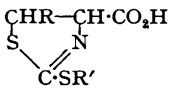
# 386. *Studies in the Azole Series. Part XXXI. The Interaction of Amines and 2-Mercapto-4-alkylidene- or -arylidene-5-thiazolinones.*

By A. H. Cook, G. D. Hunter, and J. R. A. Pollock.

Apart from certain exceptional cases, interaction of a 2-mercapto-alkylidene- or -arylidene-thiazolin-5-one and an amine gives a mixture of a thiazoline such as (III; R′ = H) and a 2-thiohydantoin (*e.g.*, XVII). The former products are converted into 5-substituted thiazolidine-4-carboxyamides (*e.g.*, IV; R′ = $NH_2$) from which the amides of substituted cysteines may be obtained.

The preparations of aminomercapto-acids from 2-mercaptothiazolines which were reported earlier in this series (*J.*, 1948, 1337, 1060; 1949, 1437, 3007; see also Cook, Heilbron, and Shaw, CPS, 311) involved the use of concentrated hydrochloric acid, with or without reducing agents. It was expected that certain of the reactions then envisaged would not succeed under these conditions, and the fission of 2-mercapto-5-*p*-methoxyphenylthiazoline-4-carboxylic acid (I; R = *p*-MeO·$C_6H_4$, R′ = H) (Cook, Harris, Pollock, and Swan, *J.*, in the press) proved to be of this kind.

The observation (Bentley, Catch, Cook, Heilbron, and Shaw, CPS, 267) that $\Delta^2$-thiazolines can be reduced to thiazolidines by amalgamated aluminium offered, however, a possible alternative approach. Exploratory attempts to reduce the methyl ester of (I; R = *p*-MeO·$C_6H_4$; R′ = H) in this way were unsuccessful, possibly because of the tendency of such compounds to behave as the corresponding thiones (II), rather than as thiazolines. Methylation of the methyl ester which was expected to yield a true thiazoline gave oils of doubtful purity, and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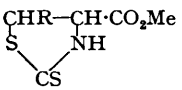
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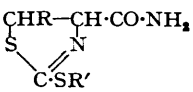
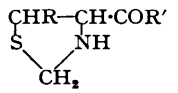
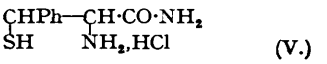

(III.)

attention was therefore directed to amides such as (III), which were expected to provide crystalline intermediates and to be of interest *per se* in leading to the hitherto unobtained amides of cysteine derivatives and thence of penicillins; the potential importance of the last series was recently demonstrated when benzylpenicillinamide was obtained from the antibiotic itself (Carpenter, *J. Amer. Chem. Soc.*, 1948, **70**, 2964).

When α-2-methylthio-5-phenylthiazoline-4-carboxyamide (III; R = Ph, R′ = Me), obtained by the reaction of (VI; R = Ph, R′ = H) with ammonia followed by methylation, was treated with amalgamated aluminium, methanethiol was evolved, and 5-phenylthiazolidine-4-carboxyamide (IV; R = Ph, R′ = $NH_2$) was produced. Thiazolidines of this type are dissociated in varying degrees into the constituent amino-mercaptans and formaldehyde in solution. Thus Ratner and Clark (*ibid.*, 1937, **59**, 200) showed that treatment of thiazolidine-4-carboxylic acid (IV; R = H, R′ = OH) with benzyl chloride or mercuric chloride gave good yields of cysteine derivatives, though distillation of solutions of the thiazolidine in dilute hydrochloric acid removed formaldehyde only slowly. Similarly, with (IV; R = Ph, R′ = $NH_2$) no formaldehyde could be detected in the distillate from dilute hydrochloric acid solution, but the mercaptide precipitated by mercuric chloride gave a good yield of 1-amino-2-mercapto-2-phenylpropionamide hydrochloride (V).

(IV.) 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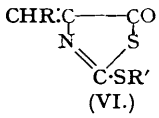
2-Mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (VI; R = *p*-MeO·$C_6H_4$, R′ = H) and ammonia gave a mixture from which the two diastereoisomerides of 2-mercapto-5-*p*-methoxyphenylthiazoline-4-carboxyamide (III; R = *p*-MeO·$C_6H_4$, R′ = H) were isolated. One of these was reduced, through its 2-methylthio-derivative (III; R = *p*-MeO·$C_6H_4$, R′ = Me), to 5-*p*-methoxyphenylthiazolidine-4-carboxyamide (IV; R = *p*-MeO·$C_6H_4$, R′ = $NH_2$). An attempt to convert the latter product into the corresponding carboxylic acid by means of nitrous acid gave a neutral product which contained one oxygen atom more than the parent compound and was tentatively formulated as the *S*-oxide (VII). The acid (IV; R = *p*-MeO·$C_6H_4$, R′ = OH) was subsequently obtained from the acid (I; R = *p*-MeO·$C_6H_4$, R′ = H) (Cook, Harris, Pollock, and Swan, *loc. cit.*).

A preparation of 2-mercapto-5-*p*-hydroxyphenylthiazoline-4-carboxylic acid (I; R = *p*-HO·$C_6H_4$, R′ = H) has already been reported (*idem, ibid.*) and an alternative route to this compound was derived from the interaction of 2-mercapto-4-*p*-acetoxybenzylidene-5-thiazolinone (VI; R = *p*-AcO·$C_6H_4$, R′ = H) with ammonia. This reaction was, however, distinguished from others between similar compounds by the elimination of hydrogen sulphide, two products being obtained: one of these, 2-thio-5-*p*-hydroxybenzylidenehydantoin (VIII; R = *p*-HO·$C_6H_4$), was also prepared (*a*) from ammonia and 2-methylthio-4-*p*-acetoxybenzyl-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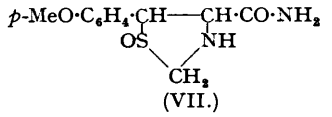
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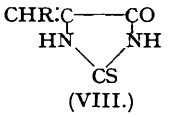
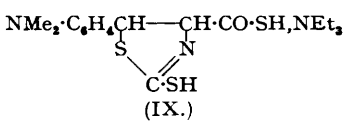

