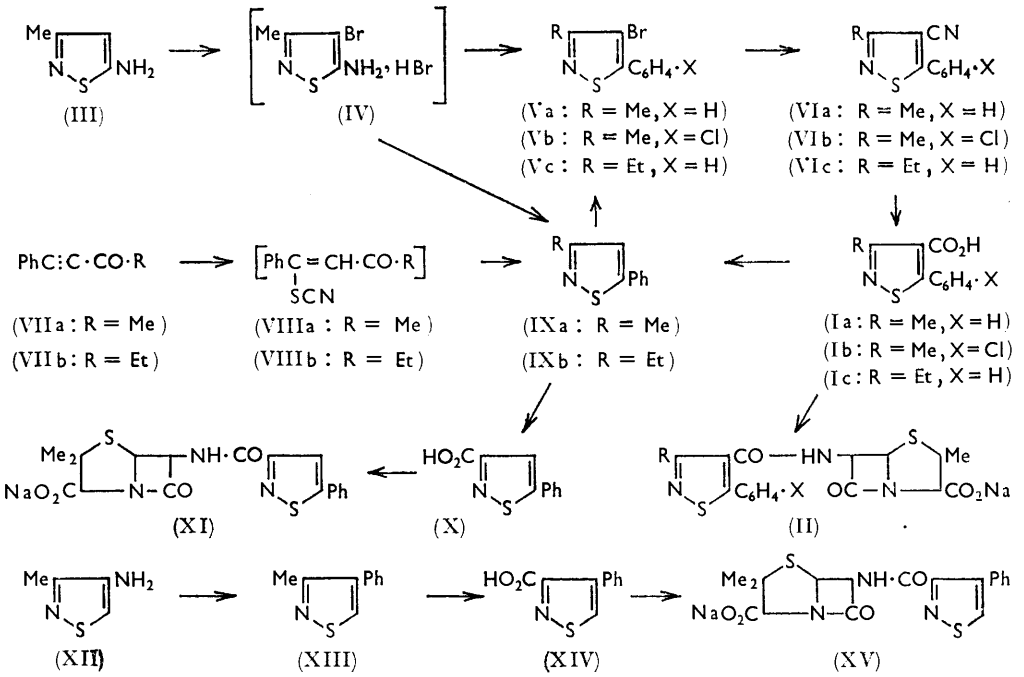
701. *Isothiazoles. Part VI.*[1] *Phenylisothiazoles*

By M. S. Grant, D. L. Pain, and R. Slack

A number of 4- and 5-phenylisothiazoles have been synthesised by an extension of the Gomberg reaction.

Isothiazolecarboxylic acids (I) were required for the preparation of penicillins of the general formula (II). The 3-methyl-acids (Ia) and (Ib) were prepared from the known 5-amino-3-methylisothiazole (III) [2] by bromination, diazotisation of the crude bromo-amine hydrobromide (IV) *in situ*, and phenylation by an extension [3] of the Gomberg reaction to



give (V). The nitriles (VIa) and (VIb) were obtained by the procedure previously described,[2] using cuprous cyanide, either alone at 220°, or in refluxing dimethylformamide. The nitriles were hydrolysed smoothly in good yields by potassium hydroxide in ethylene glycol to give the acids (Ia) and (Ib). Decarboxylation of the acid (Ia) afforded 3-methyl-5-phenylisothiazole, identical with a sample (IXa) prepared from 4-phenylbut-3-yn-2-one (VIIa) by the method of Wille *et al.*[4] For this compound, and its ethyl homologue (IXb), the thiocyanate intermediates (VIIIa) and (VIIIb) were not isolated, but were immediately cyclised in liquid ammonia to the 3-alkyl-5-phenylisothiazoles. 3-Methyl-5-phenylisothiazole was also prepared by the action of isopentyl nitrite and benzene on the amine (III).[5] The 4-bromo-5-chlorophenyl-3-methylisothiazole (Vb), prepared from the amine (IV) by the action of chlorobenzene, was a mixture of isomers which was not separated, but was converted directly into the mixture of acids (Ib). Infrared spectroscopy and gas chromatography indicated an isomer distribution of $o : m : p = 66 : 17 : 17$. Oxidation of the mixture (Vb) with potassium permanganate gave a mixture of chlorobenzoic acids.

