# 1338. *Isothiazoles. Part X.*[1] *Some Sulphonic Acid Derivatives*

By D. L. Pain and E. W. Parnell

3-Methylisothiazole- and 5-amino-3-methylisothiazole-4-sulphonic acids have been prepared, and the sulphonyl chloride of the former converted into the amide, anilide, and hydrazide. The sulphonyl chloride was also reduced to give the sulphinic acid, from which 3-methylisothiazole-4-sulphinamide was obtained.



In connection with a chemotherapeutic programme we were interested in preparing sulphonic acid derivatives of isothiazole. 3-Methylisothiazole was readily sulphonated by 20% oleum at 220—230° in the presence of a mercury catalyst. The acid formed a sulphonyl chloride and thence an amide, anilide, and hydrazide. The acid, acid chloride, and amide were mentioned, but not fully described, by Hübenett *et al.*[2] 5-Amino-3-methylisothiazole was more readily sulphonated in 20% oleum at 180—190°. These compounds are formulated as 4-sulphonic acid derivatives in view of the known[2,3] orientation of electrophilic substitution in isothiazoles. 3-Methylisothiazole-4-sulphonhydrazide formed an isopropylidene derivative, which, unlike the 3-pyridyl analogue,[4] did not react with water to give the sulphinic acid. 3-Methylisothiazole-4-sulphinic acid was prepared by reduction of the sulphonyl chloride with zinc, and was converted *via* the unstable sulphinyl chloride into the sulphinamide.

## Experimental

*3-Methylisothiazole-4-sulphonic Acid.*[2]—3-Methylisothiazole (50 g.) was added dropwise with cooling to 20% oleum (125 g., 65 ml.). Mercuric sulphate (0·75 g.) was added and the mixture heated and stirred in a metal-bath at 220—230° for 16 hr. The cooled solution was poured into ice–water (2·5 l.) and the pH adjusted to 7 with calcium carbonate. The calcium sulphate was filtered off and 2N-sulphuric acid (250 ml.) added to the filtrate. The filtrate was warmed, filtered, and evaporated to *ca.* 500 ml., and refiltered to remove calcium sulphate. Evaporation of the filtrate to dryness gave the crude acid (89 g., 97%), m. p. 275° (decomp.). Crystallisation from ethanol–ether gave the pure acid, m. p. 283° (decomp.) [lit.,[2] 278° (decomp.)] (Found: N, 7·7; S, 35·5. Calc. for $C_4H_5NO_3S_2$: N, 7·8; S, 35·8%).

*3-Methylisothiazole-4-sulphonyl Chloride.*[2]—3-Methylisothiazole-4-sulphonic acid (3 g.) and phosphorus pentachloride (3·9 g.) were heated in an oil-bath at 140—150° until liquid and then for 1·25 hr. The phosphoryl chloride was distilled off and the residual oil distilled from a bulb retort *in vacuo* to give the acid chloride as a colourless liquid (2·15 g., 65%), b. p. 150—155° (bath temp.)/18 mm. (lit.,[2] 130°/15 mm.) (Found: Cl, 17·5; S, 31·2. Calc. for $C_4H_4ClNO_2S_2$: Cl, 18·0; S, 32·4%). The compound darkened on storage. Repetition of the reaction on a larger (47 g.) scale gave a poorer yield (36%) of a product, b. p. 125—127°/18 mm.

*3-Methylisothiazole-4-sulphonamide.*[2]—Ammonia gas was passed into dry ether (50 ml.) for 10 min. and a solution of the sulphonyl chloride (12 g.) in dry ether (48 ml.) added dropwise with stirring and cooling in an ice-bath whilst passage of ammonia gas was continued. The ethereal solution was filtered and evaporated to give the amide (9·8 g.), m. p. 68—69°. Crystallisation from di-isopropyl ether raised the melting point to 75·5—76·5° (lit.,[2] 77—78°) (Found: N, 15·6; S, 35·9. Calc. for $C_4H_6N_2O_2S_2$: N, 15·7; S, 35·9%).

*3-Methylisothiazole-4-sulphonanilide.*—The sulphonyl chloride (7·0 g.) in dry ether (35 ml.) was added dropwise with stirring and cooling to aniline (7·0 ml.) in dry ether (7·0 ml.). After 2 hr. the solid was filtered off and triturated with water to give the crude anilide (4·7 g.), m. p. 103—105°. Evaporation of the ether gave a further crop (3·3 g.), m. p. 90—94°. The *anilide*

[1] Part IX, preceding Paper.
[2] F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and H. Hofmann, *Angew. Chem. Internat. Edn.*, 1963, **2**, 714.
[3] A. Adams and R. Slack, *J.*, 1959, 3060; D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1963, 2032.
[4] M. W. Goldberg and S. Teitel, U.S.P. 2,761,866.

was first purified by dissolving in aqueous sodium hydroxide and precipitating with 2N-hydrochloric acid and was then recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) as pale yellow crystals, m. p. 109—111° (Found: N, 11·1; S, 25·2. $C_{10}H_{10}N_2O_2S_2$ requires N, 11·0; S, 25·2%).

