367. *Thiazoles derived from Chrysean and* iso*Chrysean.*

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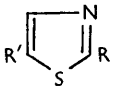
A number of derivatives of 5-amino- and 5-chloro-thiazole-2-carboxylic acids have been prepared from chrysean (5-amino-2-thiocarbamoylthiazole). *iso*Chrysean, an isomer isolated during the preparation of chrysean, has been identified as 5-amino-4-thiocarbamoylthiazole.

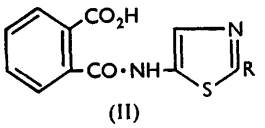
Chrysean was first prepared by Wallach [1] from hydrogen sulphide and a saturated solution of potassium cyanide. Hellsing [2] showed that the same compound could be obtained by treating thioformamide with aqueous potassium cyanide and that it was probably 5-amino-2-thiocarbamoylthiazole. More recently, Arnold and Scaife [3] have prepared 5-*p*-aminobenzenesulphonamidothiazole from chrysean and the structure was finally confirmed by Erlenmeyer and his co-workers.[4]

Although the yield of chrysean is poor (15—20%),[3] we have made numerous 1 kg. batches of crude product by passing hydrogen sulphide into ammoniated cyanide solution circulating through a packed tower. It has therefore been possible to prepare for biological examination a number of products—particularly carboxyhydrazides—derived from chrysean and to examine the chemistry of related thiazoles in some detail. The crude product melted at 204° but recrystallisation gave two isomers: one, m. p. 215—216°, which we consider to be the original chrysean; the other, which we have termed "*iso*-chrysean," m. p. 155° (cf. Ganapathi and Kulkarni [5]).

Chrysean is too fragile a molecule to permit normal degradation (cf. Arnold and Scaife [3]) and, although it is stabilised by acetylation or benzoylation, the acyl groups are resistant to subsequent hydrolysis. Protection of the amine group by conversion into a phthalimido-group which may be removed under mild, specific conditions has, however, proved advantageous. Chrysean (I; R = CS·NH_2, R′ = NH_2) with lead acetate gave 5-amino-2-cyanothiazole (I; R = CN, R′ = NH_2), but treatment of this with phthalic anhydride gave 5-*o*-carboxybenzamido-2-cyanothiazole (II; R = CN). Alkaline hydrolysis led to 5-*o*-carboxybenzamidothiazole-2-carboxylic acid (II; R = CO_2H) but attempts to convert this into the phthalimide by treatment with sulphuric acid were unsuccessful. Ring closure was effected with acetic acid but was accompanied by decarboxylation to 5-phthalimidothiazole (III; R = H). Excellent yields of 2-cyano-5-phthalimidothiazole (III; R = CN) were, however, obtained from the amino-nitrile and phthalic anhydride in boiling acetic acid. Acid-catalysed alcoholyses of this were not successful, but treatment of the corresponding ethyl imidoate with water gave ethyl 5-phthalimidothiazole-2-carboxylate



(I)



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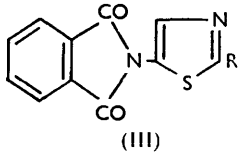


(III)

(III; R = CO_2Et). The protecting group was easily removed by treatment of the ester with hydrazine hydrate, the precise course of the reaction depending on the temperature and on the amount of hydrazine used. In boiling alcohol breakdown of the thiazole ring occurred, but the phthalimido-group was smoothly eliminated at room temperature. Excess of hydrazine hydrate gave the expected 5-aminothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = NH_2), but two mols. of hydrazine gave ethyl 5-aminothiazole-2-carboxylate (I; R = CO_2Et, R′ = NH_2) and the hydrazine salt of phthalhydrazide.

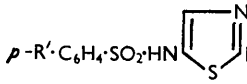
[1] Wallach, *Ber.*, 1874, **7**, 902.
[2] Hellsing, *Ber.*, (*a*) 1899, **32**, 1497; (*b*) 1900, **33**, 1774; (*c*) 1903, **36**, 3546.
[3] Arnold and Scaife, *J.*, 1944, 103.
[4] Erlenmeyer, Mengisen, and Prijs, *Helv. Chim. Acta*, 1947, **30**, 1865; Prijs, Mengisen, Fallab, and Erlenmeyer, *ibid.*, 1952, **35**, 187.
[5] Ganapathi and Kulkarni, *Proc. Indian Acad. Sci.*, 1953, **38**, *A*, 58.

The primary elimination of the phthalimide moiety from a bifunctional molecule of this nature is particularly interesting. With one mol. of hydrazine a mixture of the amino-ester and unchanged ethyl 5-phthalimidothiazole-2-carboxylate was produced.

Hellsing[2c] has prepared methyl 5-acetamidothiazole-2-carboxylate, m. p. 178°, from the silver salt of the corresponding acid. Repetition of this method gave only traces of product, but both the methyl (m. p. 216—217°) and the ethyl ester have now been prepared in good yields by hydrolysis of the methyl and the ethyl imidoate from 5-acetamido-2-cyanothiazole. Treatment of either ester with hydrazine hydrate gave 5-acetamidothiazole-2-carboxyhydrazide.

