ε 3·818). It is soluble in water and in ether, and gives crystalline derivatives with metallic salts. The *mercurichloride* forms unstable colourless needles, m. p. 173° (decomp.; bath preheated to 170°) (Found: N, 3·9; S, 9·1. $C_3H_3NS,HgCl_2$ requires N, 3·9; S, 9·0%). The chloroplatinate separates in yellow prisms, decomp., 360—370°. A satisfactory analysis could not be obtained (Found: C, 11·7; H, 2·0; N, 5·8; S, 10·6; Pt, 32·1. Calc. for $2C_3H_3NS,H_2PtCl_6$: C, 12·4; H, 1·4; N, 4·8; S, 11·1; Pt, 33·6%). The *chloroaurate* forms golden needles, melting by 250° (decomp.) before resolidifying (Found: C, 8·5; H, 1·1; N, 3·3; S, 7·5; Au, 45·8. $C_3H_3NS,HAuCl_4$ requires C, 8·5; H, 0·95; N, 3·3; S, 7·5; Au, 46·35%).

Isothiazole-4-carboxyamide (VIa).—Isothiazole-4-carboxylic acid (3·1 g.) was boiled with thionyl chloride (30 c.c.) until a clear solution was obtained, then the solvent was removed under reduced pressure. The residual acid chloride in dry ether (25 c.c.) gave, with aqueous ammonia (*d* 0·88; 10 c.c.), *isothiazole-4-carboxyamide* (2·5 g.; m. p. 183—188°), crystallizing from water in prisms, m. p. 192—193° (Found: C, 37·3; H, 3·2; N, 21·3. $C_4H_4ON_2S$ requires C, 37·5; H, 3·15; N, 21·9%).

Diethyl Isothiazole-4,5-dicarboxylate (X).—The dicarboxylic acid (8·4 g.) was boiled under reflux with thionyl chloride (50 c.c.) for 90 min. The dichloride (8·8 g.), b. p. 122—124°/10 mm., and dry ethanol (50 c.c.) were boiled under reflux for 30 min. to give the pale yellow *diethyl ester* (7·8 g.), b. p. 154°/15 mm. (Found: C, 47·3; H, 5·0; N, 6·1. $C_9H_{11}O_4NS$ requires C, 47·15; H, 4·8; N, 6·1%). The dichloride was also conveniently obtained from the monosodium salt and thionyl chloride.

4-Ethoxycarbonylisothiazole-5-carboxylic Acid (XIa).—*Method* I. The diethyl ester (3·1 g.) at −5° to −10° was treated dropwise during 1 hr. with ethanolic N-potassium hydroxide (6·8 c.c.). The precipitated potassium salt (1·1 g.; m. p. 145—153°) was collected and addition of dry ether to the filtrate gave a further 0·15 g., m. p. 137—145°. This was filtered off, ether was removed from the filtrate, and the alcoholic residue was again treated with ethanolic N-potassium hydroxide (6·8 c.c.) to give further potassium salt (1·15 g.; m. p. 162—165°; and 0·15 g., m. p. 157—160°). The combined salts (2·55 g.) were dissolved in a little water, and the solution was acidified with hydrochloric acid to give *4-ethoxycarbonylisothiazole-5-carboxylic acid* (1·2 g.; m. p. 80—83°). Crystallization from light petroleum (b. p. 40—60°) gave colourless plates, m. p. 83—84° (Found: C, 42·2; H, 3·9; N, 6·8. $C_7H_7O_4NS$ requires C, 41·8; H, 3·5; N, 7·0%). The acid was decarboxylated at 140°. The residual oil, dissolved in ethanol and treated with hydrazine hydrate, was converted into the hydrazide, m. p. 174—175°, undepressed on admixture with a specimen prepared from methyl isothiazole-4-carboxylate.

Method II.—The dicarboxylic acid (2·0 g.) in water (30 c.c.) and 0·8N-ammonia (14·45 c.c.; 1 mol.) was treated with N-silver nitrate (11·6 c.c.; 1 mol.). The silver salt was collected, washed, dried *in vacuo* (2·95 g.), powdered, and boiled under reflux with chloroform (50 c.c.) and ethyl iodide (2·5 g.) for 7 hr. The mixture was filtered, and the filtrate evaporated on the steam-bath to constant weight. The cooled residual oil partially crystallized on being seeded with 4-ethoxycarbonylisothiazole-5-carboxylic acid. The product (0·35 g.) separated from light petroleum (b. p. 40—60°) in colourless plates, m. p. 80—82°, not depressed on admixture with this half-ester. The remaining oil, dissolved in a little 2N-sodium hydroxide and treated with 2N-hydrochloric acid, gave the monosodium salt (0·45 g.), in needles, m. p. 270° (decomp.).