*5-Amino-3-methylisothiazole-4-sulphonic Acid.*—5-Amino-3-methylisothiazole (15 g.) was added portionwise to 20% oleum (75 g., 39 ml.) with stirring and cooling. The solution was heated with stirring in a metal-bath at 180—190° for 5 hr. The cooled solution was poured into ice–water (150 ml.) and set aside for 16 hr. at 0°. The crystalline solid (30 g.) was filtered off, washed with a little water, and dried at 90°. The solid was recrystallised twice from water to give the pure *acid* (7·5 g., 30%), m. p. >320° (Found: N, 14·2; S, 32·7. $C_4H_6N_2O_3S_2$ requires N, 14·4; S, 33·0%).

*3-Methylisothiazole-4-sulphonhydrazide.*—3-Methylisothiazole-4-sulphonyl chloride (3·95 g.) was added dropwise to hydrazine hydrate (100%, 3 g.) in ethanol (20 ml.) with stirring. Hydrazine hydrochloride was removed and the filtrate was azeotropically distilled with benzene and concentrated to 10 ml. More hydrazine hydrochloride was removed and the filtrate was treated with acetonitrile until turbid and kept at 0° overnight. The solid was collected and recrystallised twice from ethanol to give the *hydrazide* (1·6 g., 42%) as a colourless solid, m. p. 119° (decomp.) (Found: N, 22·1; S, 32·7. $C_4H_7N_3O_2S_2$ requires N, 21·7; S, 33·2%).

*N'-Isopropylidene-3-methylisothiazole-4-sulphonhydrazide.*—3-Methylisothiazole-4-sulphonhydrazide (3·5 g.) was heated at 100° for 5 min. with acetone (35 ml.) and water (17 ml.). Water (100 ml.) was added and the solid was collected and recrystallised from ethanol to give the *isopropylidene compound* (4·1 g., 98%) as a colourless solid, m. p. 156—157° (decomp.) (Found: N, 18·0; S, 27·5. $C_7H_{11}N_3O_2S_2$ requires N, 18·0; S, 27·5%).

*3-Methylisothiazole-4-sulphinic Acid.*—Zinc powder (3 g.) and water (0·2 ml.) were added to 3-methylisothiazole-4-sulphonyl chloride (3 g.) in ether (15 ml.) and the mixture was heated under reflux for 1·5 hr. The ether was decanted and discarded. Sodium carbonate (3 g.) and water (15 ml.) were added to the residue and the mixture was left overnight. The solid was removed and the solution was acidified with concentrated sulphuric acid and continuously extracted with ether for 48 hr. The extract was dried ($Na_2SO_4$) and evaporated *in vacuo*, and the residue was recrystallised from chloroform–light petroleum (b. p. 40—60°) to give the *sulphinic acid* (0·4 g., 16%) as colourless plates, m. p. 102° (Found: C, 29·4; H, 3·0; S, 39·0. $C_4H_5NO_2S_2$ requires C, 29·4; H, 3·1; S, 39·3%).

*3-Methylisothiazole-4-sulphinamide.*—3-Methylisothiazole-4-sulphinic acid (0·5 g.) was added to ice-cooled thionyl chloride (8 ml.) and the mixture kept at room temperature for 1 hr. A solid was precipitated but this redissolved on warming to room temperature. The excess of thionyl chloride was removed *in vacuo*, and a solution of the crude acid chloride in dry acetone (10 ml.) was added to concentrated ammonia (d 0·9, 20 ml.) with stirring at 20°. After 1 hr., the solution was extracted with ether and the extract dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was recrystallised from benzene to give the *sulphinamide* (0·3 g., 60%) as colourless crystals, m. p. 119—119·5° (Found: C, 29·8; H, 3·5; N, 16·7; S, 39·3. $C_4H_6N_2OS_2$ requires C, 29·6; H, 3·7; N, 17·3; S, 39·5%).

The authors thank Mr. S. Bance for the micro-analyses.

THE RESEARCH LABORATORIES, MAY & BAKER LTD.,
DAGENHAM, ESSEX.

[*Received, April 20th*, 1965.]