We also wished to examine the behaviour of the 5-amino-group towards diazotisation. Arnold and Scaife[3] reported that attempts to diazotise chrysean and 5-amino-2-cyanothiazole in the normal way gave highly coloured tars but they were able to diazotise the former by treating its solution in pyridine with nitrosyl chloride, and the latter by adding its aqueous solution to sodium nitrite and an excess of hydrochloric acid at 0°. We have confirmed these results but the dark red by-products which are obtained indicate that the diazonium compound couples with undiazotised material, even under acid conditions. The use of anhydrous conditions prevented self-coupling and 5-chloro-2-cyanothiazole (I; R = CN, R′ = Cl), together with varying amounts of 5-chlorothiazole-2-carboxyamide (I; R = CO·NH_2, R′ = Cl), was conveniently obtained from the amino-nitrile. The mixture from the Sandmeyer reaction was converted directly into 5-chlorothiazole-2-carboxylic acid (I; R = CO_2H, R′ = Cl) since both amide and nitrile were smoothly hydrolysed under alkaline conditions. The amide was also obtained from the nitrile by treatment with alcohol and dry hydrogen chloride, followed by hydrolysis. The acid, with diazomethane, gave methyl 5-chlorothiazole-2-carboxylate (I; R = CO_2Me, R′ = Cl), which with hydrazine hydrate gave 5-chlorothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = Cl). 5-Chloro-2-cyanothiazole reacted spontaneously with hydrazine hydrate to form 5-chlorothiazole-2-carboxyamidrazone [I; R = C(:NH)·NH·NH_2, R′ = Cl].

Thus, the reactivity of the 2-cyano-group is remarkably high (cf. 2-cyanothiazole ⟶ thiazole-2-carboxyamidrazone, Libman and Slack[6]) but we were none the less puzzled by the reported one-stage preparation of 5-*p*-aminobenzenesulphonamidothiazole (IV; R = H, R′ = NH_2), m. p. 185° (decomp.), from the corresponding acetamido-nitrile[3] (IV; R = CN, R′ = NHAc), a reaction which involves deacetylation, hydrolysis of the nitrile, *and decarboxylation*. In our opinion, the product of hydrolysis of both 5-*p*-acetamidobenzenesulphonamido-2-thiocarbamoylthiazole (IV; R = CS·NH_2, R′ = AcNH) and the nitrile is the carboxylic acid (IV; R = CO_2H, R′ = NH_2). This acid, which is decarboxylated under a variety of conditions (including recrystallisation), melts instantaneously in a bath at 150—160°, resolidifies, and remelts at *ca.* 190°. The monosodium salt (pH of 10% aqueous solution, 5—5·5) has also been prepared and the related 5-*p*-aminobenzenesulphonamido-2-thiocarbamoylthiazole (IV; R = CS·NH_2, R′ = NH_2) was made by reduction of the corresponding nitro-compound. For comparison with 5-*p*-aminobenzenesulphonamidothiazole-2-carboxylic acid (IV; R = CO_2H, R′ = NH_2), the analogous 4-carboxylic acid was prepared from ethyl 5-aminothiazole-4-carboxylate.[7]

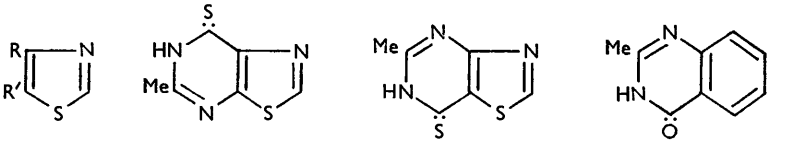


(IV)

We have also devoted particular attention to the elucidation of the structure of "*iso*chrysean," $C_4H_5N_3S_2$ (see p. 1870), which was isolated in almost 10% yield from crude chrysean by recrystallisation from dilute acetic acid and was purified by chromatography. It formed almost colourless needles, m. p. 155°; Ganapathi and Kulkarni[5] have also isolated an isomer, m. p. 146—146·5°, and maintain that it and chrysean yield the same acetyl derivative, softening at 214°, m. p. 236—237°, and that both give 5-acetamidothiazole on degradation. They conclude that chrysean exists in two stereoisomeric forms. In our hands, acetylation of chrysean with acetyl chloride in pyridine gave 5-acetamido-2-thiocarbamoylthiazole, m. p. 250°, and this yielded the same degradation products as were

[6] Libman and Slack, *J.*, 1956, in the press.
[7] Cook, Heilbron, and Levy, *J.*, 1947, 1594.

obtained by other workers. Acetylation of *iso*chrysean, however, gave a monoacetyl derivative, $C_6H_7ON_3S_2$, m. p. 208—210°, which indicated the presence of an amino-group but distinguished *iso*chrysean from chrysean. The acetyl compound with lead acetate gave lead sulphide and a nitrile, $C_6H_5ON_3S$, m. p. 202—204°. *iso*Chrysean was therefore an amino-thiocarbamoylthiazole and has now been identified as 5-amino-4-thiocarbamoylthiazole, a *position* isomer of chrysean, by the following reactions. Acetyl*iso*chrysean with warm dilute sodium hydroxide solution gave a weakly acidic yellow product, $C_6H_5N_3S_2$, formed by the loss of the elements of water. This elimination strongly suggested that the amino- and the thiocarbamoyl-group were adjacent and that the product was a thiazolopyrimidine (VI or VII) derived from [V; (*a*) R = CS·NH$_2$, R′ = NHAc, or (*b*) *vice versa*] [cf. the formation of 2-methyl-4-quinazolone (VIII) from *o*-acetamidobenzamide [8]].