(VIII.)

idene-5-thiazolinone (VI; R = *p*-AcO·$C_6H_4$, R′ = Me), and (*b*) from ammonia and an acetyl derivative prepared from *p*-hydroxybenzaldehyde, potassium thiocyanate, and acetic anhydride; the remainder of the reaction product appeared to be a mixture, from which one of the diastereoisomeric forms of 2-mercapto-5-*p*-hydroxyphenyl-2-thiazoline-4-carboxyamide (III; R = *p*-HO·$C_6H_4$, R′ = H) was isolated. The crude mixture with sodium hydroxide gave ammonia and the corresponding acid, identical with material prepared otherwise (Cook, Harris, Pollock, and Swan, *loc. cit.*).

The formation of 2-thiohydantoins as above from 2-mercapto-5-thiazolinones parallels their occurrence as the sole reaction products of amines with 2-benzylthio-5-thiazolinones (Cook, Harris, Heilbron, and Shaw, *loc. cit.*), and is now, indeed, known to be not unusual with such mercapto-compounds. Thus 2-mercapto-4-(2-furfurylidene)-5-thiazolinone (VI; R = $C_4H_3O$, R′ = H) with ammonia gave a mixture of 2-thio-5-(2-furfurylidene)hydantoin (VIII; R = $C_4H_3O$) with 2-mercapto-5-(2-furyl)thiazoline-4-carboxyamide (III; R = $C_4H_3O$, R′ = H). The thiohydantoin was characterized as its 2-methylthio-derivative and identified by comparison with specimens prepared (*a*) by the reaction of furfuraldehyde, potassium thiocyanate, and acetic anhydride, and (*b*) by treating 2-methylthio-4-(2-furfurylidene)-5-thiazolinone (VI; R = $C_4H_3O$, R′ = Me) with ammonia. Only one diastereoisomeride of the amide (III; R = $C_4H_3O$, R′ = H) appeared to be present, and this was characterized as its 2-methylthio-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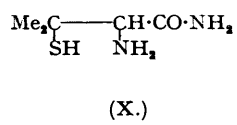
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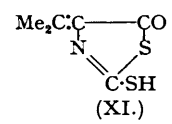
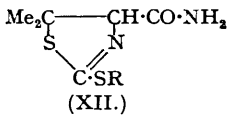

(XI.)

derivative, which was reduced to 5-(2-furyl)thiazolidine-4-carboxyamide (IV; R = $C_4H_3O$, R′ = $NH_2$). Neither the furfurylidenethiazolinone nor 2-mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (VI; R = *p*-$NO_2$·$C_6H_4$, R′ = H) gave satisfactory products under the now familiar ring-turning conditions in the presence of sodium methoxide or sodium hydroxide, and pure material was not isolated by treatment of the thiazolinones in alcoholic triethylamine with hydrogen sulphide. The *p*-nitrobenzylidenethiazolinone, which was characterized as its 2-methylthio-derivative, reacted with ammonia to yield a thiohydantoin exclusively, but the hydrogen sulphide liberated in the reaction appeared to cause reduction of the nitro-group; the major product, however, remains unidentified as, despite analytical indications, its properties did not agree with those of 5-*p*-aminobenzylidene-2-thiohydantoin given by Namjoshi and Dutt (*J. Indian Chem. Soc.*, 1931, **8**, 241). 2-Mercapto-4-*p*-dimethylaminobenzylidene-5-thiazolinone (VI; R = *p*-$NMe_2$·$C_6H_4$, R′ = H) yielded the corresponding thiohydantoin (VIII; R = *p*-$NMe_2$·$C_6H_4$) in ammonia, but on treatment with hydrogen sulphide in methanolic triethylamine it gave triethylammonium 2-mercapto-5-*p*-dimethylaminophenylthiazoline-4-thiolcarboxylate (IX). As the first step in the attempted synthesis of penicillamine amide (X), 2-mercapto-4-*iso*propylidene-5-thiazolinone (XI) was treated with ammonia, giving 2-mercapto-5 : 5-dimethylthiazoline-4-carboxyamide (XII; R = H) and thence the methylthio-derivative (XII; R = Me). The last compound was remarkable in yielding a small quantity only of methanethiol on reduction with amalgamated aluminium, and the main product was isomeric with the starting material. Its crystalline form, solubility and melting point were different, and it is tentatively formulated as 2-thio-3 : 5 : 5-trimethylthiazolidone-4-carboxyamide (XIII). Attempts to reduce (XII; R = H) directly to the thiazolidine with amalgamated aluminium or magnesium and sulphur dioxide were abortive. In attempts to prepare compounds similar to the thiazoline (XII; R = H), the thiazolinone (XI) was treated

with dimethylamine : a novel reaction occurred, leading to a basic compound, 2-dimethylamino-5 : 5-dimethylthiazoline-4-carboxydimethylamide (XIV).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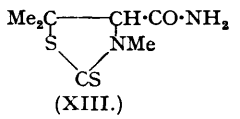
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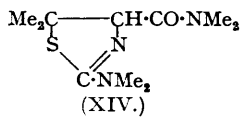
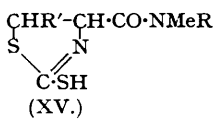

(XIV.)

This formed a water-soluble methiodide which also was not reduced to a thiazolidine by amalgamated aluminium. No analogue of the thiazoline (XII; R = H) could be obtained from 2-mercapto-4-*cyclo*pentylidene-5-thiazolinone, for, with ammonia, this compound gave 2-thio-5-*cyclo*pentylidenehydantoin.