5-Carboxyisothiazole-4-carboxyamide (XIb).—A solution of 4-ethoxycarbonylisothiazole-5-carboxylic acid (0·55 g.) in aqueous ammonia (*d* 0·88; 10 c.c.) was set aside overnight. Acidification of an aqueous solution of the crystalline product gave *5-carboxyisothiazole-4-carboxyamide* [0·35 g.; m. p. 175° (decomp.)] which recrystallized from water in colourless needles, m. p. 175° with decarboxylation, followed by resolidification to isothiazole-4-carboxyamide, m. p. 192° (Found: C, 35·2; H, 2·3; N, 16·0. $C_5H_4O_3N_2S$ requires C, 34·9; H, 2·3; N, 16·3%).

Isothiazole-4,5-dicarboxyamide (XIII).—Isothiazole-4,5-dicarbonyl chloride (0·6 g.) was added to aqueous ammonia (*d* 0·88; 1 c.c.). The precipitated *isothiazole-4,5-dicarboxyamide* crystallized from water in needles, m. p. 243° (Found: C, 35·2; H, 3·1; N, 24·8. $C_5H_5O_2N_3S$ requires C, 35·1; H, 2·9; N, 24·6%).

4,5,6,7-Tetrahydro-4,7-dioxopyridazino[4,5-d]*isothiazole* (XIV).—Diethyl isothiazole-4,5-dicarboxylate (2·8 g.), methanol (5 c.c.), and 100% hydrazine hydrate (1·85 g.) were warmed on the steam-bath for 30 min. The yellow product (1·75 g., m. p. 220° decomp.) was collected

after 12 hr., washed with water, and stirred with 2N-hydrochloric acid (20 c.c.). The resulting *hydrazide* (1·04 g.) crystallized from water in colourless needles, m. p. 320° (decomp.) (Found: C, 35·75; H, 2·0; N, 24·7. $C_5H_3O_2N_3S$ requires C, 35·5; H, 1·8; N, 24·8%).

Isothiazole-4,5-dicarboxylic Anhydride (VIII).—The dicarbonyl chloride (IX) (10 g.) was boiled for 18 hr. with yellow mercuric oxide (10·5 g.) and dry benzene (75 c.c.). The cooled mixture was filtered and the residue extracted with boiling benzene (50 c.c.). The filtrate and extract were evaporated under reduced pressure; the residue was crystallized from light petroleum (b. p. 60—80°). The product (4·7 g.; m. p. 100—115°) consisted of the anhydride contaminated with a little mercuric chloride. Repeated recrystallization from light petroleum (b. p. 60—80°) gave the pure anhydride in prisms, m. p. 118—120°. Satisfactory analytical results could not be obtained, since the anhydride rapidly absorbed water (Found: C, 38·15; H, 1·2; N, 9·1. Calc. for C_5HO_3NS: C, 38·7; H, 0·65; N, 9·0%).

4-Carboxyisothiazole-5-carboxyamide (XIIb).—*Method* I. Isothiazole-4,5-dicarboxylic anhydride (12·0 g.) and aqueous ammonia (*d* 0·88; 100 c.c.) were warmed on the steam-bath until most of the excess of ammonia had been removed. Acidification with hydrochloric acid to pH 1 gave the crude *amide* (9·0 g.), m. p. 170—245° (decomp.); when pure it formed needles, m. p. 248—251° (decomp.) after repeated recrystallization from water (Found: C, 34·9; H, 2·4; N, 16·0. $C_5H_4O_3N_2S$ requires C, 34·9; H, 2·3; N, 16·3%).

Method II. The anhydride (2·0 g.) in dry ethanol (20 c.c.) was boiled under reflux for 1 hr., the solvent was removed, and the crude 5-ethoxycarbonylisothiazole-4-carboxylic acid (2·0 g.) was dissolved in aqueous ammonia (*d* 0·88; 25 c.c.). After 12 hr., excess of ammonia was removed at 100° and the solution, on acidification with hydrochloric acid, gave 4-carboxyisothiazole-5-carboxyamide (1·0 g.), m. p. 241—243°. Recrystallization from water gave colourless needles, m. p. and mixed m. p. 248—250° (decomp.).