[1] Part V, B. A. Bennett, D. H. Jones, R. Slack, and K. R. H. Wooldridge, preceding Paper.
[2] A. Adams and R. Slack, *J.*, 1959, 3061.
[3] W. S. M. Grieve and D. H. Hey, *J.*, 1938, 108.
[4] F. Wille, L. Capeller, and A. Steiner, *Angew. Chem.* (*Internat. Edn.*), 1962, **1**, 335.
[5] J. I. G. Cadogan, *J.*, 1962, 4257.

3-Ethyl-5-phenylisothiazole-4-carboxylic acid (Ic) was synthesised from 3-ethyl-5-phenylisothiazole, by bromination, cyanation, and hydrolysis. The 3-alkyl-5-phenylisothiazoles (IXa) or (IXb) were oxidised by alkaline potassium permanganate to give a poor yield of 5-phenylisothiazole-3-carboxylic acid (X).

The amino-group of 4-amino-3-methylisothiazole (XII) [2] also underwent phenylation by the action of isopentyl nitrite in benzene,[5] yielding 3-methyl-4-phenylisothiazole (XIII), which was oxidised to give 4-phenylisothiazole-3-carboxylic acid (XIV).

Condensation of the isothiazole acids with 6-aminopenicillanic acid was effected by conventional methods, but only the compound (II; R = Me, X = H) was obtained pure. The penicillins (II) were active against penicillinase-producing *Staphylococci*, but to a lesser extent than the corresponding isoxazolylpenicillins.[6] The penicillins (XI) and (XV) had low activity.

Experimental

3-Methyl-5-phenylisothiazole (IXa).—(*a*) Isopentyl nitrite (40 ml.) was added to 5-amino-3-methylisothiazole (22·4 g.) in benzene (1 l.).[5] The solution was stirred and gently heated until the reaction started. Heating was discontinued until the reaction moderated (0·5 hr.), and then the mixture was heated under reflux for 2 hr. It was steam-distilled and the distillate was extracted with ether. The extract was dried ($MgSO_4$) and evaporated, and the residue was recrystallised from light petroleum to give *3-methyl-5-phenylisothiazole* (9 g., 26%), m. p. 69—71° (Found: C, 68·9; H, 5·0; S, 17·9. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; S, 18·3%).

(*b*) 4-Phenylbut-3-yn-2-one [7] (10·2 g., 0·071 mole), ammonium thiocyanate (6 g., 0·079 mole), 2N-hydrochloric acid (60 ml.), and ether (75 ml.) were stirred together at room temperature for 48 hr. The layers were separated and the aqueous phase was extracted with ether. The ether solutions were combined, washed with water, dried (K_2CO_3), and evaporated, and the residue was stirred with liquid ammonia (100 ml.), which was allowed to evaporate. Chromatography of the residue on alumina, and elution with light petroleum, gave 3-methyl-5-phenylisothiazole (5 g., 40%), m. p. 67—68°, not depressed by the sample prepared in (*a*).

5-Phenylisothiazole-3-carboxylic Acid (X).—3-Methyl-5-phenylisothiazole (1·3 g.) was heated at 100° with potassium permanganate (5 g.) and 2N-sodium hydroxide (2 ml.) in water (100 ml.) for 24 hr. The mixture was cooled, acidified with 2N-sulphuric acid, decolourised by sulphur dioxide, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated, and the residue was extracted with a warm solution of sodium hydrogen carbonate. The extract was cooled, filtered, and acidified with concentrated hydrochloric acid The solid was fractionally sublimed *in vacuo* (to remove benzoic acid) and recrystallised from benzene to give *5-phenylisothiazole-3-carboxylic acid* (100 mg., 7%), m. p. 145—146° (Found: C, 58·1; H, 3·4; N, 6·7; S, 15·3. $C_{10}H_7NO_2S$ requires C, 58·5; H, 3·4; N, 6·8; S, 15·6%).