Further observations showed more clearly that the new reaction with dimethylamine was limited in scope, for 2-mercapto-4-*iso*butylidene-5-thiazolinone (VI; R = $Pr^i$, R′ = H) with ammonia or dimethylamine gave 2-mercapto-5-*iso*propylthiazoline-4-carboxyamide (III; R = $Pr^i$, R′ = H) or -dimethylamide (XV; R = Me, R′ = $Pr^i$). Similarly, 2-mercapto-4-benzylidene-5-thiazolinone (VI; R = Ph, R′ = H) with dimethylamine gave 2-mercapto-5-phenylthiazoline-4-carboxydimethylamide (XV; R = Me, R′ = Ph), and again no basic product was obtained; with methylamine, the same benzylidenethiazolinone yielded two products, one of which was 2-thio-3-methyl-5-benzylidenehydantoin (XVI; R = Me), the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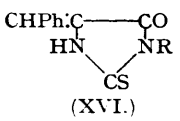
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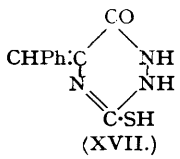
(XVII.)

other being the methylamide (XV; R = H, R′ = Ph). Again, from the reaction between the benzylidenethiazolinone and aniline, two isomeric compounds were isolated : one of these was the known 2-thio-3-phenyl-5-benzylidenehydantoin (XVI; R = Ph), and the other showed ultra-violet absorption indicating it to be probably the stereoisomeride thereof. 2-Thio-3-phenyl-5-*iso*butylidenehydantoin was isolated from the reaction between 2-mercapto-4-*iso*butylidene-5-thiazolinone (VI; R = $Pr^i$, R′ = H) and aniline; one form only was detected, as also from 2-thio-3-phenyl-5-*p*-nitrobenzylidenehydantoin, obtained in a similar way from the corresponding thiazolinone (VI; R = *p*-$NO_2$·$C_6H_4$, R′ = H).

2-Mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (VI; R = *p*-Me·$OC_6H_4$, R′ = H) with methanolic pyridine or 2-aminopyridine slowly afforded methyl 2-thio-5-*p*-methoxyphenylthiazolidine-4-carboxylate (II; R = *p*-MeO·$C_6H_4$). In a similar fashion methyl 2-thio-5-phenyl- (II; R = Ph), -5-(2-furyl)- (II; R = $C_4H_3O$) and -5-*p*-nitrophenyl-thiazolidine-4-carboxylate (II; R = *p*-$NO_2$·$C_6H_4$) were prepared. For the last two compounds, this method is the only one at present available, and it appears to offer a convenient route to several otherwise inaccessible aminomercapto-acids.

The reaction between 2-mercapto-4-benzylidene-5-thiazolinone (VI; R = Ph, R′ = H) and hydrazine gave a high-melting yellow compound of the empirical formula $C_{10}H_9ON_3S$, which was characterized as its monomethyl derivative and may be 3-mercapto-6-keto-5-benzylidene-1 : 2 : 5 : 6-tetrahydro-1 : 2 : 4-triazine (XVII).

## Experimental.

1-*Amino*-2-*mercapto*-2-*phenylpropionamide Hydrochloride*.—2-Mercapto-5-phenylthiazoline-4-carboxyamide (10 g.) (Chatterjee, Cook, Heilbron, and Levy, *J.*, 1948, 1337) in 2N-aqueous sodium hydroxide (25 c.c.) was treated with methyl sulphate (5·6 g.) and kept at 0° for 12 hours. 2-*Methylthio*-5-*phenylthiazoline*-4-*carboxyamide* (6 g.), which separated, crystallized from aqueous methanol as hexagonal plates, m. p. 93° (Found : C, 51·9; H, 5·1. $C_{11}H_{12}ON_2S_2$ requires C, 52·4; H, 5·1%). Clean aluminium foil (6 g.) was amalgamated in 3% aqueous mercuric chloride for 10 minutes and washed with water and methanol. To it was added a solution of the 2-methylthio-derivative (3 g.) in ethanol (100 c.c.), methanethiol being evolved. When reaction was complete, the liquid was boiled and filtered hot, and the alumina washed with boiling ethanol (50 c.c.). The filtrate and washings were evaporated to 50 c.c. and kept at 0° until separation of 5-*phenylthiazolidine*-4-*carboxyamide* (1 g.) was complete. It separated from water as colourless rods, m. p. 180° (Found : N, 13·1. $C_{10}H_{12}ON_2S$ requires N, 13·5%). It was soluble in hot 2N-hydrochloric acid, the *hydrochloride* separating on cooling as short colourless needles, m. p. 223—224° (decomp.) (Found : C, 48·9; H, 5·7. $C_{10}H_{12}ON_2S$,HCl requires C, 49·1; H, 5·4%). A hot solution of the thiazolidine (150 mg.) in water (15 c.c.) was poured into hot 5% aqueous mercuric chloride (20 c.c.), a copious white curd separating and formaldehyde being evolved. The

mercaptide was washed with water, dried, and decomposed by passage of hydrogen sulphide into the methanol suspension. Mercuric sulphide was removed and the filtrate evaporated to dryness. The residue was dissolved in dry methanol, the solution filtered, and the product (70 mg.) precipitated with ether. 1-*Amino*-2-*mercapto*-2-*phenylpropionamide hydrochloride* separated from methanol–ether as a methanolate in plates, m. p. 227—229° (decomp.) (Found: C, 45·2; H, 6·2. $C_9H_{12}ON_2S,HCl,CH_4O$ requires C, 45·0; H, 6·4%). In aqueous sodium hydrogen carbonate, the compound gave a transient purple colour with ferric chloride, which became deep red, slowly fading.