Desulphurization of Methyl Isothiazole-4-carboxylate.—Methyl isothiazole-4-carboxylate (5·0 g.), Raney nickel (25 g.), and methanol (150 c.c.) were boiled under reflux for 6 hr. The spent sludge was removed and the residual solution boiled with decolorizing charcoal and filtered (Hyflo). Evaporation of the filtrate gave a brown syrup which contained nitrogen but no sulphur. It was readily soluble in 2N-hydrochloric acid, less so in 2N-sodium hydroxide, did not react with aqueous sodium hydrogen carbonate, but slowly gave a crystalline precipitate with chloroplatinic acid. The syrup was triturated with ether, and the solution filtered from a sticky residue. Evaporation of the filtrate gave a gum (0·5 g.) which was dissolved in dry pyridine (5 c.c.) and treated with 3,5-dinitrobenzoyl chloride (2·5 g.) in dry pyridine (50 c.c.). After 18 hr., the solution was poured into water (250 c.c.), and the emulsion was washed with water, 2N-hydrochloric acid, water, sodium hydrogen carbonate, and water. Evaporation of the dried ($MgSO_4$) ethereal liquors left a thick syrup which yielded pale yellow crystals (0·3 g., m. p. 193—199°) on trituration with chloroform. Recrystallization from chloroform gave *methyl β-3,5-dinitrobenzamido-α-methylpropionate*, m. p. 201—202° (Found: C, 46·9; H, 3·8; N, 13·5; MeO, 10·2; *C*-Me, 4·5%; *M*, 270. $C_{12}H_{13}O_7N_3$ requires C, 46·3; H, 4·2; N, 13·5; MeO, 10·0; *C*-Me, 4·8%; *M*, 311).

β-Iminothiobutyramide (XVII).—Dry hydrogen sulphide (15—20 l./hr.) was passed through a 2·5 cm. diameter, grade 2, sintered-glass bubbler into a solution of β-iminobutyronitrile (1 kg.) in dry pyridine (3 l.) for 8 hr. at 35—40°. The reaction flask was stoppered overnight, and the solution was again treated with hydrogen sulphide for 8 hr. and set aside for a second night. The pyridine was removed on the steam-bath under reduced pressure and the residual oil set aside to crystallize. The product was triturated with ether, collected, washed with ether, and dried (683 g.; m. p. 141—142°). The ether washings were concentrated, the residue was dissolved in dry pyridine (2 l.), and the solution treated with hydrogen sulphide as before to give further product (479 g.; m. p. 124—128°) which, crystallized from chloroform, had m. p. 138—141° (244 g.). Recrystallization from benzene or chloroform gave *β-iminothiobutyramide* in yellow needles, m. p. 142° (Found: C, 41·2; H, 7·1; N, 23·9; S, 27·8. $C_4H_8N_2S$ requires C, 41·3; H, 6·9; N, 24·1; S, 27·6%).

5-Amino-3-methylisothiazole (XVIII).—*Method* I. An aqueous solution of chloramine was prepared by treating sodium hydroxide (63·0 g.) in water (300 c.c.) and ice (350 g.) with chlorine (48·7 g.), and stirring the resulting solution into aqueous ammonia (*d* 0·88; 72·0 c.c.), water (1 l.), and ice (1 kg.). Powdered β-iminothiobutyramide (80·0 g.) was added, and the mixture was stirred for 6 hr. and set aside overnight. Solids were filtered off, and the filtrate was continuously extracted with ether (1 l.) for 18 hr. The dried ($MgSO_4$) extracts were treated

with dry hydrogen chloride for 1 hr., and the *hydrochloride* (67·0 g.) collected, washed with ether, and dried for 1 hr. at 40°. Crystallization from ethanol–ether gave colourless needles, m. p. *ca.* 240° (decomp.) (Found: C, 32·2; H, 4·85; N, 18·8; Cl, 23·55; S, 21·2. $C_4H_6N_2S$,HCl requires C, 31·9; H, 4·7; N, 18·6; Cl, 23·5; S, 21·3%). The hydrochloride (67·0 g.) was dissolved in water (670 c.c.), and the solution filtered from a little flocculent residue, treated with 50% sodium hydroxide solution (67 c.c.), and continuously extracted with ether (250 c.c.) for 18 hr. Evaporation of the dried ($MgSO_4$) extracts gave crude 5-*amino*-3-*methylisothiazole* (34·0 g.); distillation gave material (29·0 g.), b. p. 100—105°/0·3 mm., pale yellow prisms, m. p. 48—49°. Recrystallization from light petroleum (b. p. 40—60°) gave colourless prisms, m. p. 52—53° (Found: C, 41·9; H, 5·4; N, 24·2. $C_4H_6N_2S$ requires C, 42·1; H, 5·3; N, 24·5%).