(V) (VI) (VII) (VIII)

Now 5-aminothiazole-4-carboxyamide (V; R = CO·NH$_2$, R′ = NH$_2$) has been prepared by Cook, Heilbron, and Smith [9] and this, with acetyl chloride, gave a monoacetyl derivative, m. p. 212—213° (V; R = CO·NH$_2$, R′ = NHAc). The acetamidocyanothiazole from *iso*chrysean, with hydrogen peroxide in dilute alkali, was smoothly converted into the same compound (identical m. p., mixed m. p., and ultraviolet spectra), and the parent thioamide, therefore, is represented by (V; R = CS·NH$_2$, R′ = NH$_2$). Some other derivatives of *iso*chrysean have also been studied. Thus, with phthalic anhydride, 5-*o*-carboxybenzamido-4-thiocarbamoylthiazole (V; R = CS·NH$_2$, R′ = NH·CO·C$_6$H$_4$·CO$_2$H-*o*) was obtained and this was converted into the 4-nitrile by treatment with lead salts and alkali. The nitrile gave the corresponding amide on alkaline hydrolysis and the cyano-phthalimidothiazole [V; R = CN, R′ = C$_6$H$_4$(CO)$_2$N] with acetic anhydride.

Experimental

Chrysean (I; R = CS·NH$_2$, R′ = NH$_2$) *and* iso*Chrysean* (V; R = CS·NH$_2$, R′ = NH$_2$).—A solution of sodium cyanide (25 kg.) in water (57 l.) and aqueous ammonia (*d* 0·88; 1 l.) was circulated through a tower (consisting of a 5′ × 6″ " Pyrex " pipeline packed with 1″ Raschig rings) and was treated with hydrogen sulphide (15—16 kg.) during 6 hr. The product was washed with water and dried at 100° (1312 g.; m. p. 201—204°). Crystallisation from water (25 l.) and acetic acid (3·15 l.) (charcoal, 100 g.) gave chrysean (920 g.; m. p. 210—212°; m. p. 215—216° after further crystallisation from N-acetic acid). The mother-liquor was treated with ammonia (to pH 6), concentrated to 6·3 l. under reduced pressure, and the mixture of crude *iso*chrysean and ammonium acetate collected and washed with water. Crystallisation of the residue from ethanol gave *iso*chrysean (20·7 g.; m. p. 131—150°). The aqueous filtrate (6·3 l.) was continuously extracted with ether for two days. Evaporation of the ether gave an acetic acid solution which was diluted with three times its bulk of water, and was cooled overnight at 0°. Filtration gave a second crop of *iso*chrysean (86·5 g.; m. p. 131—160°). The filtrate was adjusted to pH 7 by the addition of ammonia solution and was set aside overnight at 0°, to give *iso*chrysean (20·2 g.; m. p. 136—160°). Crude *iso*chrysean (50 g.) in acetone (250 c.c.) was adsorbed on a column of activated alumina (1600 g.) prepared in chloroform suspension in 3″ " Pyrex " pipeline. The product was eluted with chloroform, fractions of 600 c.c. being collected and evaporated to dryness. Fractions 1—11 (35 g.), recrystallised from ethanol, gave *iso*chrysean in pale yellow needles (26 g.), m. p. 150—155°. Further recrystallisation gave *iso*chrysean (5-*amino*-4-*thiocarbamoylthiazole*) in almost colourless needles, m. p. 155° (Found: C, 30·8; H, 3·5; N, 26·5; S, 40·2. $C_4H_5N_3S_2$ requires C, 30·2; H, 3·2; N, 26·4; S, 40·3%).

5-*Acetamido*-2-*thiocarbamoylthiazole*.—A solution of chrysean (1·0 g.) in pyridine (4 c.c.) was treated at 0—5° with acetyl chloride (0·55 g.) to give 5-acetamido-2-thiocarbamoylthiazole

[8] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1948, **70**, 2423.
[9] Cook, Heilbron, and Smith, *J.*, 1949, 1440.

(0·8 g.) as yellow needles, m. p. 250° (decomp.), from 2N-acetic acid (Found: C, 36·0; H, 4·0; N, 21·1; S, 31·9. Calc. for $C_6H_7ON_3S_2$: C, 35·8; H, 3·5; N, 20·9; S, 31·9%).

5-Benzamido-2-cyanothiazole was obtained from 5-amino-2-cyanothiazole (Arnold and Scaife [3]) and benzoyl chloride in pyridine at 5°. Dissolution in dilute ammonia solution (charcoal), reprecipitation, and crystallisation from ethanol gave the *nitrile* as colourless needles, m. p. 211—212° (Found: N, 18·4; S, 14·4. $C_{11}H_7ON_3S$ requires N, 18·3; S, 14·0%).

5-Benzamidothiazole-2-carboxylic Acid.—A solution of 5-benzamido-2-cyanothiazole (1·0 g.) in 20% aqueous sodium hydroxide (20 c.c.) was boiled under reflux for 3 hr. Acidification of the cold solution gave *5-benzamidothiazole-2-carboxylic acid* (0·4 g.) which was dissolved in N-aqueous ammonia (charcoal) and reprecipitated by acidification, then having m. p. 159° (Found: N, 11·4; S, 12·8. $C_{11}H_8O_3N_2S$ requires N, 11·3; S, 12·9%).