*Reaction of Ammonia with* 2-*Mercapto*-4-p-*methoxybenzylidenethiazolin*-5-*one*.—A solution of the thiazolinone (18 g.) in aqueous ammonia (50 c.c.) (*d* 0·880) was heated on a steam-bath for 5 minutes, diluted with water (100 c.c.), and acidified after 1 hour with concentrated hydrochloric acid. The pale yellow powder (18 g.) was extracted twice with boiling water (1 l.), leaving a white residue (3·5 g.), m. p. 220°. The extracts deposited pale yellow plates of α-2-*mercapto*-5-p-*methoxyphenylthiazoline*-4-*carboxyamide* (11 g.), m. p. 175° (Found: C, 49·4; H, 4·4. $C_{11}H_{12}O_2N_2S_2$ requires C, 49·3; H, 4·5%). The water-insoluble residue of the *β-form* of the amide recrystallized from glacial acetic acid as colourless needles (3 g.), m. p. 223—224° (decomp.) (Found: C, 49·4; H, 4·7%).

5-p-*Methoxyphenylthiazolidine*-4-*carboxyamide*.—A solution of the above α-form (8 g.) in 2N-potassium hydroxide (16 c.c.) was diluted to 50 c.c. with crushed ice, treated with methyl sulphate (3·5 g.), and kept at 0° for 12 hours. 2-*Methylthio*-5-p-*methoxyphenylthiazoline*-4-*carboxyamide* crystallized from aqueous ethanol as colourless needles (4·1 g.), m. p. 90° (Found: C, 51·6; H, 5·0. $C_{12}H_{14}O_2N_2S_2$ requires C, 51·1; H, 5·0%). The methylthio-derivative (2 g.) was reduced in methanol (50 c.c.) with amalgamated aluminium (4 g.) to give 5-p-*methoxyphenylthiazolidine*-4-*carboxyamide* (0·8 g.), which formed colourless rods (from water), m. p. 180° (Found: C, 54·7; H, 5·6. $C_{11}H_{14}O_2N_2S$ requires C, 54·3; H, 5·9%).

*Action of Nitrous Acid on* 5-p-*Methoxyphenylthiazolidine*-4-*carboxyamide*.—To a solution of the thiazolidine (0·5 g.) in 2N-hydrochloric acid (5 c.c.) at 5° was added a cold solution of sodium nitrite (0·14 g.) in water (5 c.c.). After 1 hour at room temperature, the solution was neutralized with sodium hydrogen carbonate, 5-p-*methoxyphenylthiazolidine*-4-*carboxyamide* 1-*oxide* (0·3 g.) separating. The compound crystallized from aqueous methanol in short needles, m. p. 186° (Found: C, 51·8; H, 5·6. $C_{11}H_{14}O_3N_2S$ requires C, 52·0; H, 5·6%).

*Reaction of Ammonia with* 2-*Mercapto*-4-p-*acetoxybenzylidene*-5-*thiazolinone*.—The deep-red solution of 2-mercapto-4-*p*-acetoxybenzylidene-5-thiazolinone (10 g.) in aqueous ammonia (*d* 0·88) (30 c.c.) was heated on the steam-bath for 1 hour and cooled to 0° for 2 hours. The scarlet crystals (0·8 g.) became yellow at 150° and melted at 308° (decomp.). The product was dissolved in warm glacial acetic acid, whereupon a voluminous yellow precipitate appeared almost immediately. 2-Thio-4-*p*-hydroxybenzylidenehydantoin separated from hot water as yellow needles, m. p. 308°, of a hemihydrate (Found: C, 52·4; H, 4·0; N, 12·1. Calc. for $C_{10}H_8O_2N_2S,0·5H_2O$: C, 52·1; H, 4·1; N, 12·2%). Boyd and Robson (*Biochem. J.*, 1935, **29**, 542) give m. p. 305° for the anhydrous material.

The filtrate from the scarlet product above was acidified with concentrated hydrochloric acid, giving an oil. After 18 hours at 0° the aqueous layer was decanted and the residue triturated with a little ethyl acetate, one *isomeride* of 2-*mercapto*-5-p-*hydroxyphenylthiazoline*-4-*carboxyamide* (2·1 g.), m. p. 234°, remaining insoluble. This crystallized from ethanol–light petroleum (b. p. 60—80°) as colourless rhombohedra, m. p. 234° (Found: C, 47·9; H, 4·2; N, 10·6. $C_{10}H_{10}O_2N_2S_2$ requires C, 47·3; H, 4·0; N, 11·0%). The amide was hydrolysed to the corresponding acid (Cook, Harris, Pollock, and Swan, *loc. cit.*).

*Other Preparations of* 2-*Thio*-4-p-*hydroxybenzylidenehydantoin*.—(*a*) 2-Thio-4-*p*-acetoxybenzylidene-5-thiazolinone (1 g.) was dissolved in 0·5N-potassium hydroxide (9 c.c.) and shaken with methyl sulphate (0·5 g.), 2-*methylthio*-4-p-*acetoxybenzylidene*-5-*thiazolinone* separating. The product separated from a little methanol as yellow plates and needles, m. p. 114° (Found: C, 53·6; H, 3·9. $C_{13}H_{11}O_3NS_2$ requires C, 53·3; H, 3·75%). A suspension of this compound (1 g.) in concentrated aqueous ammonia (10 c.c.) was heated at 100° for 1 hour, while methanethiol was evolved. After the mixture had been cooled to 0° for 2 hours, the scarlet material previously obtained (0·6 g.) was removed, treated with warm acetic acid, and recrystallized from water as yellow needles, m. p. and mixed m. p. 307—308°.

(*b*) Glycine (1·5 g.), potassium thiocyanate (2·5 g.), *p*-hydroxybenzaldehyde (3·5 g.), and acetic anhydride (10 c.c.) reacted violently when warmed. The mixture was heated for 1 hour, cooled, and triturated with water. The yellow solid (0·7 g.), when warmed with concentrated aqueous ammonia, gave the scarlet material above, having a transition point at 140—150° and m. p. 303—305° (decomp.).