Several by-products, not yet identified, were isolated from time to time. These substances are in the annexed Table.

Sub-stance	M. p.	Formula	Found (%) C	H	N	S	Required (%) C	H	N	S
(*a*)	191—192° (decomp.)	$C_4H_5ON_3S$	33·9	3·6	29·55	22·2	33·6	3·5	29·4	22·4
(*b*)	231	$C_8H_9N_3$	65·5	6·3	28·0		65·3	6·2	28·55	
(*c*)	300—301	$C_{16}H_{14}N_4S,0·5H_2O$	63·5	5·05	18·85	9·9	63·0	4·95	18·4	10·5
(*d*)	305—307	$C_{16}H_{16}O_2N_4$	65·0	5·7	19·7	Nil	65·0	5·4	18·9	
(*e*)	228—229 (decomp.)	$C_8H_{10}ON_2S$,HCl,1·7H_2O *	38·6	5·7	10·7	12·6	38·4	5·9	11·2	12·8
(*f*)	117—125									

* Found: Cl, 13·5; H_2O, 12·35. Required: Cl, 14·2; H_2O, 12·4%.

(*a*) Reaction residue. (*b*) Reaction residue, with S. (*c*) Separated from first ether extracts. (*d*) From (*c*), by repeated recrystn. from EtOH. (*e*) Pptd. from first ether extracts by prolonged treatment with HCl. (*f*) From first ether extracts by extraction with 2N-NaOH.

The *amine picrate* crystallized from ethanol in needles, decomp. from 185° (Found: C, 35·3; H, 2·9; N, 20·25. $C_4H_6N_2S,C_6H_3O_7N_3$ requires C, 35·0; H, 2·65; N, 20·4%). The *acetyl derivative*, from the base and acetic anhydride, crystallized from water in needles, m. p. 180—181° (Found: C, 45·9; H, 5·2; N, 17·4. $C_6H_8ON_2S$ requires C, 46·1; H, 5·2; N, 17·9%). The *dichloroacetyl* derivative, from the amine and dichloroacetyl chloride in ether, crystallized from ethyl acetate–light petroleum (b. p. 60—80°) in needles, m. p. 189—190° (Found: N, 12·5; Cl, 31·5. $C_6H_6ON_2Cl_2S$ requires N, 12·45; Cl, 31·5%). The *benzoyl derivative*, from the amine and alkaline benzoyl chloride, separated from aqueous alcohol in needles, m. p. 222—223° (Found: C, 60·8; H, 4·7; N, 12·9; S, 15·2. $C_{11}H_{10}ON_2S$ requires C, 60·5; H, 4·6; N, 12·8; S, 14·7%).

Method II. To a solution of ammonium persulphate (780 g.) and sodium hydroxide (272 g.) in water (8·5 l.) at 15°, powdered β-iminothiobutyramide (394 g.) was added, with continued stirring, during 30 min., the temperature being kept at 15—20° by the addition of ice (*ca.* 3·5 kg.); aqueous ammonia (*d* 0·88) was added as necessary (*ca.* 200 c.c.) to maintain the pH at >9. After 1 hr., the thioamide had dissolved to give a clear, wine-red solution. The solution was stirred for a further 4 hr. and was set aside overnight. It was then filtered and the filtrate treated as described in Method I.* Distilled amine was obtained in 36% yield.

3-*Methyl*-5-*nitraminoisothiazole* (XXVII).—A solution of 5-amino-3-methylisothiazole (10 g.) in concentrated sulphuric acid (25 c.c.) was slowly treated with fuming nitric acid (*d* 1·51; 5 c.c.) below 40°. After 16 hr., the clear yellow solution was stirred with ice (500 g.), and the precipitated 3-*methyl*-5-*nitraminoisothiazole* [13·9 g.; m. p. 193° (decomp.)] was collected, washed with water, and dried. Recrystallization from ethanol gave pale yellow needles, m. p. 200—201° (Found: N, 26·4. $C_4H_5O_2N_3S$ requires N, 26·4%).

