38. 5-(p-*Aminobenzenesulphonamido*)*thiazole.*

By M. H. M. Arnold and C. W. Scaife.

5-(p-*Aminobenzenesulphonamido*)*thiazole*, isomeric with sulphathiazole, is prepared from 5-amino-2-thioamidothiazole (I) by acylation, followed by removal of the $CS{\cdot}NH_2$ group. Although it has considerable bacteriostatic power, it is not pharmaceutically promising. The only derivatives of (I) that can be prepared without first protecting the amino-group are the nitrile and the *amide*.

Wallach (*Ber.*, 1874, **7**, 902) obtained a compound, $C_4H_5N_3S_2$, which he called "chrysean," by passing hydrogen sulphide into a saturated aqueous solution of potassium cyanide. Hellsing (*Ber.*, 1899, **32**, 1497; 1900, **33**, 1774; 1903, **36**, 3546) prepared derivatives of it and showed that it was probably 5-amino-2-thioamidothiazole. We have confirmed the simple formula by molecular-weight determinations. Chrysean appeared to us to be of interest as a potentially cheap source of thiazole derivatives, and especially as a starting material for the synthesis of 5-(p-*aminobenzenesulphonamido*)*thiazole* for examination as a bactericide, "sulphathiazole" being 2-(*p*-aminobenzenesulphonamido)thiazole.

The earlier workers obtained chrysean in only 15—20% yield; we have been unable to increase this, but have improved the preparation by the replacement of potassium cyanide by sodium cyanide and by its acceleration with ammonia.

The chrysean molecule is fragile, and the 5-aminothiazole cannot be prepared by the nitrile, carboxylic acid, and decarboxylation route. Hellsing prepared 5-aminothiazole-2-nitrile from chrysean by treatment with lead or silver salts, but we have confirmed that attempts to hydrolyse this to the acid usually result in rupture of the ring, especially under alkaline conditions. Cautious acid hydrolysis has given 5-*aminothiazole*-2-*carboxylic acid* in poor yield. On the other hand, in neutral solution with excess of calcium carbonate the nitrile gives 5-*aminothiazole*-2-*amide* in very good yield. Hellsing showed that acylation of the amino-group permits normal degradation of the thioamide group, but that the products are all so resistant to hydrolysis that the acyl group cannot be removed. On the other hand, both 5-benzylideneaminothiazole-2-thioamide (Hellsing, *loc. cit.*) and 5-*benzylideneaminothiazole*-2-*nitrile* are too easily hydrolysed for this method of protecting the amino-group to be of any use.

The possibility of protecting the amino-group by diazotisation and formation of an azo-compound was then considered. Attempts to diazotise chrysean and the nitrile in the normal way gave highly coloured tars, which appeared to be formed by intermolecular condensation. 5-Aminothiazole-2-nitrile was diazotised by gradual addition of the solution to excess of hydrochloric acid and sodium nitrite at 0°. Chrysean is too sparingly soluble in water at 0° for this method to be successful, but diazotisation was achieved by adding its solution in pyridine to excess of nitrosyl chloride in benzene. This approach to the problem was not followed up.

It became clear that, since chrysean and its derivatives are only tractable when the amino-group is protected, appropriate acylation would have to precede attempts to remove the $-CS{\cdot}NH_2$ group. *p*-Nitrobenzenesulphonyl chloride gave 5-(p-*nitrobenzenesulphonamido*)*thiazole*-2-*thioamide*, which was converted into the 2-*nitrile*, and thence (or directly) into the 2-*carboxylic acid*, but this compound could not be decarboxylated satisfactorily. *p*-Acetamidobenzenesulphonyl chloride gave with chrysean 5-(p-*acetamidobenzenesulphonamido*)*thiazole*-2-*thioamide*, and with 5-aminothiazole-2-amide the corresponding 2-*amide*. 5-(*p*-Aminobenzenesulphonamido)thiazole was obtained from the 2-thioamide by converting this into the 2-nitrile (not isolated) and boiling the solution with sodium hydroxide; deacetylation, hydrolysis of the nitrile group, and decarboxylation then took place.

Dr. A. R. Martin of I.C. (Pharmaceuticals) Ltd., to whom our thanks are due, has examined 5-(*p*-acetamidobenzenesulphonamido)thiazole-2-thioamide and 5-(*p*-aminobenzenesulphonamido)thiazole for their bactericidal action, *in vitro* and *in vivo*, and has reported that against streptococcal infections in mice the latter substance, although active, has no advantage over established sulphonamide drugs, whereas the former substance is completely inactive.