*Reaction of Ammonia with* 2-*Mercapto*-4-(2-*furfurylidene*)-5-*thiazolinone*.—Piperidine (0·1 c.c.) was added to a solution of redistilled furfuraldehyde (18 g.) and 2-mercapto-5-thiazolinone (25 g.) in boiling glacial acetic acid (200 c.c.). After 2 hours, 2-*mercapto*-4-(2-*furfurylidene*)-5-*thiazolinone* (28 g.) was removed, and a further 2 g. were obtained by dilution of the mother-liquor with water (1 l.). The product crystallized from glacial acetic acid as golden plates, m. p. 186° (Found: C, 45·5; H, 2·5. $C_8H_5O_2NS_2$ requires C, 45·5; H, 2·4%). A solution of the thiazolinone (15 g.) in aqueous ammonia (*d* 0·880) was heated at 100° during 1 hour and kept at 0° for 1 hour. 2-Thio-4-(2-furfurylidene)hydantoin (3·5 g.) was recrystallized from glacial acetic acid and then from water, forming pale yellow needles, m. p. 250° (Found: C, 49·6; H, 3·1; N, 14·3. Calc. for $C_8H_6O_2N_2S$: C, 49·5; H, 3·1; N, 14·4%). Deulofeu (*Anal. Asoc. Quim. Argentina*, 1932, **20**, 190; *Z. physiol. Chem.*, 1932, **204**, 214) gives m. p. 250—251°. The compound gave a bright green colour in warm concentrated sulphuric acid. The filtrate from this material, when acidified with concentrated hydrochloric acid, gave an oil, which solidified to a yellow powder (10·5 g.), m. p. 170—172°. 2-*Mercapto*-5-(2-*furyl*)*thiazoline*-4-*carboxyamide* crystallized from water as colourless laths, m. p. 174—176° (Found: C, 42·5; H, 3·6. $C_8H_8O_2N_2S_2$ requires C, 42·1; H, 3·5%).

*Alternative Preparations of* 2-*Thio*-4-(2-*furfurylidene*)*hydantoin*.—2-Mercapto-4-(2-furfurylidene)-5-thiazolinone (4 g.) was methylated in the usual way with diazomethane to give the *methylthio*-compound (4 g.), which separated from aqueous methanol in yellow hair-like needles, m. p. 74° (Found: C, 47·9; H, 3·2; N, 6·0. $C_9H_7O_2NS_2$ requires C, 48·0; H, 3·1; N, 6·2%). When treated with aqueous ammonia

in the same way as the *p*-acetoxybenzylidene compound, this methylthio-derivative (3 g.) gave 2-thio-4-(2-furfurylidene)hydantoin (1·2 g.) which, on recrystallization from water, formed yellow needles, m. p. and mixed m. p. with the previous material, 250°. The hydantoin (1 g.) was shaken with 0·5N-potassium hydroxide, a potassium salt separating. Methyl sulphate (0·6 g.) was added, and, after 1 hour's shaking, the 2-*methylthio*-derivative (0·6 g.) was collected and recrystallized from aqueous methanol as short yellow needles, m. p. 220° (Found: C, 51·6; H, 3·7. $C_9H_8O_3N_2S$ requires C, 51·9; H, 3·9%). Furfuraldehyde (3 g.), glycine (1·5 g.), potassium thiocyanate (2·5 g.), and acetic anhydride (10 c.c.) were heated at 100° to give a dark brown oil which on being stirred with water yielded the thiohydantoin (1·4 g.). Recrystallization from water gave yellow needles, m. p. and mixed m. p. with the previous material, 250°.

5-(2-*Furyl*)*thiazolidine*-4-*carboxyamide*.—2-Mercapto-5-(2-furyl)thiazoline-4-carboxyamide (10 g.), dissolved in 2N-potassium hydroxide (22 c.c.), was shaken for 0·5 hour with methyl sulphate (4·8 g.), an oil separating. The mixture was kept at 0° overnight and the solid (6·2 g.) recrystallized from aqueous methanol as pale yellow plates, m. p. 103° (Found: C, 44·5; H, 4·1. $C_9H_{10}O_2N_2S_2$ requires C, 44·6; H, 4·1%). The *methylthio*-derivative (5 g.) in methanol (300 c.c.) was added to amalgamated aluminium prepared from aluminium foil (10 g.). Methanethiol was evolved and, after refluxing of the mixture, the alumina was filtered off and the combined filtrates and washings were evaporated to 50 c.c. and kept at 0°; the product (2·5 g.), m. p. 107°, separated slowly. 5-(2-*Furyl*)*thiazolidine*-4-*carboxyamide* formed long colourless rods, m. p. 108°, from hot ethanol (Found: C, 48·4; H, 5·1. $C_8H_{10}O_2N_2S$ requires C, 48·5; H, 5·1%).

*Preparation and Reactions of* 2-*Mercapto*-4-p-*nitro- and* 2-*Mercapto*-4-p-*dimethylamino-benzylidene*-5-*thiazolinone*.—*p*-Nitrobenzaldehyde (12·5 g.) and 2-mercapto-5-thiazolinone (10 g.) were condensed in boiling glacial acetic acid (200 c.c.) containing morpholine (0·1 c.c.) to give 2-*mercapto*-4-p-*nitrobenzylidene*-5-*thiazolinone* (15·5 g.), which recrystallized from glacial acetic acid in orange plates, m. p. 220° (decomp.) (Found: C, 45·0; H, 1·9; H, 10·7. $C_{10}H_6O_3N_2S_2$ requires C, 45·1; H, 2·3; N, 10·5%). Methylation in the usual way with ethereal diazomethane gave the 2-*methylthio*-compound, which formed short orange needles, m. p. 215°, from acetic acid (Found: C, 47·0; H, 3·0. $C_{11}H_8O_3N_2S_2$ requires C, 47·1; H, 2·9%). 2-Mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (2 g.), in aqueous ammonia (*d* 0·880) (15 c.c.) was heated at 100° for 0·5 hour. The *substance* (0·8 g.) was recrystallized from ethanol as purple-red prisms, m. p. 265° (decomp.) (Found: C, 54·7; H, 4·3; N, 18·8. $C_{10}H_9ON_2S$ requires C, 54·8; H, 4·1; N, 19·2%). Namjoshi and Dutt (*J. Indian Chem. Soc.*, 1931, **8**, 241) state that 2-thio-4-*p*-aminobenzylidenehydantoin, prepared by the hydrolysis of its diacetyl derivative, forms yellow needles having no m. p. below 285°. The purple material was soluble in concentrated hydrochloric acid; on neutralization, unchanged starting material was recovered.