5-*Dichloroacetamido*-3-*methyl*-4-*nitroisothiazole* (XXVb).—Fuming nitric acid (*d* 1·51; 4·7 c.c.) was added dropwise, with stirring, to 5-dichloroacetamido-3-methylisothiazole (21·0 g.) in concentrated sulphuric acid (63 c.c.) at <5°. The mixture was allowed to reach room temperature and was set aside overnight. Treatment with ice (200 g.) and water (1 l.) gave 5-*dichloroacetamido*-3-*methyl*-4-*nitroisothiazole* (24·4 g.) as a white solid, m. p. 91—92°. Crystallization from light petroleum (b. p. 60—80°) gave fluffy white needles, m. p. 91—92° (Found: N, 15·7; Cl, 26·1. $C_6H_5O_3N_3Cl_2S$ requires N, 15·6; Cl, 26·25%).

5-*Acetamido*-3-*methyl*-4-*nitroisothiazole* (XXVa) was similarly prepared (90% yield) from

* No second hydrochloride was obtained, nor were any by-products noted.

5-acetamido-3-methylisothiazole and crystallized from alcohol in plates, m. p. 187° (Found: C, 35·85; H, 3·5; N, 20·95. $C_6H_7O_3N_3S$ requires C, 35·8; H, 3·5; N, 20·9%).

5-Amino-3-methyl-4-nitroisothiazole (XXII).—5-Dichloroacetamido-3-methyl-4-nitroisothiazole (19·0 g.) was boiled with 4N-hydrochloric acid (190 c.c.) until dissolution was complete (1 hr.). Hot water (190 c.c.) and charcoal (1 g.) were added, boiling was continued for 5 min., and the hot solution was filtered. *5-Amino-3-methyl-4-nitroisothiazole* (7·8 g.) separated as pale yellow prisms, m. p. 185—186°, unchanged by recrystallization from ethanol (Found: C, 30·3; H, 3·23; N, 26·15. $C_4H_5O_2N_3S$ requires C, 30·2; H, 3·2; N, 26·4%). The amine was also obtained (80% yield) in a similar manner from 5-acetamido-3-methyl-4-nitroisothiazole.

5-Acetamido-4-amino-3-methylisothiazole (XXIX).—A suspension of 5-acetamido-3-methyl-4-nitroisothiazole (40·0 g.) and platinum oxide catalyst (2·0 g.) in ethanol (350 c.c.) was reduced with hydrogen at 66° under a pressure of 300 lb./sq. in. Uptake was complete in 4 hr. Hydrated *5-acetamido-4-amino-3-methylisothiazole* (30·0 g.; m. p. 222—223°) crystallized from water in colourless needles, m. p. 225—226° (Found: C, 38·3; H, 6·0; N, 21·6; H_2O, 9·7. $C_6H_9ON_3S,H_2O$ requires C, 38·1; H, 5·9; N, 22·2; H_2O, 9·5%).

5-p-*Acetamidobenzenesulphonamido-3-methylisothiazole.*—A solution of *p*-acetamidobenzenesulphonyl chloride (130 g.) in dry pyridine (225 c.c.) was added, with stirring, to a solution of 5-amino-3-methylisothiazole (57 g.) in dry pyridine (225 c.c.). The temperature rose to 50—60°, and the mixture was then heated at 90—95° for 30 min. The mixture was cooled and stirred into 2N-hydrochloric acid (5·5 l.) and ice (1 kg.). After 30 min., the solid product was collected, washed with water, and drained. It was then stirred with 2N-ammonia (1·5 l.) for 30 min., insoluble material was removed, and the filtrate was stirred while 2N-acetic acid was added to bring the pH to 7·4. A small amount of highly coloured impurity was removed, and the filtrate stirred with charcoal (10 g.) for 1 hr. and treated with 2N-hydrochloric acid to pH 1. 5-p-*Acetamidobenzenesulphonamido-3-methylisothiazole* separated as a pale yellow powder (83·5 g.), m. p. 265—268°. Crystallization from acetic acid gave straw-coloured, lenticular crystals, m. p. 271·5—272·5° (Found: C, 45·6; H, 4·2; N, 12·9. $C_{12}H_{13}O_3N_3S_2$ requires C, 46·3; H, 4·2; N, 13·5%).

