## 700. *Isothiazoles. Part V.*[1] *Some Isothiazole Analogues of Histidine, Histamine, and Amphetamine*

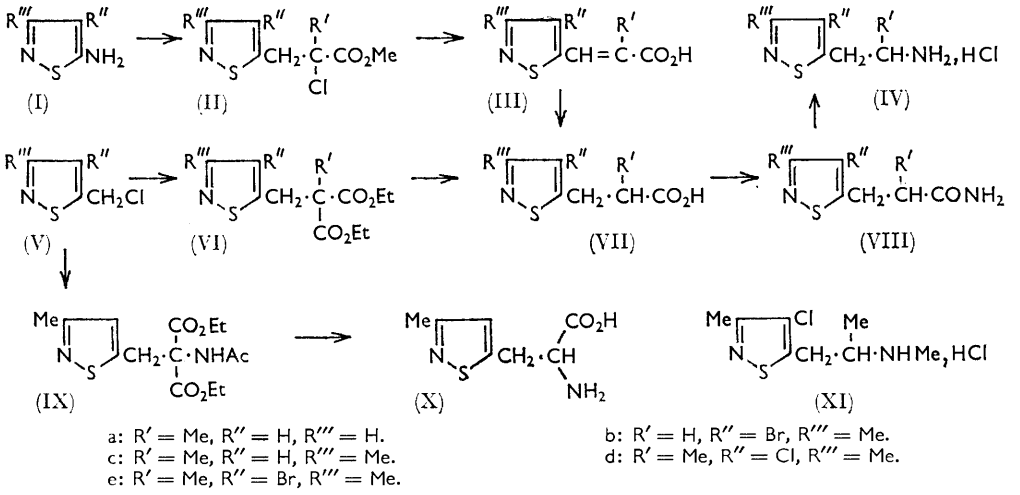
By B. A. Bennett, D. H. Jones, R. Slack, and K. R. H. Wooldridge

Analogues of histidine (X, XIX), histamine (IVb, XVa), and amphetamine (IVa, IVc—e, XVII) have been synthesised in which the imidazole or phenyl ring has been replaced by the isothiazole nucleus.

The chemistry of simple isothiazoles has received considerable attention during the last few years [2] and it is now possible to consider introducing the isothiazole nucleus into many compounds of biological interest in order that relationships between chemical constitution and biological activity may be studied. This Communication describes the synthesis of some isothiazole amino-acids related to histidine, and amines related to histamine and amphetamine.

[1] Part IV, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1964, 3114.
[2] R. Slack and K. R. H. Wooldridge, "Advances in Heterocyclic Chemistry," Academic Press, New York and London, 1965, vol. IV, p. 107.

Isothiazol-5-yl analogues of histamine (IV; R′ = H) and amphetamine (IV; R′ = Me) were prepared by Hoffmann reactions on the corresponding amides (VIII). The reaction failed with 2-methyl-3-(3-methylisothiazol-5-yl)propionamide (VIIIc) but the amphetamine analogue (IVc) was obtained by a Curtius reaction on the appropriate hydrazide. The



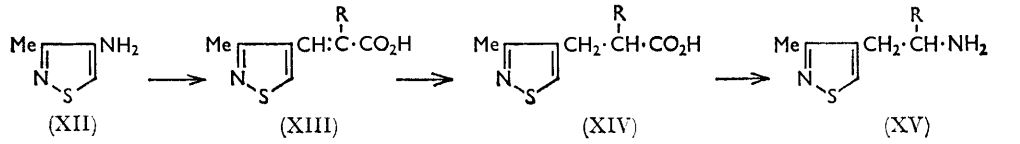
a: R′ = Me, R″ = H, R‴ = H. b: R′ = H, R″ = Br, R‴ = Me.
c: R′ = Me, R″ = H, R‴ = Me. d: R′ = Me, R″ = Cl, R‴ = Me.
e: R′ = Me, R″ = Br, R‴ = Me.

acids (VII) were obtained either by a malonic ester synthesis from 5-chloromethylisothiazoles (V) or by reduction of the acrylic acids (III) obtained by Meerwein reactions on 5-aminoisothiazoles (I). It was not possible to effect catalytic hydrogenation of the unsaturated acids containing α-methyl groups (IIIc, d), but sodium amalgam reduction proceeded smoothly in high yield. Under the conditions of the Meerwein reaction 5-amino-4-bromo-3-methylisothiazole (Ie) underwent halogen exchange to give 2-methyl-3-(4-chloro-3-methylisothiazol-5-yl)acrylic acid (IIId).

One amphetamine analogue (IVd) was converted into the *N*-methyl derivative (XI) by successive tosylation, methylation, and hydrolysis.

Treatment of the chloro-ester (II; R′ = R″ = H, R‴ = Me) with ammonia gave 3-(3-methylisothiazol-5-yl)acrylamide rather than an amino-amide, and similar treatment of 2-chloro-3-(3-methylisothiazol-5-yl)propionic acid gave the corresponding acrylic acid. 3-Methylisothiazol-5-ylalanine (X) was, however, prepared readily by the acetamidomalonic ester route.

An isothiazol-4-yl analogue (XVa) of histamine was prepared from 4-amino-3-methylisothiazole (XII) as indicated in the reaction scheme. However, the amphetamine

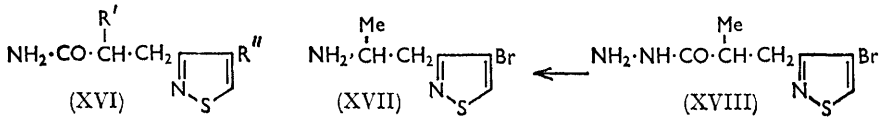


a: R = H. b: R = Me.

analogue (XVb) could not be obtained because we were unable to reduce the α-methylacrylic acid (XIIIb) catalytically, by sodium amalgam, dissolving metals, or by di-imide.[3] The alternative route to (XIVb) was precluded by the inaccessibility of 4-chloromethylisothiazoles.