*p*-Dimethylaminobenzaldehyde (10 g.), condensed with 2-mercapto-5-thiazolinone (8 g.) in boiling glacial acetic acid (100 c.c.), gave, after dilution with water (700 c.c.), 2-*mercapto*-4-p-*dimethylamino-benzylidene*-5-*thiazolinone* (12·5 g.) which separated from acetic acid as rectangular red plates, m. p. 208° (Found: C, 54·7; H, 4·3. $C_{12}H_{12}ON_2S_2$ requires C, 54·6; H, 4·3%). The compound was soluble in concentrated hydrochloric acid to give a pale yellow solution, and was recovered, unchanged on diluting the solution. The thiazolinone (2·0 g.) was dissolved in aqueous ammonia (*d* 0·88) (20 c.c.) and heated at 100° for 2 hours. The red mass was chromatographed in ethyl acetate on activated alumina, and the red band eluted with ethyl acetate. Evaporation left 2-thio-4-*p*-dimethylamino-benzylidenehydantoin, m. p. 258°. The compound separated as glistening red needles, m. p. 261° (decomp.) (Found: N, 16·4. Calc. for $C_{12}H_{13}ON_3S$: N, 17·0%). Namjoshi and Dutt (*loc. cit.*) give m. p. 252°. Hydrogen sulphide was passed for 24 hours through a suspension of the thiazolinone (5 g.) in methanol (100 c.c.) containing triethylamine, the product (3 g.) having m. p. 130—132°. *Triethylammonium* 2-*mercapto*-5-p-*dimethylaminophenylthiazoline*-4-*thiocarboxylate* separated from methanol as pale yellow plates, m. p. 133° (decomp.) (Found: C, 54·0; H, 7·3; N, 10·9. $C_{15}H_{29}ON_3S_3$ C, 54·1; H, 7·3; N, 10·5%).

2-*Mercapto*-4-iso*propylidene*-5-*thiazolinone*.—Anhydrous zinc chloride (20 g.) and 2-mercapto-5-thiazolinone (20 g.) were heated in acetone (130 c.c.) under reflux for 5 hours. The bright green solution was kept at 0° for 4 hours, to give 2-mercapto-4-*iso*propylidene-5-thiazolinone (16 g.) as bright yellow needles, m. p. and mixed m. p. with authentic material, 211°. A further crop (2 g.), m. p. 208—210°, was obtained by diluting the filtrate with water (130 c.c.).

2-*Mercapto*-5 : 5-*dimethylthiazoline*-4-*carboxyamide*.—2-Mercapto-4-*iso*propylidene-5-thiazolinone (15 g.) was dissolved in aqueous ammonia (*d* 0·88) (100 c.c.), and after 0·5 hour at 100° the solution was cooled and acidified. On stirring, the oil gave the *carboxyamide* as a white powder (15·6 g.), which recrystallized from ethyl acetate–light petroleum (b. p. 40—60°) as small colourless prisms and needles, m. p. 145° (Found: C, 38·3; H, 5·4; N, 14·5. $C_6H_{10}ON_2S_2$ requires C, 37·9; H, 5·3; N, 14·7%). Methyl sulphate (7 c.c.) was added to a solution of the 2-mercaptothiazoline (12 g.) in N-potassium hydroxide (75 c.c.), whereupon the product (9 g.) separated. 2-*Methylthio*-5 : 5-*dimethylthiazoline*-4-*carboxyamide* separated from acetone–light petroleum (b. p. 40—60°) as sparkling rhombic plates, m. p. 206° (Found: N, 13·3. $C_7H_{12}ON_2S_2$ requires N, 13·7%). The methylthio-derivative (1·4 g.) in methanol (40 c.c.) was added to amalgamated aluminium foil (from 0·5 g.). After the initial reaction, the methanolic solution was boiled under reflux for 10 minutes and filtered hot. The alumina was extracted with boiling methanol (2 × 20 c.c.), and the combined filtrates and washings were evaporated to 20 c.c. and kept at 0° for 24 hours. Crude 2-*thio*-3 : 5 : 5-*trimethylthiazolidone*-4-*carboxyamide* (0·5 g.) had m. p. 198—200°, undepressed on admixture with starting material. Recrystallized from water, it formed long colourless rods, m. p. 200° (Found: C, 41·4; H, 6·1; N, 13·4. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7%). The starting material dissolved in water only on prolonged boiling, methanethiol being evolved but no crystalline material separating on cooling.

*Reaction of* 2-*Mercapto*-4-iso*propylidene*-5-*thiazolinone with Dimethylamine*. [With E. FREDERIKSEN].—A solution of the thiazolinone (5 g.) in 33% aqueous dimethylamine (25 c.c.) was heated for 0·5 hour at 100°, and cooled. The product (3·7 g.), m. p. 185° (decomp.), was removed. It was insoluble in alkali and readily soluble in acid and was recrystallized from ethanol, 2-*dimethylamino*-5 : 5-*dimethyl*-

*thiazoline-4-carboxydimethylamide* forming colourless crystals, m. p. 185° (Found: C, 52·1; H, 8·4. $C_{10}H_{19}ON_3S$ requires C, 52·4; H, 8·3%). The compound, on treatment with methyl iodide in acetone, yielded the insoluble *methiodide* which crystallized from water–acetone as a hemihydrate, m. p. 110—111° (Found: C, 34·7; H, 6·2. $C_{11}H_{22}ON_3SI,0·5H_2O$ requires C, 34·6; H, 6·1%).