5-o-*Carboxybenzamido-2-cyanothiazole* (II; R = CN).—Chlorobenzene was slowly distilled from a mixture of 5-amino-2-cyanothiazole (1 g.), phthalic anhydride (1·4 g.), and chlorobenzene (20 c.c.), fresh solvent being added to keep the volume constant. After 1 hr., the product was collected, washed with chlorobenzene, and dried at 100° (1·45 g.). 5-o-*Carboxybenzamido-2-cyanothiazole* crystallised from methanol in pale yellow needles, m. p. 253°, or at 210° (decomp.) when placed into a pre-heated bath (Found: N, 15·1; S, 12·0. $C_{12}H_7O_3N_3S$ requires N, 15·4; S, 11·7%).

5-o-*Carboxybenzamidothiazole-2-carboxylic Acid* (II; R = CO_2H).—5-*o*-Carboxybenzamido-2-cyanothiazole (1 g.) was boiled with 2N-sodium hydroxide (10 c.c.) for 1 hr. Acidification of the cold, filtered solution gave the crude *acid* (0·9 g.) which, purified by dissolution in dilute ammonia (charcoal) and precipitation with dilute aqueous hydrochloric acid, had m. p. 154° (decomp.) (Found: C, 49·3; H, 2·2; N, 9·6; S, 11·65. $C_{12}H_8O_5N_2S$ requires C, 49·3; H, 2·8; N, 9·6; S, 11·0%).

5-Phthalimidothiazole (III; R = H).—5-*o*-Carboxybenzamidothiazole-2-carboxylic acid (1·0 g.) was boiled with acetic acid (15 c.c.) for 1 hr. The cooled solution deposited pale yellow needles (0·15 g.; m. p. 147—148°), and treatment of the filtrate with water gave further material (0·35 g., m. p. 141—143°). Recrystallisation from aqueous acetic acid gave 5-phthalimidothiazole, m. p. 147° (Found: N, 12·35; S, 14·2. Calc. for $C_{11}H_6O_2N_2S$: N, 12·2; S, 13·9%).

2-Cyano-5-phthalimidothiazole (III; R = CN).—5-Amino-2-cyanothiazole (10 g.) and powdered phthalic anhydride (16·5 g.) were heated under reflux in acetic acid (150 c.c.) for 6 hr. The *2-cyano-5-phthalimidothiazole* (18·4 g.) which separated was recrystallised from acetic acid to give orange needles, m. p. 255—256° (Found: N, 16·1; S, 12·6. $C_{12}H_5O_2N_3S$ requires N, 16·5; S, 12·6%).

Ethyl 5-Phthalimidothiazole-2-carboxylate (III; R = CO_2Et).—A stirred suspension of 2-cyano-5-phthalimidothiazole (50·0 g.) in dry chloroform (825 c.c.) and dry ethanol (20 g.) was saturated at 0—5° with dry hydrogen chloride. The stoppered flask was kept at 0° for 5 days. The mixture was filtered, and the residue was heated on the steam-bath with water (2 l.) for 1 hr. The flocculent product (49·1 g.), crystallised from light petroleum (b. p. 80—100°, 24 l.) (residue of substantially unchanged nitrile, 14·8 g.), gave pale yellow needles (28·4 g.), m. p. 162—165°. Alternate recrystallisation from light petroleum (b. p. 80—100°) and ethanol gave *ethyl 5-phthalimidothiazole-2-carboxylate* as pale yellow needles, m. p. 171° (Found: C, 55·7; H, 3·6; N, 9·3; S, 10·3. $C_{14}H_{10}O_4N_2S$ requires C, 55·6; H, 3·3; N, 9·3; S, 10·6%). Concentration of the chloroform–alcohol filtrate gave unchanged 2-cyano-5-phthalimidothiazole (1·2 g.).

5-Aminothiazole-2-carboxyhydrazide (I; R = CO·NH·NH_2, R′ = NH_2).—The yellow solution formed by stirring hydrazine hydrate (100%; 90 c.c.) into a suspension of ethyl 5-phthalimidothiazole-2-carboxylate (58 g.) in ethanol (850 c.c.) was filtered and set aside overnight. The matted needles were collected and washed with a little ethanol. The filtrate and washings, concentrated to small bulk under reduced pressure at room temperature, gave yellow prisms [6·0 g.; m. p. 181—183° (decomp.)]. The needles (53·5 g.; m. p. 180—>360°) were dissolved in 2N-sodium hydroxide. Acidification of this solution gave phthalhydrazide (31·4 g.; m. p. 340—342°). The filtrate, made neutral with ammonia, deposited more crude amino-hydrazide [12·3 g.; m. p. 183—184° (decomp.)], and concentration of the mother-liquor under reduced pressure gave a further amount [1·7 g.; m. p. 181—182° (decomp.)]. The combined solids (20·0 g.) were recrystallised from water and then from ethanol, to give the *hydrazide*, m. p. 190° (decomp.) (Found: C, 30·4; H, 3·8; N, 34·6; S, 20·4. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8; N, 35·4; S, 20·3%).