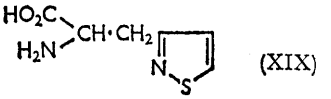
[3] E. Schmitz and R. Ohme, *Angew. Chem.*, 1961, **73**, 807; R. S. Dewey and E. E. Tamelen, *J. Ame Chem. Soc.*, 1961, **83**, 3729; R. Appel and W. Büchner, *Annalen*, 1962, **654**, 1.

Several isothiazol-3-ylpropionamides (XVIa—c) were prepared by the malonic ester route from the readily available 3-bromomethylisothiazoles,[4] but none of them underwent the Hoffmann reaction. 2-Amino-3-(isothiazol-3-yl)propane (XVII) was prepared from the corresponding hydrazide (XVIII) by the Curtius reaction.



(XVI) (XVII) (XVIII)

(a : R′ = H, R″ = Br)
(b : R′ = Me, R″ = Br)
(c : R′ = Me, R″ = H)



(XIX)

Condensation of 3-bromomethylisothiazole and diethyl acetamidomalonate took place readily in the presence of sodium hydride in dimethylformamide but only to a small extent in the presence of sodium ethoxide in ethanol. Hydrolysis of the condensation product gave isothiazol-3-ylalanine (XIX) in good yield.

## Experimental

*5-Hydroxymethylisothiazole.*—5-Formylisothiazole [5] (34 g., 0·30 mole) in methanol (150 ml.) was added during 60 min. to a stirred solution of potassium borohydride (5·4 g., 0·10 mole) in methanol (150 ml.) and 0·2N-sodium hydroxide (60 ml.) at 10—15°. After 18 hr. at room temperature, the methanol was removed under reduced pressure, and the residue extracted with ether. Fractional distillation of the extract afforded 5-hydroxymethylisothiazole (27 g., 78%), b. p. 148—150°/22 mm. (Found: C, 41·8; H, 4·2. $C_4H_5NOS$ requires C, 41·7; H, 4·4%). The *acetyl derivative* had b. p. 122—123°/21 mm. (Found: N, 9·1; S, 20·3. $C_6H_7NO_2S$ requires N, 8·9; S, 20·4%). 4-Bromo-5-hydroxymethyl-3-methylisothiazole [6] (77%) was prepared similarly.

*5-Chloromethylisothiazole* (Va).—Thionyl chloride (20 ml.) was added during 15 min. to a vigorously stirred solution of 5-hydroxymethylisothiazole (23 g., 0·20 mole) in anhydrous benzene (80 ml.) at 5—10°. After a further 15 min. at 10°, the mixture was refluxed for 10 min. and then cooled and poured on 2N-sodium carbonate (250 ml.). The benzene layer was separated, dried ($MgSO_4$), and fractionally distilled to give *5-chloromethylisothiazole* (20 g., 75%), b. p. 90—92°/18 mm. (Found: Cl, 26·5; S, 24·3. $C_4H_4ClNS$ requires Cl, 26·5; S, 24·0%).

*4-Bromo-5-chloromethyl-3-methylisothiazole* (Vb) (78%), b. p. 73—74°/1 mm. (Found: C, 26·8; H, 2·4; S, 14·1. $C_5H_5BrClNS$ requires C, 26·5; H, 2·2; S, 14·2%) was prepared similarly.

*5-(2,2-Diethoxycarbonylpropyl)isothiazole* (VIa).—5-Chloromethylisothiazole (15 g., 0·113 mole) in anhydrous ethanol (100 ml.) was added during 5 min. to a solution at 45—50° of sodium diethyl methylmalonate [from diethyl methylmalonate (43·5 g., 0·25 mole) and sodium (3·45 g., 0·15 mole)] in anhydrous ethanol (200 ml.). The mixture was successively refluxed for 48 hr., concentrated to *ca.* 50 ml., cooled, poured on water, and extracted with ether (3 × 150 ml.). Fractional distillation of the dried ($MgSO_4$) extract afforded the *diester* (25·5 g., 84%), b. p. 109—112°/0·25 mm. (Found: C, 53·5; H, 6·1. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·2%).

*4-Bromo-5-(2,2-diethoxycarbonylethyl)-3-methylisothiazole* (VIb) (46%), b. p. 137—138°/0·1 mm. (Found: N, 4·0; S, 9·1. $C_{12}H_{16}BrNO_4S$ requires N, 4·0; S, 9·2%), and *4-bromo-5-(2,2-diethoxycarbonylpropyl)-3-methylisothiazole* (VIe) (57%), b. p. 156°/0·35 mm. (Found: N, 3·9. $C_{13}H_{18}BrNO_4S$ requires N, 3·8%) were prepared similarly.

*3-(2,2-Diethoxycarbonylpropyl)isothiazole.*—3-Bromomethylisothiazole [4] (28 g., 0·158 mole) was added at 20—25° during 15 min. to a stirred solution of sodium diethyl methylmalonate [from diethyl methylmalonate (29·5 g., 0·164 mole) and sodium hydride (4·0 g., 0·166 mole)] in dry dimethylformamide (250 ml.). The mixture was successively stirred for 2 hr., heated on the steam-bath for 1 hr., cooled, poured on water (*ca.* 600 ml.), and ether extracted. Fractional distillation afforded *3-(2,2-diethoxycarbonylpropyl)isothiazole* (25 g.,

[4] D. Buttimore, M. P. L. Caton, J. D. Renwick, and R. Slack, in preparation.
[5] M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1964, 446.
[6] D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1963, 2032.