Experimental.

5-Aminothiazole-2-thioamide (*Chrysean*).—Hydrogen sulphide (20—30 l./hr.) is passed into a saturated aqueous solution of sodium cyanide (200 g.) and a little ammonia; after a time plates appear. The chrysean is collected after 3—4 hours and recrystallised from hot water, forming yellow plates (25 g.), m. p. 204° (decomp.) (Found: C, 29·9; H, 3·1; N, 27·0; S, 39·7; *M*, cryoscopic in water, 155. Calc.: C, 30·2; H, 3·1; N, 26·4; S, 40·2%; *M*, 159). Acidific-

ation of the filtrate from the preparation of chrysean gives a flocculent reddish-brown precipitate in amount corresponding to 30—40% of the original cyanide (Found: C, 27·7; H, 2·7; N, 17·2; S, 46·3%). The substance, of high molecular weight, is soluble in alkali to give a deep brown solution; it is decomposed on heating with water to give hydrogen sulphide and a black alkali-soluble tar.

Attempts to increase the Yield of Chrysean:

Method.		Temp.	Yield of chrysean, %.	Rate of reaction.
1	H_2S into sat. aq. KCN (Wallach)	Room	15—20	—
2	H_2S into sat. aq. NaCN	,,	15—20	As (1)
3	H_2S into sat. aq. NaCN	0°	15—20	Much lower
4	H_2S into sat. aq. NaCN + NaOH	Room	15—20	Accelerated
5	H_2S into sat. aq. NaCN + dil. NH_3	,,	15—20	Much accelerated
6	H_2S into sat. aq. NaCN + dil. acid	,,	nil	—
7	Dil. AcOH added to theoretical amounts of NaCN + Na_2S	,,	nil	—
8	NaCN aq. added to NH_4Cl + Na_2S solution	,,	nil	—
9	NaCN aq. added to NH_4Cl + Na_2S solution sat. with H_2S	,,	nil	—
10	NaCN aq. added to NH_3 aq. sat. with H_2S	,,	nil	—
11	Liquid H_2S + solid HCN at 15 ats.	,,	nil	—
12	H_2S, HCN and trace of NaOH aq. at 15 ats.	,,	nil	—
13	H_2S + NaCN aq. at 15 ats.	,,	17—25 (product dark and difficult to purify)	—
14	H_2S into ($Ca(OH)_2$ + HCN) solution	,,	nil	—
15	H_2S, HCN, and trace NH_4OH at 15 ats.	,,	nil	—
16	$H{\cdot}CS{\cdot}NH_2$ + KCN solution	,,	15	—

High yields of chysean are invariably accompanied by large amounts of the by-product of high molecular weight.

5-Aminothiazole-2-nitrile (Hellsing's method, *loc. cit.*, slightly modified).—10 G. of chrysean were refluxed with 23·9 g. of lead acetate in 70 ml. of water for 3 hours, lead sulphide removed, and the filtrate evaporated to small volume, cooled in ice-water, and kept overnight. The product, recrystallised from water, formed fine yellow needles, m. p. 103° (Hellsing, m. p. 103°) (Found: C, 37·9; H, 2·9; N, 33·2; S, 25·8. Calc.: C, 38·4; H, 2·4; N, 33·6; S, 25·6%).

5-Aminothiazole-2-amide.—10 G. of chrysean were treated as above to give a solution of the crude nitrile; to the filtrate from lead sulphide was added precipitated calcium carbonate slightly in excess of that required to neutralise the acetic acid present, and the mixture refluxed for 2 hours. After filtration, the solution was evaporated cautiously to dryness, and the solid recrystallised from ether (alcohol easier for large amounts), affording in good yield small lemon-yellow crystals (not decolorised by charcoal) of *5-aminothiazole-2-amide*, decomp. 156° (Found: C, 33·8; H, 3·8; N, 29·6; S, 21·9. $C_4H_5ON_3S$ requires C, 33·5; H, 3·5; N, 29·4; S, 22·2%).

5-Aminothiazole-2-carboxylic Acid.—5-Aminothiazole-2-nitrile was refluxed with dilute hydrochloric acid, and a red flocculent precipitate obtained. Recrystallisation from alcohol gave a small yield of small colourless crystals of the *2-carboxylic acid*, decomp. 185° (Found: S, 22·0. $C_4H_4O_2N_2S$ requires S, 22·2%).