5-p-*Aminobenzenesulphonamido-3-methylisothiazole* (XXVIIIa).—5-*p*-Acetamidobenzenesulphonamido-3-methylisothiazole (107 g.) was added to boiling 2N-sodium hydroxide (1070 c.c.), boiling was continued for 30 min. and then for a further 10 min. after the addition of decolorizing charcoal (6 g.). The cooled, filtered solution was stirred and treated with sulphur dioxide to pH 4—5. The precipitated 5-p-*aminobenzenesulphonamido-3-methylisothiazole* (78 g.; m. p. 186—189°) was purified by dissolution in water containing the minimum of ammonia, treatment with charcoal, and reprecipitation with acetic acid at pH 4—5 (72 g.; m. p. 189—191°). Recrystallization from water gave the sulphonamide in cream needles, m. p. 192—192·5° (Found: C, 44·9; H, 4·3; N, 15·7; S, 24·1. $C_{10}H_{11}O_2N_3S_2$ requires C, 44·6; H, 4·1; N, 15·6; S, 23·8%). The *sodium derivative* separated from ethanol–ether as pale cream needles, m. p. 345° (decomp.), which absorbed moisture to give the stable hydrate (Found: N, 13·8; Na, 7·35; H_2O, 6·2. $C_{10}H_{10}O_2N_3S_2Na,H_2O$ requires N, 13·6; Na, 7·4; H_2O, 5·8%). The N^4-*succinamido-derivative hemihydrate* was precipitated from 0·5N-aqueous ammonia by the addition of 2N-hydrochloric acid, as a white powder, m. p. 228—229° (Found: C, 44·3; H, 4·1; N, 11·1; H_2O, 2·2. $C_{14}H_{15}O_5N_3S_2,0{\cdot}5H_2O$ requires C, 44·4; H, 4·3; N, 11·1; H_2O, 2·4), and the N^4-*phthalamido-derivative* similarly, m. p. 201—202° (Found: C, 51·9; H, 3·8; N, 10·3. $C_{18}H_{15}O_5N_3S_2$ requires C, 51·8; H, 3·6; N, 10·1%).

5-p-*Nitrobenzenesulphonamido-3-methylisothiazole* (XXVIIIb) was prepared in only 6% yield in a manner analogous to that described for the *p*-acetamido-derivative. It was precipitated from 0·5N-aqueous ammonia, by treatment with 2N-hydrochloric acid, as fine yellow needles, m. p. 218—219° (Found: C, 40·2; H, 3·2; N, 14·0; S, 21·1. $C_{10}H_9O_4N_3S_2$ requires C, 40·1; H, 3·0; N, 14·0; S, 21·4%).

5-Chloro-3-methylisothiazole.—A solution of 5-amino-3-methylisothiazole (5·7 g.) in 86% phosphoric acid (20 c.c.) was cooled to 5° and treated with concentrated nitric acid (10 c.c.) below 10°. The suspension of nitrate was cooled to 0° and diazotized by cautious addition of sodium nitrite (4·0 g.) in a little water below 5°. After 30 min., the diazotized solution was slowly stirred into a solution of cuprous chloride [prepared in the usual manner from cupric sulphate ($5H_2O$; 15·6 g.), sodium chloride (4·1 g.), and sodium metabisulphite (3·15 g.)] in 50% hydrochloric acid. Evolution of nitrogen was complete in 15 min. The mixture was set

aside overnight, adjusted to pH 4—5 with 2N-sodium hydroxide, and steam-distilled. The distillate (100 c.c.) was extracted with ether (3 × 25 c.c.), and the dried ($MgSO_4$) extracts were concentrated, and distilled at atmospheric pressure (2·1 g.; b. p. 148—155°). Redistillation gave *5-chloro-3-methylisothiazole*, b. p. 154—155°/767 mm. (A satisfactory analysis for chlorine could not be obtained. Found: N, 10·3; Cl, 25·5. C_4H_4NClS requires N, 10·5; Cl, 26·5%.)

5-Bromo-3-methylisothiazole (XX) was prepared in 73% yield in a manner analogous to that described above for the chloro-compound, except that after addition of the diazotized amine solution to cuprous bromide–hydrobromic acid solution it was desirable to leave the cooled mixture for only 1 hr. before dilution and partial neutralization in order to avoid spontaneous decomposition. It distilled as a colourless, mobile liquid, b. p. 72°/13 mm. (Found: N, 8·0; Br, 45·0. C_4H_4NBrS requires N, 7·9; Br, 44·9%).

5-Bromo-3-methyl-4-nitroisothiazole (XXI).—*Method* I. 5-Amino-3-methyl-4-nitroisothiazole (7·85 g.) was diazotized as described for 5-amino-3-methylisothiazole, and the solution was added to one of cuprous bromide and hydrobromic acid prepared from cupric sulphate (15·4 g.). After 1 hr. at 0—5°, the mixture was diluted with an equal volume of water, adjusted to pH 4—5 with 50% sodium hydroxide, and steam-distilled. The distillate was extracted with ether (3 × 50 c.c.), and the dried ($MgSO_4$) extracts were evaporated to give *5-bromo-3-methyl-4-nitroisothiazole* (7·25 g.). Recrystallization from ethanol gave pale yellow needles, m. p. 77—78° (Found: N, 12·45; Br, 35·4. $C_4H_3O_2N_2BrS$ requires N, 12·6; Br, 35·8%).