59%), b. p. 141—145°/0·45 mm. (Found: C, 53·5; H, 6·4; N, 5·1. $C_{12}H_{17}NO_4S$ requires C, 53·1; H, 6·3; N, 5·2%).

*4-Bromo-3-(2,2-diethoxycarbonylpropyl)-isothiazole* (54%), b. p. 138—143°/0·25 mm. (Found: Br, 22·7; N, 3·9; S, 9·0. $C_{12}H_{16}BrNO_4S$ requires Br, 22·8; N, 4·0; S, 9·2%), and *4-bromo-3-(2,2-diethoxycarbonylethyl)isothiazole* (67%), b. p. 136—139°/0·4 mm. (Found: Br, 24·2; S, 9·3. $C_{11}H_{14}BrNO_4S$ requires Br, 23·8; S, 9·5%) were prepared similarly.

*5-(2,2-Dicarboxypropyl)isothiazole.*—5-(2,2-Diethoxycarbonylpropyl)isothiazole (25·5 g., 0·085 mole), 6N-sodium hydroxide (40 ml.), and ethanol (50 ml.) were refluxed for 2 hr. The ethanol was then distilled off and the residue acidified with concentrated hydrochloric acid with cooling, to give the *di-acid* (17·8 g., 98%), m. p. 152—154° (decomp.) (Found: C, 44·9; H, 4·1; S, 15·0. $C_8H_9NO_4S$ requires C, 44·7; H, 4·2; S, 14·9%).

*4-Bromo-5-(2,2-dicarboxypropyl)-3-methylisothiazole* (63%), m. p. 168° (decomp.) (Found: C, 35·2; H, 3·5; S, 10·5. $C_9H_{10}BrNO_4S$ requires C, 35·1; H, 3·3; S, 10·4%), and *3-(2,2-dicarboxypropyl)isothiazole* (79%), m. p. 154—155° (Found: N, 6·3; S, 15·0. $C_8H_9NO_4S$ requires N, 6·5; S, 14·9%) were prepared similarly.

*3-(Isothiazol-5-yl)-2-methylpropionic Acid* (VIIa).—5-(2,2-Dicarboxypropyl)isothiazole (17·8 g.) was heated at 200°. When carbon dioxide evolution had ceased (30 min.), the residue was distilled to give the *acid* (10 g., 71%), m. p. 44—46°, b. p. 140—143°/0·15 mm. (Found: C, 49·3; H, 5·3; S, 18·6. $C_7H_9NO_2S$ requires C, 49·2; H, 5·3; S, 18·7%).

*3-(4-Bromo-3-methylisothiazol-5-yl)-2-methylpropionic acid* (VIIe) (99%), m. p. 75—78° (Found: C, 36·1; H, 3·8; S, 12·1. $C_8H_{10}BrNO_2S$ requires C, 36·4; H, 3·8; S, 12·1%), and *3-(isothiazol-3-yl)-2-methylpropionic acid* (80%), m. p. 48—50° (Found: C, 49·0; H, 5·3; S, 18·7. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; S, 18·7%) were prepared similarly.

*3-(4-Bromo-3-methylisothiazol-5-yl)propionic Acid* (VIIb).—4-Bromo-5-(2,2-diethoxycarbonyl ethyl)-3-methylisothiazole (12·7 g.), 6N-sodium hydroxide (40 ml.), and methanol (15 ml.) were refluxed for 30 min. The solution was then strongly acidified with concentrated hydrochloric acid and refluxed for 1 hr. On cooling, a solid separated and was crystallised from aqueous ethanol to give the *acid* (8·2 g., 90%). m. p. 161—164° (Found: C, 33·8; H, 3·4; N, 5·7. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; N, 5·6%).

*3-(4-Bromoisothiazol-3-yl)propionic Acid.*—4-Bromo-3-(2,2-diethoxycarbonylethyl)isothiazole (21·7 g., 0·065 mole) and concentrated hydrochloric acid (200 ml.) were refluxed for 12 hr. Isolation with ether afforded the *mono-acid* (13·5 g., 89%), prisms from aqueous ethanol, m. p. 102—104° (Found: N, 6·1; S, 13·2. $C_6H_6BrNO_2S$ requires N, 5·9; S, 13·6%).

*3-(4-Bromoisothiazol-3-yl)-2-methylpropionic acid* (70%), prisms from light petroleum (b. p. 60—80°), m. p. 68—70° (Found: C, 33·5; H, 3·2; S, 12·8. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; S, 12·8%) was prepared similarly.

*Methyl 2-Chloro-2-methyl-3-(3-methylisothiazol-5-yl)propionate* (IIc).—Sodium nitrite (148 g., 2·15 mole) in water (220 ml.) was added during 15 min. to a mixture of 5-amino-3-methylisothiazole [7] (228 g., 2 mole), concentrated hydrochloric acid (1000 ml.), and glacial acetic acid (500 ml.) kept below 20° by cooling. After being cooled to 0—2° and stirring for 15 min., the solution was added to methyl methacrylate (600 g., 6·0 mole), cupric chloride dihydrate (40 g., 0·23 mole), and acetone (2000 ml.) at such a rate that the temperature of the reaction mixture did not rise above 40°. The mixture was stirred for 1 hr. and poured on water (3000 ml.). Isolation with ether afforded the *ester* (280 g., 60%), b. p. 99—100°/0·05 mm. (Found: C, 46·0; H, 5·0; N, 5·8. $C_9H_{12}ClNO_2S$ requires C, 46·2; H, 5·2; N, 6·0%). Similarly 5-amino-3-methylisothiazole and methyl acrylate gave *methyl 2-chloro-3-(3-methylisothiazol-5-yl)propionate* (28%), b. p. 110—115°/0·1 mm. (Found: C, 43·5; H, 5·5; Cl, 15·8. $C_8H_{10}ClNO_2S$ requires C, 43·7; H, 4·6; Cl, 16·2%).