5-Benzylideneaminothiazole-2-nitrile.—10 G. of 5-aminothiazole-2-nitrile were dissolved in ethyl alcohol and refluxed with 8·5 g. of benzaldehyde. Small needles separated; these were removed, and the liquor concentrated to give a further crop of crystals. Recrystallisation from alcohol gave a good yield of small, light yellow needles of *5-benzylideneaminothiazole-2-nitrile*, m. p. 141° (Found: S, 14·9. $C_{11}H_7N_3S$ requires S, 15·0%).

5-(p-Nitrobenzenesulphonamido)thiazole-2-thioamide.—To a stirred suspension of 9 g. of chrysean in 30 ml. of pyridine cooled in ice-water, 11·2 g. of *p*-nitrobenzenesulphonyl chloride were added during 1 hour. The solution was kept at room temperature for 1 hour, diluted with 100 ml. of water, and acidified with dilute hydrochloric acid until just acid to Congo-red, the mixture being ice-cooled during acidification. After 12 hours the solid was collected and mixed with 200 ml. of water, and dilute aqueous ammonia added until the mixture was alkaline to thymol-blue. The solution was filtered, decolorised with charcoal, and acidified with dilute hydrochloric acid, and the precipitate of *5-(p-nitrobenzenesulphonamido)thiazole-2-thioamide* recrystallised from alcohol; m. p. 185° (decomp.) (Found: C, 34·0; H, 2·8; N, 15·7. $C_{10}H_8O_4N_4S_3$ requires C, 34·9; H, 2·3; N, 16·3%).

5-(p-Nitrobenzenesulphonamido)thiazole-2-nitrile.—7 G. of 5-aminothiazole-2-nitrile in 30 ml. of pyridine were treated with 11·2 g. of *p*-nitrobenzenesulphonyl chloride as in the preceding preparation. *5-(p-Nitrobenzenesulphonamido)thiazole-2-nitrile*, recrystallised from alcohol, had m. p. 148° (Found: C, 38·5; H, 2·0; N, 17·8; S, 20·6. $C_{10}H_6O_4N_4S_2$ requires C, 38·7; H, 1·9; N, 18·1; S, 20·6%).

5-(p-Acetamidobenzenesulphonamido)thiazole-2-thioamide, similarly prepared from 9 g. of chrysean in 30 ml. of pyridine and 11·6 g. of *p*-acetamidobenzenesulphonyl chloride and recrystallised from alcohol, had m. p. 237° (decomp.) (Found: C, 41·1; H, 3·4; N, 16·0; S, 26·7. $C_{12}H_{12}O_3N_4S_3$ requires C, 40·4; H, 3·4; N, 15·7; S, 26·9%).

(With Mr. J. Starr.) *5-(p-Acetamidobenzenesulphonamido)thiazole-2-amide*, prepared from 9·1 g. of 5-aminothiazole-2-amide, 34 ml. of pyridine, and 13·2 g. of *p*-acetamidobenzenesulphonyl chloride and recrystallised from water, had m. p. 253—255° (decomp.) (Found: C, 41·9; N, 16·2; S, 18·7. $C_{12}H_{12}O_4N_4S_2$ requires C, 42·4; N, 16·5; S, 18·8%).

5-(p-Aminobenzenesulphonamido)thiazole.—A solution of 21·36 g. of 5-(acetamidobenzenesulphonamido)thiazole-2-thioamide in 214 ml. of 10% aqueous sodium hydroxide was shaken with 16·03 g. of lead carbonate, filtered from lead sulphide, refluxed for 3 hours, and cooled. After filtration from a small amount of lead sulphide, it was acidified with 10% sodium bisulphate solution. The small yellow crystals obtained were recrystallised from boiling water, affording a moderately good yield of small needles or plates of *5-(p-aminobenzenesulphonamido)thiazole*, m. p. 185° (decomp.) (Found: C, 43·0; H, 3·5; N, 16·7; S, 24·9. $C_9H_9O_2N_3S_2$ requires C, 42·3; H, 3·5; N, 16·5; S, 25·1%).

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I.C.I. (Fertilizer and Synthetic Products) Limited,
Research Department, Billingham, Stockton-on-Tees.

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