Ethyl 5-Aminothiazole-2-carboxylate (I; R = CO_2Et, R′ = NH_2).—The solution formed by stirring hydrazine hydrate (100%; 3·53 g., 2 mol.) into a suspension of ethyl 5-phthalimidothiazole-2-carboxylate (10·65 g.; 1 mol.) in ethanol (160 c.c.) was filtered immediately. The filtrate,

from which yellow needles quickly separated, was set aside overnight. The solid was collected, and washed with a little ethanol. The filtrate and washings, evaporated to dryness under reduced pressure at room temperature, gave the crude ester as a yellow crystalline powder (4·0 g.; m. p. 117—118°). The needles (5·7 g.; m. p. >250°) were stirred with 2N-hydrochloric acid, phthalhydrazide (4·7 g.; m. p. 336—338°) was collected, and the filtrate was neutralised with ammonia and evaporated under reduced pressure to give a further small amount of crude ester (0·05 g.). The combined solids, recrystallised from water, gave *ethyl 5-aminothiazole-2-carboxylate* as cream-coloured needles, m. p. 118° (Found: C, 42·0; H, 4·8; N, 16·45; S, 19·0. $C_6H_8O_2N_2S$ requires C, 41·85; H, 4·7; N, 16·3; S, 18·6%).

n-*Butyl 5-Phthalimidothiazole-2-carboxylate* (III; R = CO_2Bu^n).—Prepared in 54% yield in the same manner as ethyl 5-phthalimidothiazole-2-carboxylate, the n-*butyl ester* crystallised (alternately from light petroleum and ethanol) as pale yellow needles, m. p. 167—169° (Found: C, 58·2; H, 4·4; N, 8·4; S, 9·5. $C_{16}H_{14}O_4N_2S$ requires C, 58·2; H, 4·3; N, 8·5; S, 9·7%).

n-*Butyl 5-Aminothiazole-2-carboxylate* (I; R = CO_2Bu^n, R′ = NH_2).—Prepared in 69% yield (cf. prep. of ethyl 5-aminothiazole-2-carboxylate), n-*butyl 5-aminothiazole-2-carboxylate* crystallised from 2N-acetic acid as fawn prisms, m. p. 81—82° (Found: C, 48·25; H, 6·0; N, 14·0; S, 16·4. $C_8H_{12}O_2N_2S$ requires C, 48·0; H, 6·0; N, 14·0; S, 16·0%).

Ethyl 5-Acetamidothiazole-2-carboxylate.—A suspension of 5-acetamido-2-cyanothiazole [2b] (10 g.) in dry chloroform (90 c.c.) and dry ethanol (30 c.c.) was saturated, at 0—5°, with dry hydrogen chloride. The stoppered flask was kept at 0° for two days, and the solid was collected and warmed with water (300 c.c.) for 15 min. The mixture was cooled and the residue (10·3 g.) crystallised from water, to give ethyl 5-acetamidothiazole-2-carboxylate as colourless needles, m. p. 191—192° (Found: N, 13·1. Calc. for $C_8H_{10}O_3N_2S$: N, 13·1%).

Methyl 5-acetamidothiazole-2-carboxylate (82 %), m. p. 216—217°, was prepared as above (Found: C, 42·5; H, 4·0; N, 14·0; S, 16·4. Calc. for $C_7H_8O_3N_2S$: C, 42·0; H, 4·0; N, 14·0; S, 16·0%). Hellsing [2c] gave m. p. 178° (decomp.).

5-Acetamidothiazole-2-carboxyhydrazide.—A mixture of hydrazine hydrate (100%; 2 c.c.), ethyl 5-acetamidothiazole-2-carboxylate (2 g.), and ethanol (25 c.c.) was heated at 100° for 15 min. and set aside overnight. The product (1·6 g.) recrystallised from ethanol to give cream-coloured *5-acetamidothiazole-2-carboxyhydrazide*, m. p. 286° (decomp.) (Found: C, 36·25; H, 4·3; N, 28·05; S, 16·35. $C_6H_8O_2N_4S$ requires C, 36·0; H, 4·0; N, 28·0; S, 16·0%). The hydrazide was also prepared similarly from the methyl ester.

5-Chloro-2-cyanothiazole (I; R = CN, R′ = Cl).—Freshly precipitated cuprous chloride (from 300 g. of $CuSO_4,5H_2O$) was dissolved in water (500 c.c.) and concentrated hydrochloric acid (375 c.c.). Dry, powdered sodium nitrite (9·4 g.) was added slowly, with stirring, to sulphuric acid (*d* 1·84; 63 c.c.), and the mixture was stirred at 65° until dissolution was complete. To this solution, at 0°, was added dropwise, with stirring, a cold solution of 5-amino-2-cyanothiazole (15·7 g.) in acetic acid (188 c.c.). The red syrup was stirred into a mixture of crushed ice (1500 g.), concentrated hydrochloric acid (180 c.c.), and cuprous chloride solution (210 c.c.), prepared as described above. After 16 hr., the brown copper complex was collected, washed with water, and dried at 100° (17·35 g.). Sublimation at 140—210°/0·1 mm. gave crude 5-chloro-2-cyanothiazole (5·75 g.). Resublimation at 60—100°/0·1 mm. gave colourless prisms (4·7 g.; m. p. 44—48°) and a pale yellow sublimate of the corresponding amide (0·2 g.; m. p. 175—180°) when the temp. was raised to 200°. Crystallisation of the low-melting product from light petroleum (b. p. 60—80°) gave *5-chloro-2-cyanothiazole* as colourless prisms, m. p. 50° (Found: N, 19·3; Cl, 24·4. C_4HN_2ClS requires N, 19·4; Cl, 24·5%). The crude amide, from ethanol, gave colourless needles, m. p. and mixed m. p. 189—191°.