*3-(3-Methylisothiazol-5-yl)acrylamide.*—Methyl 2-chloro-3-(3-methylisothiazol-5-yl)propionate (1 g.) and aqueous ammonia (25 ml., d. 0·900) were stirred at room temperature for 2 days to give the *amide* (0·68 g., 89%), prisms from aqueous ethanol, m. p. 151—152° (Found: C, 49·6; H, 4·9. $C_7H_8N_2OS$ requires C, 50·0; H, 4·8%).

*2-Chloro-3-(3-methylisothiazol-5-yl)propionic Acid.*—Methyl 2-chloro-3-(3-methylisothiazol-5-yl)propionate (3·12 g.), 90% formic acid (6 ml.), and concentrated hydrochloric acid (3 ml.) were heated on the steam-bath for 1 hr. The reaction mixture was then neutralised with solid sodium carbonate, filtered, and the filtrate acidified to give the *acid* (1·7 g., 58%), prisms from

[7] A. Adams and R. Slack, *J.*, 1959, 3061.

aqueous ethanol, m. p. 133—134° (Found: C, 41·2; H, 4·0; Cl, 17·6. $C_7H_8ClNO_2S$ requires C, 40·9; H, 3·9; Cl, 17·3%).

2-*Methyl*-3-(3-*methylisothiazol*-5-*yl*)*acrylic Acid* (IIIc).—Methyl 2-chloro-2-methyl-3-(3-methylisothiazol-5-yl)propionate (280 g., 1·2 mole), sodium hydroxide (140 g., 3·5 mole), water (300 ml.), and ethanol (1000 ml.) were refluxed with stirring for 3 hr. The ethanol was distilled off and the residue acidified with concentrated hydrochloric acid to give the *acid* (151 g., 69%), prisms, m. p. 204—205° (Found: C, 52·4; H, 4·7; N, 7·5. $C_8H_9NO_2S$ requires C, 52·4; H, 5·0; N, 7·6%).

3-(3-*Methylisothiazol*-5-*yl*)*acrylic acid* (90%), prisms, m. p. 174—175° (Found: C, 49·8; H, 4·2; S, 19·1. $C_7H_7NO_2S$ requires C, 49·7; H, 4·2; S, 18·9%) was prepared similarly.

3-(3-*Methylisothiazol*-4-*yl*)*acrylic Acid* (XIIIa).—By the procedure described for methyl 2-chloro-2-methyl-3-(3-methylisothiazol-5-yl)propionate, 4-amino-3-methylisothiazole [7] and methyl acrylate afforded the corresponding chloro-ester which on treatment with sodium hydroxide afforded the *acid* (44%), m. p. 194° (Found: C, 49·4; H, 4·0; S, 19·0. $C_7H_7NO_2S$ requires C, 49·7; H, 4·2; S, 19·0%).

2-*Methyl*-3-(3-*methylisothiazol*-4-*yl*)*acrylic acid* (XIIIb) (37%), m. p. 170—173° (Found: C, 52·8; H, 5·4; N, 7·2; S, 17·3. $C_8H_9NO_2S$ requires C, 52,4; H, 5·0; N, 7·6; S, 17·5% was prepared similarly.

2-*Methyl*-3-(4-*chloro*-3-*methylisothiazol*-5-*yl*)*acrylic Acid* (IIId).—5-Amino-4-bromo-3-methylisothiazole [6] was diazotised and treated with methyl methacrylate as above to give a liquid, b. p. 100—110°/0·05 mm. which was refluxed with aqueous ethanolic sodium hydroxide for 4 hr. Removal of the ethanol followed by acidification with concentrated hydrochloric acid afforded the *acid* (33%), prisms, m. p. 214—217°, from dimethylformamide (Found: Cl, 16·3; N, 6·3; S, 14·6. $C_8H_8ClNO_2S$ requires Cl, 16·3; N, 6·4; S, 14·7%). Treatment with thionyl chloride followed by ammonia gave 3-(4-*chloro*-3-*methylisothiazol*-5-*yl*)-2-*methylacrylamide*, prisms, m. p. 188—190° from ethanol (Found: N, 13·3; S, 14·6. $C_8H_9ClN_2OS$ requires N, 12·9; S, 14·8%).

2-*Methyl*-3-(3-*methylisothiazol*-5-*yl*)*propionic Acid* (VIIc).—Sodium amalgam [from sodium (23 g., 1·0 mole) and mercury (888 g.)] was added during 20 min. to a stirred mixture of 2-methyl-3-(3-methylisothiazol-5-yl)acrylic acid (60 g., 0·324 mole) and N-sodium hydroxide (600 ml.) at 45—50°. After being stirred for a further 90 min., the mercury was removed, and the aqueous solution acidified and extracted with ether. Concentration of the extract followed by distillation afforded the *acid* (48 g., 79%), b. p. 150—155°/0·5 mm., m. p. 44—47° (Found: N, 7·4; S, 16·9. $C_8H_{11}NO_2S$ requires N, 7·6; S, 17·3%).