5-Phenylisothiazole-3-carbohydrazide.—5-Phenylisothiazole-3-carboxylic acid (0·7 g.) in thionyl chloride (7 ml.) was boiled under reflux for 0·5 hr. The excess of thionyl chloride was removed *in vacuo*, and the residue was recrystallised from light petroleum (b. p. 60—80°) to give 5-phenylisothiazole-3-carbonyl chloride (0·21 g., 26%), m. p. 55—56°. The acid chloride was added to dry methanol with cooling, the mixture was heated at 50°, and cooled to give methyl 5-phenylisothiazole-3-carboxylate, m. p. 74—75°. The ester was boiled under reflux with an excess of hydrazine hydrate (100%) in methanol for 0·5 hr., and the solution was concentrated. The solid which separated was recrystallised from 20% ethanol to give the *hydrazide* (0·25 g., 33% from the acid), m. p. 122° (Found: N, 18·9; S, 14·8. $C_{10}H_9N_3OS$ requires N, 19·2; S, 14·6%).

3-Methyl-4-phenylisothiazole (XIII).—This *compound* (36%), b. p. 100—101°/0·18 mm., was prepared similarly to the 5-phenyl compound (IXa) by method (*a*) (Found: N, 7·7; S, 17·9. $C_{10}H_9NS$ requires N, 8·0; S, 18·3%).

4-Phenylisothiazole-3-carboxylic Acid (XIV).—3-Methyl-4-phenylisothiazole (17·5 g.), *N*-bromosuccinimide (19·6 g.), and benzoyl peroxide (0·5 g.) in carbon tetrachloride (100 ml.) were boiled under reflux for 21 hr. with stirring. The mixture was cooled and filtered, and the

[6] J. H. C. Nayler *et al.*, *Nature*, 1962, **195**, 1264.
[7] D. Nightingale and F. Wadsworth, *J. Amer. Chem. Soc.*, 1945, **67**, 416.

solvent was removed. The residue was distilled to give crude 3-bromomethyl-4-phenylisothiazole (11·5 g.), b. p. 100—120°/0·07 mm. Potassium permanganate (28·5 g.) was added in portions during 1·5 hr. to a refluxing solution of the bromomethyl compound (11·5 g.) and sodium carbonate (3·5 g.) in water (600 ml.). Refluxing was continued for a further 2·5 hr. The mixture was cooled, decolourised by sulphur dioxide, acidified to pH 2, and extracted with ether. The extract was extracted with sodium hydrogen carbonate solution, and the aqueous layer was acidified and again extracted with ether. This extract was dried (Na_2SO_4) and evaporated, and the residue was fractionally sublimed *in vacuo* (to remove benzoic acid) and recrystallised from water to give the *acid* (0·2 g., 1%), m. p. 143—146° (decomp.) (Found: C, 58·1; H, 3·4; S, 15·6. $C_{10}H_7NO_2S$ requires C, 58·5; H, 3·4; S, 15·6%).

3-*Ethyl*-5-*phenylisothiazole* (IXb).—This *compound* (22%), b. p. 84°/0·1 mm., was prepared as for 3-methyl-5-phenylisothiazole [method (*b*)] from 1-phenylpent-1-yn-3-one [7] (Found: C, 69·7; H, 6·1; N, 7·2. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·9; N, 7·4%). Oxidation by alkaline potassium permanganate as described above gave 5-phenylisothiazole-3-carboxylic acid (11%), m. p. 145—146°, undepressed by the previous sample.

4-*Bromo*-3-*ethyl*-5-*phenylisothiazole* (Vc).—3-Ethyl-5-phenylisothiazole (10 g., 0·053 mole) was heated at 100° with glacial acetic acid (40 ml.) and acetic anhydride (4 ml.) for 0·5 hr. with stirring. *N*-Bromosuccinimide (9·5 g., 0·053 mole) was added, and the mixture was stirred and heated for a further 3 hr., cooled, poured on ice, and extracted with methylene chloride. The extract was washed with water, aqueous sodium hydrogen carbonate, and aqueous sodium thiosulphate, and dried (Na_2SO_4). After removal of the solvent, distillation of the residue gave 4-*bromo*-3-*ethyl*-5-*phenylisothiazole* (5·9 g., 41%), b. p. 105—115°/0·2 mm. (Found: N, 5·6; S, 11·9. $C_{11}H_{10}BrNS$ requires N, 5·2; S, 12·0%).