5-Chlorothiazole-2-carboxyamide (I; R = CO·NH_2, R′ = Cl).—A solution of 5-chloro-2-cyanothiazole (2·0 g.) in dry chloroform (20 c.c.) and dry ethanol (1·5 c.c.) at 0—5°, saturated with dry hydrogen chloride, was set aside at 0° for 4 days. The colourless solid was warmed on the steam-bath with N-hydrochloric acid, triturated with aqueous sodium hydrogen carbonate, washed with water, and dried (0·47 g.; m. p. 190—193°). The chloroform filtrate, evaporated to dryness, gave a colourless residue which was treated in the same way (1·25 g.; m. p. 190—193°). Recrystallisation from ethanol gave *5-chlorothiazole-2-carboxyamide* in colourless needles, m. p. 193° (Found: N, 17·35. $C_4H_3ON_2ClS$ requires N, 17·2%). The amide was converted by boiling 2N-sodium hydroxide into 5-chlorothiazole-2-carboxylic acid.

5-Chlorothiazole-2-carboxylic Acid (I; R = CO_2H, R′ = Cl).—5-Chloro-2-cyanothiazole (4·25 g.) was treated for 1 hr. with boiling 2N-sodium hydroxide (40 c.c.). The crude product, which separated on cooling, was dissolved in hot water (30 c.c.) and reprecipitated with hydrochloric acid to give the *acid* (3·2 g.), m. p. 109° (decomp.). Acidification of the original alkaline

filtrate gave less pure material, m. p. 105° (decomp.) (0·95 g.). A sample, purified by repeated dissolution in 2N-sodium hydroxide (charcoal) and reprecipitation with 2N-hydrochloric acid, formed colourless needles, m. p. 111—112° (decomp.) (Found: N, 8·5. $C_4H_2O_2NClS$ requires N, 8·6%).

Methyl 5-chlorothiazole-2-carboxylate (I; R = CO_2Me, R′ = Cl) was prepared from 5-chlorothiazole-2-carboxylic acid (62·7 g.) and diazomethane (prepared from 150 g. of *N*-nitrosomethylurea) in dry ether (1600 c.c.) at 0—5°. The *ester* (46·6 g.), b. p. 76—80°/0·1 mm., solidified, and crystallisation from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 53° (Found: N, 8·0. $C_5H_4O_2NClS$ requires N, 7·9%).

5-*Chlorothiazole*-2-*carboxyhydrazide* (I; R = CO·NH·NH_2, R′ = Cl).—Hydrazine hydrate (100%; 40 c.c.) in ethanol (250 c.c.) at 0°, and methyl 5-chlorothiazole-2-carboxylate (40·4 g.) in ethanol (250 c.c.), gave the crude *hydrazide* (37·9 g.). Recrystallisation from ethanol gave colourless needles, m. p. 197° (Found: N, 23·8; Cl, 20·2. $C_4H_4ON_3ClS$ requires N, 23·8; Cl, 20·1%).

5-*Chlorothiazole*-2-*carboxyamidrazone* [I; R = C(:NH)·NH·NH_2, R′ = Cl].—A mixture of 5-chloro-2-cyanothiazole (1·0 g.) and hydrazine hydrate (100%; 2 c.c.) gave, after 2 hr. at room temp., 5-*chlorothiazole*-2-*carboxyamidrazone* (1·12 g.) which crystallised from ethanol as pale yellow needles, m. p. 148° (decomp.), resolidifying and re-melting at *ca.* 220° (Found: N, 31·25. $C_4H_5N_4ClS$ requires N, 31·7%).

(With Mrs. J. A. Murphy.) 5-p-*Aminobenzenesulphonamidothiazole*-2-*carboxylic Acid* (IV; R = CO_2H; R′ = NH_2).—5-*p*-Acetamidobenzenesulphonamido-2-thiocarbamoylthiazole (45 g.) (Arnold and Scaife [3]) and 2N-sodium hydroxide were boiled under reflux for 1¼ hr. The cooled solution was treated with ice and then acidified with 2N-hydrochloric acid to pH 1. The precipitate (27 g.) was dissolved in N-ammonia and stirred with charcoal during ½ hr. The filtered solution was adjusted to pH 1 by the addition of concentrated hydrochloric acid (no precipitation occurred at higher pH values) and the pale yellow solid was collected and dried. Dissolution in ethanol and addition of light petroleum (b. p. 60—80°) gave the product as an oil, which solidified, to give 5-p-*aminobenzenesulphonamidothiazole*-2-*carboxylic acid* as a yellowish-white solid, m. p. 189° (decomp.),* decarboxylated at 124° if plunged into a bath from 110°. The acid was also decarboxylated in boiling water (Found: N, 14·25; S, 22·1. $C_{10}H_9O_4N_3S_2$ requires N, 14·0; S, 21·4%). The acid (24·0 g.), in cold dry methanol (240 c.c.), with sodium (1·84 g.) in dry methanol (120 c.c.) gave the yellow, crystalline *monosodium salt monomethanol solvate* (22·5 g.), decomp. by 200°. Precipitation was completed by the addition of a little dry ether. The salt was purified by solution in cold methanol and reprecipitation by the addition of dry ether (Found: N, 11·6; S, 18·4; Na, 6·15. $C_{10}H_8O_4N_3S_2Na,CH_3·OH$ requires N, 11·9; S, 18·1; Na, 6·5%. Loss *in vacuo* at 100° could not be determined accurately since dried material gained rapidly in wt. during weighing).