2-*Thio*-4-cyclo*pentylidenehydantoin*.—A solution of 2-mercapto-4-*cyclo*pentylidene-5-thiazolinone (1 g.; Cook and Pollock, *loc. cit.*) in aqueous ammonia (*d* 0·880) (5 c.c.) was heated at 100° for 0·5 hour. The *thiohydantoin* was recrystallized from acetic acid, forming colourless needles, m. p. 252° (decomp.) (Found: C, 52·2; H, 5·6; N, 15·0. $C_8H_{10}ON_2S$ requires C, 52·7; H, 5·6; N, 15·4%).

*Reactions with* 2-*Mercapto*-4-iso*butylidene*-5-*thiazolinone*. The thiazolinone (2 g.; Billimoria and Cook, *J.*, 1949, 2323) in aqueous ammonia (*d* 0·880) (20 c.c.) was heated at 100° for 1 hour and then kept at room temperature for 18 hours. 2-*Mercapto*-5-iso*propylthiazoline*-4-*carboxyamide* (1·2 g.) formed colourless plates, m. p. 131°, from hot water (Found: C, 41·5; H, 5·9; N, 13·7. $C_7H_{12}ON_2S_2$ requires C, 41·2; H, 5·9; N, 13·7%). The original thiazolinone was warmed in 30% aqueous dimethylamine (20 c.c.) for 1 hour, and the solution cooled and acidified with hydrochloric acid. The corresponding *dimethylamide* (1·5 g.) recrystallized from hot water as colourless plates, m. p. 144° (Found: C, 46·3; H, 6·9. $C_9H_{16}ON_2S_2$ requires C, 46·6; H, 7·0%). A solution of 2-mercapto-4-*iso*butylidene-5-thiazolinone (2·0 g.) and aniline (1·0 g.) in methanol (30 c.c.) was refluxed for 24 hours. The colourless gum remaining on evaporation was treated with 2N-hydrochloric acid and dissolved in acetone (10 c.c.). 2-*Thio*-3-*phenyl*-5-iso*butylidenehydantoin* was precipitated on addition of water (20 c.c.) and separated from aqueous methanol in colourless plates, m. p. 209° (Found: C, 63·1; H, 5·8. $C_{13}H_{14}ON_2S$ requires C, 63·4; H, 5·7%).

*Reactions with* 2-*Mercapto*-4-*benzylidene*-5-*thiazolinone*.—The thiazolinone (2 g.) in 40% aqueous dimethylamine (10 c.c.) was heated at 100° for 0·5 hour, cooled, diluted with water (10 c.c.), and filtered. The sticky residue was extracted with boiling methanol (20 c.c.), the mixture cooled to 0° for 1 hour, and the product (0·7 g.), m. p. 190°, filtered off. 2-Thio-3-methyl-5-benzylidenehydantoin recrystallized from acetic acid as pale yellow needles, m. p. 207° (Found: C, 60·7; H, 4·3; N, 13·0. Calc. for $C_{11}H_{10}ON_2S$: C, 60·6; H, 4·6; N, 12·8%). The filtrate from the reaction mixture was acidified with hydrochloric scid, and the product crystallized from aqueous methanol as brown needles (0·4 g.), m. p. 165°, of the methylamide which probably contained a small amount of the hydantoin as impurity. 2-Mercapto-4-benzylidene-5-thiazolinone (2 g.) was heated at 100° in 30% aqueous dimethylamine (10 c.c.) for 0·5 hour. The dark oil was extracted with chloroform (20 c.c.) and the aqueous layer extracted with chloroform (20 c.c.) and acidified with 2N-hydrochloric acid to give a sticky brown solid, which was rubbed with methanol to give 2-*mercapto*-5-*phenylthiazoline*-4-*carboxydimethylamide* (0·5 g.); the last recrystallized from aqueous methanol as colourless needles, m. p. 191—192° (Found: C, 54·2; H, 5·4. $C_{12}H_{14}ON_2S_2$ requires C, 54·1; H, 5·3%). The combined chloroform extracts were evaporated to leave an oil which was stirred with 2N-hydrochloric acid to give a further quantity of the dimethylamide (0·9 g.), m. p. and mixed m. p. 191°. 2-Mercapto-4-benzylidenethiazolin-5-one (3·0 g.) and aniline (10 c.c.) were heated together at 100° for 0·5 hour, and the mixture cooled to 0° and treated with 2N-hydrochloric acid. The yellow oil gave, on trituration with methanol (10 c.c.), a pale yellow solid, which on treatment with hot acetic acid (50 c.c.) and cooling yielded *trans*-2-thio-3-phenyl-5-benzylidenehydantoin (1·2 g.); this separated from acetic acid as pale yellow needles, m. p. 206—207° (Found: C, 69·0; H, 4·3; N, 9·6. Calc. for $C_{16}H_{12}ON_2S$: C, 68·6; H, 4·3; N, 10·0%), $\lambda_{max.}$ (in methanol): 248 and 370 mμ., $E^{1\%}_{1cm.}$ = 470 and 1220 respectively.

The acetic acid filtrate was diluted with water (50 c.c.) to give the cis-*isomer*, which recrystallized from aqueous methanol as fine yellow needles, m. p. 160° (Found: C, 68·3; H, 4·8; N, 10·5%), $\lambda_{max.}$ (in methanol) 228, 249, 280, and 370 mμ., $E^{1\%}_{1cm.}$ = 530, 500, 530, and 800 respectively.