4-*Bromo*-3-*methyl*-5-*phenylisothiazole* (Va).—Bromine (160 g., 1 mole) was added during 1 hr. with vigorous stirring (stainless steel Herschberg stirrer) to 5-amino-3-methylisothiazole [2] (114 g., 1 mole) in glacial acetic acid (120 ml.) and benzene (1 l.). The temperature rose to 40° and the bromo-amine hydrobromide separated. This was diazotised *in situ* at 10° by the dropwise addition of sodium nitrite (69 g., 1 mole) in water (200 ml.). The mixture was stirred for a further 3 hr., kept overnight, and steam-distilled (12 l. distillate). The distillate was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated. The residue was distilled to give 4-*bromo*-3-*methyl*-5-*phenylisothiazole* (50 g., 20%), b. p. 105—110°/0·1 mm. (Found: N, 5·9; S, 12·4. $C_{10}H_8BrNS$ requires N, 5·5; S, 12·6%).

4-*Cyano*-3-*methyl*-5-*phenylisothiazole* (VIa).—4-Bromo-3-methyl-5-phenylisothiazole (38 g., 0·15 mole) and cuprous cyanide (20 g., 0·22 mole) were heated at 220° in a 100-ml. Claisen flask for 2·5 hr. The product was distilled rapidly *in vacuo*, the bath temperature being raised to 380°, to give the *nitrile* (24·6 g., 82%), b. p. 140—142°/0·1 mm., m. p. 43—48°. A sample recrystallised from light petroleum had m. p. 69—70° (Found: C, 65·8; H, 4·0; S, 15·6. $C_{11}H_8N_2S$ requires C, 66·0; H, 4·0; S, 16·0%).

3-*Methyl*-5-*phenylisothiazole*-4-*carboxylic Acid* (Ia).—4-Cyano-3-methyl-5-phenylisothiazole (24·6 g.) was boiled under reflux with potassium hydroxide (15 g.) in ethylene glycol (150 ml.) and water (30 ml.) for 50 hr. The mixture was cooled, diluted with water (500 ml.), and filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. The solid was collected, washed with water, dried at 60°, and recrystallised from benzene to give the *acid* (21·8 g., 81%), m. p. 186—188° (Found: C, 60·7; H, 3·9; N, 6·7; S, 14·6. $C_{11}H_9NO_2S$ requires C, 60·2; H, 4·1; N, 6·4; S, 14·6%).

This acid (2·5 g.) was decarboxylated by heating for 1 hr. with copper chromite catalyst (0·2 g.) in refluxing quinoline (3 ml.) in an atmosphere of nitrogen. The cooled mixture was diluted with ether, filtered, washed free from quinoline with 2N-hydrochloric acid, and then with sodium hydrogen carbonate solution. Evaporation of the ether gave 3-methyl-5-phenylisothiazole (0·9 g., 45%), m. p. 67—69°, not depressed by the samples prepared as described above.

3-*Methyl*-5-*phenylisothiazole*-4-*carboxyamide*.—3-Methyl-5-phenylisothiazole-4-carbonyl chloride (from 30 g. of the corresponding acid) in dry acetone (75 ml.) was added slowly with stirring to an excess of concentrated ammonia (*d* 0·9) containing ice. After a further 10 min. at 0°, the solid was collected, and recrystallised from ethanol to give the *amide* (20 g., 67%), m. p. 169—170° (Found: N, 12·4; S, 15·0. $C_{11}H_{10}N_2OS$ requires N, 12·8; S, 14·7%).

Sodium 6-(3-*Methyl*-5-*phenylisothiazol*-4-*yl*)*penicillanate* (II; R = Me, X = H).—3-Methyl-5-phenylisothiazole-4-carbonyl chloride (4·8 g., 0·022 mole), prepared by the action of thionyl

chloride on the corresponding acid, in acetone (120 ml.), was added slowly with stirring below 10° to 6-aminopenicillanic acid (4·32 g., 0·02 mole) in 3% aqueous sodium hydrogen carbonate (168 ml.) and acetone (50 ml.). Stirring was continued for a further 4 hr., and the mixture was washed with ether. The aqueous solution was layered with ether (50 ml.), brought to pH 2 with 1N-hydrochloric acid and extracted with ether (2 × 50 ml.). The combined extracts were washed with water, and extracted with 1N-sodium hydrogen carbonate solution until the aqueous phase had pH 7. The aqueous solution was washed with ether, and freeze-dried to give the *penicillin monohydrate* (7·05 g., 76%) (Found: C, 50·0; H, 4·2; N, 8·5; S, 14·2; H_2O, 4·2. $C_{19}H_{18}N_3NaO_4S_2,H_2O$ requires C, 49·9; H, 4·0; N, 9·2; S, 14·0; H_2O, 3·9%).