(With Mrs. J. A. Murphy.) 5-p-*Aminobenzenesulphonamido*-2-*thiocarbamoylthiazole*.—5-*p*-Nitrobenzenesulphonamido-2-thiocarbamoylthiazole (10 g.) (Arnold and Scaife [3]) in N-ammonia (100 c.c.) was added with stirring to a boiling solution of ferrous sulphate (60 g.) in water (150 c.c.). The solution was made alkaline by the addition of aqueous ammonia (*d* 0·88), the mixture was boiled for 5 min., and again made alkaline. The solution was filtered (Hyflo), and the filtrate acidified to pH 4—5 with 2N-hydrochloric acid. The sulphonamide (8·5 g.) was dissolved in N-ammonia (100 c.c.) (charcoal) and reprecipitated (5 g.) by adjusting the pH to 4 with 2N-hydrochloric acid. Further purification was effected by dissolution in ethanol, and precipitation with light petroleum (b. p. 60—80°), and finally by recrystallisation from acetic acid, to give 5-p-*aminobenzenesulphonamido*-2-*thiocarbamoylthiazole* as golden needles, m. p. 219—220° (Found: C, 38·3; H, 3·4; N, 17·7; S, 30·3. $C_{10}H_{10}O_2N_4S_3$ requires C, 38·1; H, 3·2; N, 17·8; S, 30·5%).

5-*Acetamido*-4-*thiocarbamoylthiazole* (V; R = CS·NH_2, R′ = NHAc).—*iso*Chrysean (6·0 g.) in dry pyridine (24 c.c.) was treated at 0—5° with acetyl chloride (3·7 g.). After 1 hr. at room temperature, the mixture was stirred into water (250 c.c.) and kept overnight. The yellow 5-*acetamido*-4-*thiocarbamoylthiazole* (6·3 g.) crystallised from 2N-acetic acid as pale yellow needles, m. p. 208—210° (Found: C, 35·9; H, 3·6; N, 20·9; S, 32·1. $C_6H_7ON_3S_2$ requires C, 35·8; H, 3·5; N, 20·9; S, 31·9%).

5-*Acetamido*-4-*cyanothiazole* (V; R = CN, R′ = NHAc).—*Method* I. 5-Acetamido-4-thiocarbamoylthiazole (2·2 g.), lead acetate (4·2 g.), and water (20 c.c.) were boiled under reflux for ¾ hr. The hot solution was filtered and the black residue was extracted with boiling N-acetic

* This is the m. p. of the decarboxylated product *with which there is no depression on slow heating.*

acid (30 c.c.). This extract was added to the filtrate. The product separated in yellow needles (0·8 g.). Recrystallisation from N-acetic acid gave *5-acetamido-4-cyanothiazole* in almost colourless needles, m. p. 202° (Found : C, 43·4; H, 3·2; N, 25·5. $C_6H_5ON_3S$ requires C, 43·1; H, 3·0; N, 25·1%).

Method II. A concentrated aqueous solution of lead nitrate (3·3 g.) was treated with 10% aqueous sodium hydroxide until the precipitate redissolved. 5-Acetamido-4-thiocarbamoylthiazole (2·0 g.) was added, and the mixture was shaken overnight. Lead sulphide was removed and the filtrate slowly acidified (pH 4; critical) with 2N-hydrochloric acid, and set aside overnight. The solid (1·4 g.) on crystallisation from 2N-acetic acid (charcoal) gave faintly pink needles, m. p. 202—204°, not depressed on admixture with 5-acetamido-4-cyanothiazole.

1 : 6-*Dihydro-2-methyl-6-thiothiazolo*(4′ : 5′-5 : 4)*pyrimidine* (VI).—5-Acetamido-4-thiocarbamoylthiazole (1·0 g.) was treated with boiling 2N-sodium hydroxide (10 c.c.) for 90 min. The solution was treated at 0° with 2N-hydrochloric acid, to give the bright yellow anhydroderivative. This (0·65 g.) was purified by dissolution in 2N-sodium hydroxide (charcoal), followed by reprecipitation with aqueous hydrochloric acid. 1 : 6-*Dihydro-2-methyl-6-thiothiazolo*(4′ : 5′-5 : 4)*pyrimidine* was obtained as a yellow powder, m. p. 266°, soluble in aqueous sodium hydrogen carbonate, but not in dilute acid (Found : C, 39·7; H, 2·8; N, 22·8; S, 35·8. $C_6H_5N_3S_2$ requires C, 39·3; H, 2·75; N, 22·9; S, 35·0%).

5-Acetamidothiazole-4-carboxyamide (V; R = CO·NH_2, R′ = NHAc).—*Method* I. A suspension of 5-acetamido-4-cyanothiazole (1 g.) in acetone (10 c.c.) was treated with 20% aqueous hydrogen peroxide (25 c.c.) and 2N-sodium carbonate (3 c.c.). The mixture was warmed on the steam-bath for 45 min., with the addition of further acetone as required to prevent the precipitation of the solid, and of aqueous hydrogen peroxide (20%; 1 c.c.) after 25 min. The colourless crystalline *amide* (0·8 g.) was collected after 16 hr. at room temperature. Crystallisation from water gave colourless needles, m. p. 212—213°. The m. p. was not depressed on admixture with an authentic sample and their light absorptions in methanol were identical [$\lambda_{max.}$ 282 mμ (log ε 4·15); $\lambda_{min.}$ 235 mμ (log ε 3·60); $\lambda_{infl.}$ 260 mμ (log ε 3·93)] (Found : C, 38·65; H, 3·95; N, 22·5; S, 17·5. $C_6H_7O_2N_3S$ requires C, 38·9; H, 3·8; N, 22·7; S, 17·3%).