Method II. A solution of 5-bromo-3-methylisothiazole (3·0 g.) in concentrated sulphuric acid (10 c.c.) was treated with fuming nitric acid (*d* 1·51; 1·0 c.c.), then heated at 115° for 2 hr. The cooled mixture was stirred with ice (100 g.), and the solid product (2·8 g.; m. p. 76—78°) collected, washed with water, and dried. Crystallization from ethanol gave pale yellow needles, m. p. and mixed m. p. 77—78°.

5-Iodo-3-methyl-4-nitroisothiazole.—5-Bromo-3-methyl-4-nitroisothiazole (1·9 g.) and sodium iodide (3·2 g.) were heated in acetone (16·5 c.c.) and acetic acid (1·1 c.c.) for 2 hr. at 100°, then set aside for 16 hr. at room temperature. Solids were filtered off and the filtrate was treated with sodium pyrosulphite (1·07 g.) in water (68 c.c.), to give *5-iodo-3-methyl-4-nitroisothiazole* (1·6 g.; m. p. 94—109°). Recrystallization from light petroleum (b. p. 60—80°) gave pale yellow plates, m. p. 120—121° [Found: C, 17·4; H, 1·3; N, 9·9; I (specific), 46·9; S, 12·05. $C_4H_3O_2N_2IS$ requires C, 17·8; H, 1·1; N, 10·4; I, 47·0; S, 11·9%).

5-Cyano-3-methylisothiazole (XI).—5-Bromo-3-methylisothiazole (10·0 g.) was heated with cuprous cyanide (7·5 g.) at 160° for 3 hr. Distillation gave *5-cyano-3-methylisothiazole* (6·3 g.), b. p. 90—100°/20 mm., m. p. 38—40°. Recrystallization from light petroleum (b. p. 60—80°) gave colourless prisms, m. p. 39—40° (Found: C, 48·0; H, 3·25; N, 22·3. $C_5H_4N_2S$ requires C, 48·4; H, 3·25; N, 22·3%).

3-Methylisothiazole-5-carboxylic acid (XXIII).—5-Cyano-3-methylisothiazole (5·0 g.) was boiled with 2N-sodium hydroxide (50 c.c.) until dissolution was complete. The cooled, filtered solution was acidified with concentrated hydrochloric acid, to give the *acid* (5·35 g.), colourless needles, m. p. 206° (decomp.) (from water) (Found: C, 41·8; H, 3·8; N, 9·45; S, 22·5. $C_5H_5O_2NS$ requires C, 41·8; H, 3·5; N, 9·8; S, 22·4%).

3-Methylisothiazole (XXVI).—3-Methylisothiazole-5-carboxylic acid (6·3 g.) was gently heated over a free flame. *3-Methylisothiazole* (3·0 g.) distilled at 125—135°/751 mm. Redistillation gave a colourless, mobile liquid, b. p. 133°/751 mm., (n_D^{21} 1·5180) (Found: C, 48·6; H, 5·0; N, 13·9; S, 32·1. C_4H_5NS requires C, 48·45; H, 5·1; N, 14·1; S, 32·3%), having an odour similar to that of isothiazole.

3-Methyl-5-thiocarbamoylisothiazole.—5-Cyano-3-methylisothiazole (24·0 g.) in pyridine (240 c.c.) was saturated with hydrogen sulphide during 8 hr. Removal of the solvent gave *3-methyl-5-thiocarbamoylisothiazole* (26·0 g.; m. p. 160—162°) which recrystallized from benzene in yellow needles, m. p. 163—164° (Found: C, 38·25; H, 4·0; N, 17·6. $C_5H_6N_2S_2$ requires C, 37·95; H, 3·8; N, 17·7%).

Methyl 3-Methylisothiazole-5-carboxylate.—Powdered 3-methylisothiazole-5-carboxylic acid (22·0 g.) was added to ethereal (600 c.c.) diazomethane, prepared from *N*-nitrosomethylurea (60 g.). After 16 hr., evaporation gave the *ester* (21·5 g.). Distillation gave colourless needles, m. p. 29°, b. p. 100°/11 mm. (Found: C, 45·8; H, 4·5; N, 8·7; S, 20·4. $C_6H_7O_2NS$ requires C, 45·8; H, 4·5; N, 8·9; S, 20·4%).