2-*Methyl*-3-(4-*chloro*-3-*methylisothiazol*-5-*yl*)*propionic acid* (VIId) (69%), needles, m. p. 71—73°, from light petroleum (b. p. 100—120°) (Found: C, 43·6; H, 4·5; Cl, 16·2. $C_8H_{11}ClNO_2S$ requires C, 43·7; H, 4·6; Cl, 16·1%) was prepared similarly.

3-(3-*Methylisothiazol*-4-*yl*)*propionic Acid* (XIVa).—3-(3-Methylisothiazol-4-yl)acrylic acid (40 g.) in 2N-sodium hydroxide (700 ml.) was subjected to hydrogenation at 80 p.s.i. at 60° using a Raney nickel catalyst (*ca.* 20 g.). The theoretical uptake required 13 hr. The reaction mixture was filtered and acidified with concentrated hydrochloric acid and continuously extracted with chloroform for 24 hr. Concentration of the extract afforded the *acid* (25 g., 63%), m. p. 167—168°, from water (Found: C, 49·5; H, 5·3; S, 18·7. $C_7H_9NO_2S$ requires C, 49·1; H, 5·3; S, 18·7%).

*Methyl* 3-(*Isothiazol*-5-*yl*)-2-*methylpropionate*.—3-(Isothiazol-5-yl)-2-methylpropionic acid (10·5 g.) was added to excess of ethereal diazomethane. After standing at room temperature for 1 hr., the ethereal solution was washed successively with dilute hydrochloric acid, 2N-sodium carbonate, and water, and dried ($MgSO_4$). Fractional distillation afforded the *ester* (8·1 g., 76%), b. p. 78—82°/0·5 mm. (Found: C, 52·3; H, 6·3; S, 16·9. $C_8H_{11}NO_2S$ requires C, 51·9; H, 6·0; S, 17·3%).

*Methyl* 2-*methyl*-3-(3-*methylisothiazol*-5-*yl*)*propionate* (93%), b. p. 88°/0·5 mm. (Found: N, 6·7; S, 15·9; OMe, 16·2. $C_9H_{13}NO_2S$ requires N, 7·0; S, 16·1; OMe, 15·6%), *methyl* 3-(4-*bromoisothiazol*-3-*yl*)*propionate* (90%), m. p. 41—42°, b. p. 113—115°/0·2 mm. (Found: C, 33·5; H, 3·3; S, 12·8. $C_7H_8BrNO_2S$ requires C, 33·6; H, 3·2; S, 12·8%), *methyl* 3-(*isothiazol*-3-*yl*)-2-*methylpropionate* (59%), b. p. 74—77°/0·5 mm. (Found: N, 7·3; S, 17·3. $C_8H_{11}NO_2S$ requires N, 7·6; S, 17·3%), and *methyl* 3-(4-*bromoisothiazol*-3-*yl*)-2-*methylpropionate* (77%), m. p. 45—47°, b. p. 98—103°/0·8 mm. (Found: Br, 30·4; S, 12·0. $C_8H_{10}BrNO_2S$ requires Br, 30·3; S, 12·1%) were prepared similarly.

3-(*Isothiazol-5-yl*)-2-*methylpropionamide* (VIIIa).—Methyl 3-(isothiazol-5-yl)-2-methylpropionate (8 g.) was mixed with ammonia (50 ml.) and ethanol (25 ml.) for 4 days. Concentration under reduced pressure, followed by cooling afforded the *amide* (3·6 g., 49%), needles, m. p. 101—103°, from ethanol (Found: C, 49·2; H, 6·2; N, 16·2. $C_7H_{10}N_2OS$ requires C, 49·4; H, 5·9; N, 16·5%).

3-(4-*Bromo*-3-*methylisothiazol*-5-*yl*)*propionamide* (VIIIb).—3-(4-Bromo-3-methylisothiazol-5-yl)propionic acid (8·2 g.) and thionyl chloride (15 ml.) were refluxed for 30 min. Excess of thionyl chloride was distilled off and the residue in acetone (10 ml.) treated with ammonia (50 ml.) at 0—5°. After 30 min. the reaction mixture was evaporated to dryness under reduced pressure, and the residue washed with aqueous sodium hydrogen carbonate and water. Crystallisation from ethyl acetate afforded the *amide* (6·85 g., 84%), m. p. 140·5—141·5° (Found: N, 10·9; S, 13·1. $C_7H_9BrN_2OS$ requires N, 11·2; S, 12·9%).

3-(4-*Bromo*-3-*methylisothiazol*-5-*yl*)-2-*methylpropionamide* (VIIIe) (78%), needles, m. p. 145—147°, from ethyl acetate and light petroleum (b. p. 40—60°) (Found: C, 36·6; H, 4·2; S, 12·3. $C_8H_{11}BrN_2OS$ requires C, 36·5; H, 4·2; S, 12·2%), 3-(4-*chloro*-3-*methylisothiazol*-5-*yl*)-2-*methylpropionamide* (VIIId) (80%), m. p. 138—140° (Found: Cl, 16·0; N, 12·7. $C_8H_{11}ClN_2OS$ requires Cl, 16·2; N, 12·8%), and 3-(3-*methylisothiazol*-4-*yl*)*propionamide hydrate* (27%), m. p. 172—174° (Found: C, 44·2; H, 6·5; S, 17·0. $C_7H_{10}N_2OS,H_2O$ requires C, 44·6; H, 6·4; S, 17·0%) were obtained similarly.