The *trans*-isomer (1·0 g.) in 10% sodium hydroxide solution (30 c.c.) was treated with methyl sulphate; the resultant 2-methylthio-derivative (1·0 g.) recrystallized from methanol as pale yellow prisms, m. p. 151° (Found: C, 68·6; H, 4·9; N, 9·4. Calc. for $C_{17}H_{14}ON_2S$: C, 68·4; H, 4·8; N, 9·5%).

*Reaction between Aniline and* 2-*Mercapto*-4-p-*nitrobenzylidene*-5-*thiazolinone*.—The thiazolinone (3·5 g.) was heated with aniline (10 c.c.) at 100° for 1 hour, and the mixture cooled to 0° and treated with 2N-hydrochloric acid. Treatment of the gummy product with methanol gave 2-*thio*-3-*phenyl*-5-p-*nitrobenzylidenehydantoin* (2·7 g.) which from aqueous acetic acid formed a hemihydrate, m. p. 266° (decomp.) (Found: C, 57·7; H, 3·8; N, 12·4. $C_{16}H_{11}O_3N_3S,0·5H_2O$ requires C, 57·5; H, 3·6; N, 12·6%).

*Reactions with* 2-*Aminopyridine and Pyridine*.—2-Mercapto-4-benzylidene-5-thiazolinone (2·1 g.) and 2-aminopyridine (0·95 g.) were heated in refluxing methanol (30 c.c.) for 12 hours. Dilution with water (60 c.c.) gave a gum which yielded *methyl* 2-*thio*-5-*phenylthiazolidine*-4-*carboxylate* (2·0 g.) on crystallization from ether–light petroleum (b. p. 40—60°). The compound separated from aqueous methanol as colourless hexagonal plates, m. p. 109° (Found: C, 52·6; H, 4·4; N, 5·5. $C_{11}H_{11}O_2NS_2$ requires C, 52·2; H, 4·4; N, 5·5%).

The original thiazolinone (1·0 g.) and pyridine (0·5 c.c.), heated in refluxing methanol (10 c.c.) for 12 hours, acidified with acetic acid and diluted with water (30 c.c.) gave a gum which was crystallized from aqueous methanol to yield the methyl ester (0·8 g.) identical with the material described above.

A solution of 2-mercapto-4-*p*-methoxybenzylidene-5-thiazolinone (3·8 g.) and 2-aminopyridine (1·4 g.) in refluxing methanol (25 c.c.) was heated for 12 hours and worked up in the same way, to give a gum which solidified under methanol to give methyl 2-thio-5-*p*-methoxyphenylthiazolidine-4-carboxylate (2·7 g.), m. p. and mixed m. p. with authentic material, 110° after recrystallization from chloroform–light petroleum (b. p. 40—60°) (Cook, Harris, Pollock, and Swan, *loc. cit.*).

2-Mercapto-4-(2-furfurylidene)-5-thiazolinone (2·5 g.) and 2-aminopyridine (1·5 g.), heated in refluxing methanol (20 c.c.) for 12 hours and diluted with water (30 c.c.), gave a black oil, which on repeated precipitation from aqueous methanol (charcoal) yielded *methyl* 2-*thio*-5-(2-*furyl*)*thiazolidine*-4-*carboxylate* (0·5 g.) as yellow rods or prisms, m. p. 89° (Found: C, 44·7; H, 3·9; N, 5·8. $C_9H_9O_3NS_2$ requires C, 44·5; H, 3·7; N, 5·8%).

A solution of 2-mercapto-4-*p*-nitrobenzylidene-5-thiazolinone (5·2 g.) and 2-aminopyridine (1·8 g.) was heated in methanol (50 c.c.) for 12 hours and diluted with water (50 c.c.), to give a yellow gum which crystallized under methanol. *Methyl 2-thio-5-p-nitrophenylthiazolidine-4-carboxylate* (4·8 g.) separated from ethanol as pale yellow rods, m. p. 148—149° (Found: C, 44·3; H, 3·5; N, 9·6. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4%). The thiazolidine (2·9 g.), treated in 5% sodium hydroxide solution (10·5 c.c.) with methyl sulphate (0·6 c.c.) and kept at 0° for 24 hours, yielded *2-methylthio-5-p-nitrophenylthiazoline-4-carboxylic acid* (2·1 g.). The acid recrystallized from methanolic acetic acid in massive golden cubes, m. p. 167° (Found: C, 44·6; H, 3·7; N, 9·2. $C_{11}H_{10}O_4N_2S_2$ requires C, 44·3; H, 3·4; N, 9·4%).

*3-Mercapto-6-keto-5-benzylidene-1 : 2 : 5 : 6-tetrahydro-1 : 2 : 4-triazine.*—2-Mercapto-4-benzylidene-5-thiazolinone (1·5 g.) and hydrazine hydrate (2 c.c.) were heated together in methanol (10 c.c.) under reflux for 1 hour, hydrogen sulphide being evolved. The solution was diluted with ice, which precipitated a sticky solid (*A*). This crystallized under 2N-hydrochloric acid to give the *triazine* (0·2 g.), which was recrystallized from acetic acid as yellow rods, m. p. 251°. The hydrochloric acid filtrate gave a small precipitate, m. p. >300°, on neutralization with sodium hydrogen carbonate. The original aqueous solution (decanted from solid *A*) was kept at room temperature for 48 hours, while further material (0·7 g.), m. p. 250°, alone and mixed with the previously-obtained material, separated (Found: C, 54·8; H, 4·4. $C_{10}H_9ON_3S$ requires C, 54·8; H, 4·1%). Methylation in alkaline solution gave the *3-methylthio*-derivative, which recrystallized from aqueous methanol as yellow rods or prisms, m. p. 227° (decomp.) (Found: C, 56·6; H, 4·9. $C_{11}H_{11}ON_3S$ requires C, 56·7; H, 4·8%).

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