Method II. A solution of 5-aminothiazole-4-carboxyamide (2·0 g.) (Cook *et al.*[9]) in dry pyridine (20 c.c.) was treated, at 0—5°, with acetyl chloride (1·5 g.). After 2 hr., water (150 c.c.) was added, and the solution was filtered from a little impurity and treated with concentrated hydrochloric acid to pH 6—7. The mixture was set aside for 2 hr., during which the product crystallised in almost colourless needles (1·9 g.). Recrystallisation from water gave the amide as colourless needles, m. p. 212—213°. The m. p. was not depressed on admixture with the specimen prepared from *iso*chrysean, and their light absorptions in methanol were identical.

5-o-Carboxybenzamido-4-thiocarbamoylthiazole.—*iso*Chrysean (10 g.), powdered phthalic anhydride (12·5 g.), and acetic acid (150 c.c.) were boiled under reflux for 2 hr., then kept overnight. The product (17·6 g.), crystallised from acetic acid, gave *5-o-carboxybenzamido-4-thiocarbamoylthiazole* as pale yellow needles, m. p. 243—244° (Found : C, 46·2; H, 3·1; N, 13·9. $C_{12}H_9O_3N_3S_2$ requires C, 46·9; H, 2·95; N, 13·7%).

5-o-Carboxybenzamido-4-cyanothiazole.—A concentrated aqueous solution of lead nitrate (2·65 g.) was treated with 2N-sodium hydroxide until the precipitate redissolved. 5-*o*-Carboxybenzamido-4-thiocarbamoylthiazole (2·2 g.) was added, and the mixture was shaken overnight. The solution was filtered from lead sulphide and acidified with 2N-nitric acid. The product (1·8 g.) was purified by repeated dissolution in 2N-sodium hydroxide and reprecipitation with 2N-nitric acid, to give *5-o-carboxybenzamido-4-cyanothiazole* as a white powder, m. p. 224° (decomp.) (Found : C, 52·7; H, 2·8; N, 15·4; S, 12·0. $C_{12}H_7O_3N_3S$ requires C, 52·7; H, 2·6; N, 15·4; S, 11·7%). The use of a lead carbonate suspension instead of lead nitrate gave the nitrile in 96% yield.

5-o-Carboxybenzamidothiazole-4-carboxyamide.—5-*o*-Carboxybenzamido-4-cyanothiazole (7·9 g.) was boiled under reflux with 2N-sodium hydroxide (79 c.c.) for 2 hr. The cooled solution was filtered and acidified with 2N-hydrochloric acid to give the *phthalamic acid* (5·85 g.) which was purified by repeated dissolution in 2N-sodium hydroxide followed by reprecipitation with 2N-hydrochloric acid to give a white powder, m. p. 203° (decomp.), resolidifying to yellow rhombohedra, m. p. 345—350° (Found : C, 49·5; H, 3·1; N, 14·6; S, 11·25. $C_{12}H_9O_4N_3S$ requires C, 49·5; H, 3·1; N, 14·4; S, 11·0%).

4-Cyano-5-phthalimidothiazole.—A mixture of 5-*o*-carboxybenzamido-4-cyanothiazole (11·0 g.) and acetic anhydride (50 c.c.) was boiled under reflux for 2 hr. The solution was

filtered (charcoal) and cooled, to give colourless prisms (6·45 g.) of the phthalimide, which were finally washed with acetic anhydride. Recrystallisation from acetic anhydride gave *4-cyano-5-phthalimidothiazole*, m. p. 196° (Found: C, 56·7; H, 2·2; N, 16·2. $C_{12}H_5O_2N_3S$ requires C, 56·5; H, 2·0; N, 16·5%).

5-p-*Aminobenzenesulphonamidothiazole-4-carboxylic Acid.*—A solution of ethyl 5-aminothiazole-4-carboxylate (50·5 g.) (Cook *et al.*[7]) in dry pyridine (505 c.c.) was treated at 0°, with stirring, with *p*-acetamidobenzenesulphonyl chloride (79 g.). The solution was set aside for 4 days, and was then poured on ice (2 kg.) and sufficient concentrated hydrochloric acid to keep the mixture acid. The product was hydrolysed by boiling with 2N-sodium hydroxide (1 l.) for 2 hr. The boiling solution was filtered (charcoal), cooled, and again filtered. Treatment with concentrated hydrochloric acid (ice-cooling) gave a sticky product (41·3 g.) which eventually crystallised. After being washed with very dilute hydrochloric acid and drying at 40° (41·3 g.), this was repeatedly dissolved in dilute ammonia (charcoal) and reprecipitated with dilute hydrochloric acid at 0°, to give 5-p-*aminobenzenesulphonamidothiazole-4-carboxylic acid* in almost colourless needles, m. p. 184° (decomp.) on slow heating, but immediate decomp. in a bath at 160° (Found: C, 38·95; H, 3·2; N, 13·6; S, 21·1; loss in wt. at 100°, 3·2. $C_{10}H_9O_4N_3S_2,\frac{1}{2}H_2O$ requires C, 38·9; H, 3·3; N, 13·6; S, 20·8; H_2O, 2·9%).

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