1-*Methyl*-2-(3-*methylisothiazol*-5-*yl*)*ethanecarbohydrazide*.—Methyl 2-methyl-3-(3-methylisothiazol-5-yl)propionate (19 g.) was added during 10 min. to refluxing hydrazine hydrate (30 ml.). After 2 min. the clear solution was concentrated under reduced pressure to give an oil which solidified on standing. Crystallisation from benzene afforded the *hydrazide* (17 g., 89%), m. p. 75—77° (Found: N, 20·7; S, 16·2. $C_8H_{13}N_3OS$ requires N, 21·1; S, 16·1%).

3-(4-*Bromoisothiazol*-3-*yl*)*propionamide* (XVIa).—Ammonia was passed into a solution of methyl 3-(4-bromoisothiazol-3-yl)propionate (24 g., 0·096 mole) in dry methanol (150 ml.) for 10 hr. and the solution was allowed to stand for 2 days. Evaporation of the solvent afforded the *amide* (16·9 g., 75%), needles from water, m. p. 115—117° (Found: Br, 33·7; N, 11·9; S, 13·7. $C_6H_7BrN_2OS$ requires Br, 34·0; N, 11·9; S, 13·6%).

3-(*Isothiazol*-3-*yl*)-2-*methylpropionamide* (XVIc) (70%), prisms from benzene, m. p. 118—120° (Found: N, 16·2; S, 18·7. $C_7H_{10}N_2OS$ requires N, 16·5; S, 18·8%), and 3-(4-*bromoisothiazol*-3-*yl*)-2-*methylpropionamide* (XVIb) (89%), prisms from aqueous ethanol, m. p. 120—122° (Found: C, 34·0; H, 3·6; Br, 31·9. $C_7H_9BrN_2OS$ requires C, 33·8; H, 3·6; Br, 32·1%) were prepared similarly.

2-(4-*Bromoisothiazol*-3-*yl*)-1-*methylethanecarbohydrazide* (XVIII).—Methyl 3-(4-bromoisothiazol-3-yl)-2-methylpropionate (15·7 g., 0·0595 mole) was added dropwise during 10 min. to hydrazine hydrate (30 ml.) at reflux. After 2 min. the clear solution was cooled to give the *hydrazide* (13·0 g., 83%), plates from benzene, m. p. 130—131° (Found: C, 31·5; H, 3·7; N, 15·8. $C_7H_{10}BrN_3OS$ requires C, 31·8; H, 3·8; N, 15·9%).

2-*Amino*-1-(*isothiazol*-5-*yl*)*propane Hydrochloride* (IVa).—3-(Isothiazol-5-yl)-2-methylpropionamide (3·5 g., 0·0206 mole) was added during 5 min. to a mixture of bromine (6 g., 0·0375 mole) and 3N-sodium hydroxide (50 ml.) at 0°. After being stirred for a further 60 min. at 0°, the mixture was heated on the steam-bath for 30 min., cooled, and continuously extracted with ether for 24 hr. Hydrogen chloride was passed into the dried ($MgSO_4$) extract to give an oil which slowly crystallised. Recrystallisation from ethanol–ether afforded the *amine hydrochloride* (0·83 g., 23%), m. p. 97—101° (Found: C, 40·0; H, 6·2; S, 18·2. $C_6H_{11}N_2ClS$ requires C, 40·3; H, 6·2; S, 17·9%).

2-*Amino*-1-(4-*bromo*-3-*methylisothiazol*-5-*yl*)*propane hydrochloride* (IVe) (55%), m. p. 206—208° (decomp.) (Found: C, 31·1; H, 4·7; N, 10·1. $C_7H_{12}BrClN_2S$ requires C, 31·0; H, 4·5; N, 10·3%), 1-*amino*-2-(4-*bromo*-3-*methylisothiazol*-5-*yl*)*ethane hydrochloride* (IVb) (30%), m. p. 187—190° (Found: C, 28·0; H, 3·9; Cl, 13·9; S, 12·7. $C_6H_{10}BrClN_2S$ requires C, 28·0; H, 3·5; Cl, 13·8; S, 12·5%), 2-*amino*-1-(4-*chloro*-3-*methylisothiazol*-5-*yl*)-*propane hydrochloride* (IVd) (63%), m. p. 190—193° (Found: S, 14·2. $C_7H_{12}Cl_2N_2S$ requires S, 14·1%) [free *base*, b. p. 88°/0·6 mm. (Found: Cl, 18·1; N, 14·8; S, 16·3. $C_7H_{11}ClN_2S$ requires Cl, 18·6; N, 14·8; S, 16·8%)], and 1-*amino*-2-(3-*methylisothiazol*-4-*yl*)*ethane hydrochloride* (XVa) (33%), m. p. 154—156° (Found: C, 40·3; H, 6·3; S, 17·6. $C_6H_{11}ClN_2S$ requires C, 40·3; H, 6·2; S, 17·9%) were prepared similarly.