3-Methylisothiazole-5-carboxyhydrazide.—The methyl ester (21·5 g.) and 100% hydrazine hydrate (21·5 c.c.) dissolved in alcohol (80 c.c.) were heated at 100° for 30 min. After 3 hr.,

filtration gave the *hydrazide* (19·3 g.) which recrystallized from water in cream plates, m. p. 167—168° (Found: C, 38·5; H, 4·5; N, 26·75. $C_5H_7ON_3S$ requires C, 38·2; H, 4·5; N, 26·7%).

3-*Methyl*-4-*nitroisothiazole* (XXX).—Potassium nitrate (6·0 g.) was slowly stirred into a solution of 3-methylisothiazole (6·0 g.) in 20% oleum (15 c.c.) at 20—30°, and the mixture was set aside at room temperature for 16 hr. before being heated at 100° for 24 hr. The cold solution was added to ice (150 g.), neutralized with sodium carbonate, and extracted with ether (3 × 100 c.c.). Evaporation of the dried ($MgSO_4$) extracts gave 3-*methyl*-4-*nitroisothiazole* (7·1 g.) which distilled as a yellow oil (6·2 g.), b. p. 108°/14 mm. (Found: C, 33·65; H, 3·05; N, 19·1. $C_4H_4O_2N_2S$ requires C, 33·3; H, 2·8; N, 19·4%).

4-*Amino*-3-*methylisothiazole* (XXXI).—Aqueous ammonia (*d* 0·88; 70 c.c.) and 3-methyl-4-nitroisothiazole (4·0 g.) in hot alcohol (150 c.c.) were divided into 3 equal portions which were added at 5 min. intervals to a boiling, vigorously stirred solution of ferrous sulphate ($7H_2O$; 61 g.) in water (195 c.c.). Boiling was continued for 15 min., inorganic material was removed, and the filtrate and alcoholic washings were evaporated to dryness. Concentration of dried ($MgSO_4$) ethereal extracts (2 × 250 c.c.) of the residue gave crude 4-*amino*-3-*methylisothiazole* (2·1 g.). Distillation yielded colourless prisms (1·7 g.), b. p. 63°/0·08 mm., m. p. 28° (Found: C, 42·0; H, 5·3; N, 24·2. $C_4H_6N_2S$ requires C, 42·1; H, 5·3; N, 24·5%). The hydrated acetyl derivative separated from water in needles, m. p. 62—63°, unstable to drying. A satisfactory analysis could not be obtained (Found: C, 35·3; H, 7·3; N, 12·6; S, 15·5; H_2O, 26·4. Calc. for $C_6H_8ON_2S,3H_2O$: C, 34·3; H, 6·7; N, 13·3; S, 15·25; H_2O, 25·7%).

4-p-*Acetamidobenzenesulphonamido*-3-*methylisothiazole*.—*p*-Acetamidobenzenesulphonyl chloride (2·33 g.) was added at <10° to 4-amino-3-methylisothiazole (1·14 g.) in pyridine (10 c.c.), and the solution set aside for 16 hr. Treatment with ice (200 g.) and 2N-hydrochloric acid (100 c.c.) gave 4-p-*acetamidobenzenesulphonamido*-3-*methylisothiazole* (2·7 g.), m. p. 192—196°. Repeated dissolution in 0·5N-ammonia (charcoal) and reprecipitation with N-acetic acid gave a white powder, m. p. 198—199° (Found: C, 46·15; H, 4·3; N, 13·2. $C_{12}H_{13}O_3N_3S_2$ requires C, 46·3; H, 4·2; N, 13·5%).

4-p-*Aminobenzenesulphonamido*-3-*methylisothiazole* (XXXII).—4-*p*-Acetamidobenzenesulphonamido-3-methylisothiazole (2·7 g.) was boiled for 2 hr. with 2N-sodium hydroxide (25 c.c.) (charcoal), and the cooled, filtered solution acidified with acetic acid. The *aminobenzenesulphonamide* (2·15 g.) separated from alcohol in colourless prisms, m. p. 175° (Found: C, 44·25; H, 4·3; N, 15·8; S, 23·8. $C_{10}H_{11}O_2N_3S_2$ requires C, 44·6; H, 4·1; N, 15·6; S, 23·8%).

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