The following penicillins were prepared similarly, but were not obtained pure.

Sodium 6-(3-methyl-5-chlorophenylisothiazol-4-yl)penicillanate monohydrate (II; R = Me, X = Cl), sodium 6-(3-ethyl-5-phenylisothiazol-4-yl)penicillanate dihydrate (II; R = Et, X = H), sodium 6-(5-phenylisothiazol-3-yl)penicillanate (XI), and sodium 6-(4-phenylisothiazol-3-yl)penicillanate dihydrate (XV).

4-Bromo-5-chlorophenyl-3-methylisothiazole (Vb).—Hydrobromic acid (50% w/w; 300 ml., 3 mole) was added with stirring to 5-amino-4-bromo-3-methylisothiazole [8] (193 g., 1 mole) in chlorobenzene (1 l.) and glacial acetic acid (115 ml.). The mixture was cooled to 5°, diazotised at 5—10° by the dropwise addition of sodium nitrite (76 g., 1·1 mole) in water (250 ml.), stirred for a further 3 hr., and kept overnight. It was then steam-distilled, and the distillate was extracted with ether. The extract was dried ($MgSO_4$) and evaporated, and the residue was distilled *in vacuo* to give two products: (i) a solid (22 g.), b. p. 52—100°/0·2 mm., m. p. 52—53°, not depressed by an authentic sample of 4,5-dibromo-3-methylisothiazole [8] (Found: C, 18·6; H, 1·1; Br, 61·4. Calc. for $C_4H_3Br_2NS$: C, 18·7; H, 1·2; Br, 62·2%), and (ii) a liquid (54 g., 19%), b. p. 100—112°/0·2 mm., corresponding to a mixture of *4-bromo-5-chlorophenyl-3-methylisothiazoles* (Found: Br, 27·5; Cl, 12·5; N, 5·4. $C_{10}H_7BrClNS$ requires Br, 27·6; Cl, 12·3; N, 4·9%). Gas chromatography using Apiezon L as stationary phase at 165° gave three peaks, the areas under which indicated a weight ratio of 66 : 17 : 17. This mixture of isomers (Vb) (1·7 g.) was boiled under reflux with potassium permanganate (7 g.) and potassium hydroxide (1·7 g.) in water (100 ml.) for 48 hr. to give a mixture of chlorobenzoic acids (350 mg.), m. p. 128—130° (Found: C, 54·1; H, 2·7; Cl, 22·8. Calc. for $C_7H_5ClO_2$ C, 53·7; H, 3·2; Cl, 22·7%).

5-Chlorophenyl-3-methylisothiazole-4-carboxylic Acid (Ib).—The mixture of 4-bromo-5-chlorophenyl-3-methylisothiazoles (Vb) (14·4 g., 0·05 mole) was added during 10 min. to cuprous cyanide (4·5 g., 0·05 mole) in boiling dimethylformamide (50 ml.). The mixture was boiled under reflux for 2 hr., boiling water (115 ml.) was added as quickly as possible, and the mixture was boiled for a further 2 hr. The copper complex was separated by decantation, ground finely, and boiled under reflux with potassium hydroxide (11·3 g.) in ethylene glycol (100 ml.) for 24 hr. The mixture was cooled, diluted with water (260 ml.), and filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. The solid was collected, and recrystallised from aqueous ethanol to give *5-chlorophenyl-3-methylisothiazole-4-carboxylic acid* (mixed isomers; 1·2 g., 10%), m. p. 189—191° (Found: C, 52·2; H, 3·2; Cl, 13·7. $C_{11}H_8ClNO_2S$ requires C, 52·1; H, 3·2; Cl, 14·0%). *3-Ethyl-5-phenylisothiazole-4-carboxylic acid* (Ic) (32%), m. p. 134—135° (from benzene), was prepared similarly (Found: N, 5·8; S, 14·0. $C_{12}H_{11}NO_2S$ requires N, 6·0; S, 13·8%).

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[8] D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1963, 2032.