2-*Amino*-1-(4-*bromoisothiazol*-3-*yl*)*propane Hydrochloride* (XVII).—Sodium nitrite (4·2 g.,

0·06 mole) in water (20 ml.) was added dropwise to a stirred mixture of 2-(-bromoisothiazol-3-yl)-1-methylethane carbohydrazide (10·6 g., 0·04 mole), 5N-hydrochloric acid (100 ml.), and ether (400 ml.) at 0°. The mixture was stirred for 1 hr., and the ethereal layer was separated. The aqueous layer was extracted with ether (2 × 100 ml.), and the combined extracts were washed with sodium hydrogen carbonate solution and dried ($MgSO_4$). The ethereal solution was added slowly to dry ethanol (150 ml.) and the ether was distilled off. The ethanolic solution was refluxed for 1 hr. and evaporated to dryness under reduced pressure. The residual, crude ethylurethane was refluxed with concentrated hydrochloric acid (100 ml.) for 3 hr. and the solution was evaporated to dryness under reduced pressure. The residue was treated with ethanol (250 ml.) and the solution was concentrated to *ca.* 60 ml. Dilution with dry ether (600 ml.) gave the *amine hydrochloride* (5·6 g., 54%), m. p. 135—136° (Found: C, 27·6; H, 4·0; N, 10·5. $C_6H_{10}BrClN_2S$ requires C, 28·0; H, 3·9, N, 10·9%).

2-*Amino*-1-(3-*methylisothiazol*-5-*yl*)*propane dihydrochloride* (IVc) (71%), m. p. 144—147° (Found: C, 36·9; H, 6·9; Cl, 29·7; S, 13·9. $C_7H_{14}Cl_2N_2S$ requires C, 36·7; H, 6·2; Cl, 31·0; S, 14·0%) was prepared similarly.

1-(4-*Chloro*-3-*methylisothiazol*-5-*yl*)-2-(*toluene*-p-*sulphonamido*)*propane*.—2-Amino-1-(4-chloro-3-methylisothiazol-5-yl)propane (4·75 g., 0·025 mole) was shaken with toluene-*p*-sulphonyl chloride (4·75 g., 0·025 mole) and N-sodium hydroxide (30 ml., 0·030 mole) for 30 min. The resulting solid was collected and crystallised from aqueous ethanol to give the *tosylate* (6·4 g., 74%), m. p. 98—100° (Found: C, 48·4; H, 4·7; S, 18·9. $C_{14}H_{17}ClN_2O_2S_2$ requires C, 48·8; H, 5·0; S, 18·6%).

1-(4-*Chloro*-3-*methylisothiazol*-5-*yl*)-2-(N-*methyltoluene*-p-*sulphonamido*)*propane*.—1-(4-Chloro-3-methylisothiazol-5-yl)-2-(toluene-*p*-sulphonamido)propane (15 g., 0·0436 mole), dimethyl sulphate (13·3 g., 0·105 mole), and 2N-sodium hydroxide (60 ml., 0·12 mole) were shaken for 20 min. The resulting solid was collected and crystallised from ethanol to give the N-*methyltosylate* (14 g., 90%), m. p. 91—92° (Found: C, 50·0; H, 5·2; S, 17·9. $C_{15}H_{19}ClN_2O_2S_2$ requires C, 50·2; H, 5·3; S, 17·9%).

1-(4-*Chloro*-3-*methylisothiazol*-5-*yl*)-2-*methylaminopropane Hydrochloride* (XI).—1-(4-Chloro-3-methylisothiazol-5-yl)-2-*N*-methyltoluene-p-sulphonamido)propane (14 g.) and concentrated hydrochloric acid (750 ml.) were refluxed for 12 days. The solution was then concentrated to dryness and the residue crystallised from methanol–ether to give the *hydrochloride* (4·9 g., 52%), m. p. 200—203° (Found: C, 40·2; H, 6·0; S, 13·5. $C_8H_{14}Cl_2N_2S$ requires C, 39·8; H, 5·9; S, 13·3%).

5-(2,2-*Diethoxycarbonyl*-2-*acetamidoethyl*)-3-*methylisothiazole* (IX).—5-Chloromethyl-3-methylisothiazole [8] (9·79 g., 0·066 mole) was added during 10 min. to a stirred solution of sodium diethyl acetamidomalonate [from diethyl acetamidomalonate (14·3 g., 0·066 mole) and sodium hydride (1·58 g., 0·066 mole)] in dry dimethylformamide (55 ml.). The mixture was stirred for 15 min., heated to 40° for 30 min., and stirred at room temperature for 2 days. The solution was poured on a mixture of ice (200 g.) and concentrated hydrochloric acid (50 ml.) to give 5-(2,2-*diethoxycarbonyl*-2-*acetamidoethyl*)-3-*methylisothiazole* 15·5 g., 71%), m. p. 90—92°. A sample was crystallised from light petroleum (b. p. 60—80°) to give colourless needles, m. p. 92—94° (Found: C, 51·0; H, 6·0; N, 8·2. $C_{14}H_{20}N_2O_5S$ requires C, 51·2; H, 6·4; N, 8·53%).

3-(2,2-*Diethoxycarbonyl*-2-*acetamidoethyl*)*isothiazole* (69%), m. p. 67—69° (Found: C, 49·7; H, 5·6; S, 10·3. $C_{13}H_{18}N_2O_5S$ requires C, 49·7; H, 5·8; S, 10·9%) was prepared similarly.

5-(2,2-*Dicarboxy*-2-*acetamidoethyl*)-3-*methylisothiazole*.—5-(2,2-Diethoxycarbonyl-2-acetamidoethyl)-3-methylisothiazole (96 g., 0·292 mole), ethanol (180 ml.), and 3N-sodium hydroxide (400 ml.) were refluxed for 2 hr. The ethanol was distilled off and the residue diluted with water (300 ml.) and extracted with ether (3 × 200 ml.). Acidification of the aqueous layer afforded 5-(2,2-*dicarboxy*-2-*acetamidoethyl*)-3-*methylisothiazole* (71·5 g., 90%) as a white crystalline solid, m. p. 154—156° (Found: C, 44·5; H, 4·6; N, 10·3. $C_{10}H_{12}N_2O_5S$ requires C, 44·1; H, 4·4; N, 10·3%).

3-(2,2-*Dicarboxy*-2-*acetamidoethyl*)*isothiazole hydrate* (90%), m. p. 113—115° (Found: C, 39·4; H, 4·1; S, 11·7. $C_9H_9N_2O_5S,H_2O$ requires C, 39·3; H, 4·0; S, 11·6%) was prepared similarly.

5-(2-*Carboxy*-2-*acetamidoethyl*)-3-*methylisothiazole*.—5-(2,2-Diethoxycarbonyl-2-acetamidoethyl)-3-methylisothiazole (66·5 g., 0·245 mole) was heated at 145° for 45 min. After being

[8] A. J. Layton and E. Lunt, in preparation.

cooled the solid was dissolved in N-sodium hydrogen carbonate (250 ml.), treated with charcoal, filtered, cooled to 0°, and acidified with concentrated hydrochloric acid to give 5-(2-*carboxy*-2-*acetamidoethyl*)-3-*methylisothiazole* (47·5 g., 85%), m. p. 139—140°. A sample purified by reprecipitation had m. p. 140—141° (Found: C, 47·1; H, 5·3; N, 12·0. $C_9H_{12}N_2O_3S$ requires C, 47·35; H, 5·3; N, 12·3%).

3-(2-*Carboxy*-2-*acetamidoethyl*)*isothiazole* (65%), m. p. 127—128° (Found: C, 44·6; H, 4·5; S, 14·9. $C_8H_{10}N_2O_3S$ requires C, 44·9; H, 4·7; S, 15·0%) was prepared similarly.

3-*Methylisothiazol*-5-*ylalanine* (X).—5-(2-Acetamido-2-carboxyethyl)-3-methylisothiazole (42·5 g.) and concentrated hydrochloric acid (400 ml.) were refluxed for 2 hr. and then evaporated to dryness under reduced pressure. The residue was dissolved in water (180 ml.) treated with charcoal, filtered, and the pH adjusted to 7 with 12N-sodium hydroxide solution to give 3-*methylisothiazol*-5-*ylalanine* (26 g., 75%), m. p. 235—236° (decomp.) (Found: C, 45·4; H, 5·5; N, 15·1. $C_7H_{10}N_2O_2S$ requires C, 45·2; H, 5·4; N, 15·0%).

*Isothiazol*-3-*ylalanine* (XIX) (65%), m. p. 236—238° (decomp.) (Found: C, 42·1; H, 4·7; S, 18·3. $C_6H_8N_2O_2S$ requires C, 41·9; H, 4·7; S, 18·6%) was prepared similarly.

5-(2-*Carboxy*-2-p-*nitrobenzyloxycarbonylaminoethyl*)-3-*methylisothiazole*.—3-Methylisothiazol-5-ylalanine (6 g., 0·323 mole) was dissolved in 4N-sodium hydroxide (9·5 ml.). *p*-Nitrobenzyloxycarbonyl chloride (8·1 g., 0·375 mole) in dioxan (19·2 ml.) was added simultaneously with 4N-sodium hydroxide (9·5 ml.) in 5 portions at 5 min. intervals with vigorous shaking. Shaking was continued at room temperature for 1 hr. and the mixture was filtered. The filtrate was treated with charcoal and acidified with 2N-hydrochloric acid to give 5-(2-*carboxy*-2-p-*nitrobenzyloxycarbonylaminoethyl*)-3-*methylisothiazole* (10·5 g., 89%), m. p. 175—178°. Recrystallisation from ethanol gave colourless needles (9·5 g.), m. p. 202—204° (Found: N, 11·5; S, 8·8. $C_{15}H_{15}N_3O_6S$ requires N, 11·5; S, 8·8%).

3-(2-*Carboxy*-2-p-*nitrobenzyloxycarbonylaminoethyl*)*isothiazole* (90%) (Found: C, 48·1; H, 3·6; S, 9·15. $C_{14}H_{13}N_3O_6S$ requires C, 47·9; H, 3·7; S, 9·1%), and 5-(2-*benzyloxycarbonylamino*-2-*carboxyethyl*)-3-*methylisothiazole* (64%), m. p. 98—100° (Found: C, 55·8; H, 5·1; S, 10·1. $C_{15}H_{16}N_2O_4S$ requires C, 56·2; H, 5·0; S, 10·0%) were prepared similarly.

5-(2-*Carboxy*-2-*ethoxythiocarbonylaminoethyl*)-3-*methylisothiazole*.—3-Methylisothiazol-5-ylalanine (5 g., 0·027 mole) was dissolved in N-potassium hydroxide (27 ml.) and a solution of ethylethoxydithioformate (4·5 g., 0·030 mole) in ethanol (100 ml.) was added. The mixture was refluxed for 18 hr. and then diluted with water (50 ml.), and extracted with ether. Acidification of the aqueous layer afforded 5-(2-*carboxy*-2-*ethoxythiocarbonylaminoethyl*)-3-*methylisothiazole* (4·54 g., 62%), m. p. 148—163°. Crystallisation from aqueous ethanol gave needles, m. p. 164—166° (Found: C, 44·1; H, 5·2; S, 23·4. $C_{10}H_{14}N_2O_3S_2$ requires C, 43·8; H, 5·1; S, 23·4%).

The authors are indebted to Mr. S. Bance, and his staff for analyses and Messrs. R. V. Sutton, D. G. J. Frewin, D. Gell, and D. C. Mills for preparative assistance.

RESEARCH LABORATORIES, MAY AND BAKER LTD.,
DAGENHAM, ESSEX.

[*Received, December 11th*, 1964.]