593. *Cyclisation, Ring-fission, and Acyl-migration Reactions in the Thiazoline Field.*

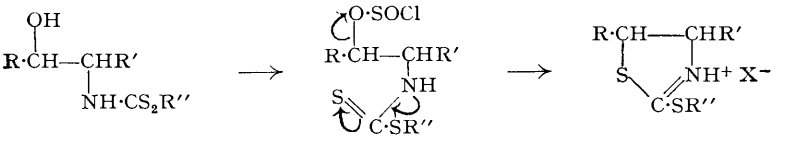
By J. C. Crawhall and D. F. Elliott.

Some *S*-substituted 2-mercapto-Δ^2-thiazolines have been prepared for a study of hydrolytic fission of the thiazoline ring. The mechanisms involved in thiazoline ring formation and ring fission, which have been discussed, have a direct bearing on recent theories regarding acyl migrations and intramolecular displacements in molecules containing contiguous amino- and hydroxy-groups. Somewhat unexpected was the discovery of the dual mechanism involved in the cyclisation of certain *N*-thioacylamino-alcohols with thionyl chloride; this demonstrates the need for caution in the stereochemical interpretation of results obtained with this reagent in the field of acylated amino-alcohols. During this work some dithiolcarbonic acid derivatives and 2-ketothiazolidines have been prepared.

Linderström-Lang and Jacobsen (*Compt. rend. Lab. Carlsberg, Sér. chim.*, 1940, **23**, 289) studied the fission of the ring in 2-methyl-Δ^2-thiazoline under hydrolytic conditions and found that the main product was 2-acetamidoethanethiol, resulting from cleavage of the ring between the sulphur atom and the 2-carbon atom, but the presence of a certain amount of 2-acetylthioethylamine in the product was inferred from analytical data. Recently, an example of exclusive cleavage of the Δ^2-thiazoline ring between $C_{(2)}$ and the nitrogen atom was recorded (Crawhall and Elliott, *J.*, 1951, 2071). It was of interest, therefore, to prepare a number of benzylthio- and methylthio-Δ^2-thiazolines and study their reactions. During this work some facts emerged which have a direct bearing on the various mechanisms involved in intramolecular displacements and acyl migrations in amino-alcohols. Some observations have also been made on the structure of compounds prepared by

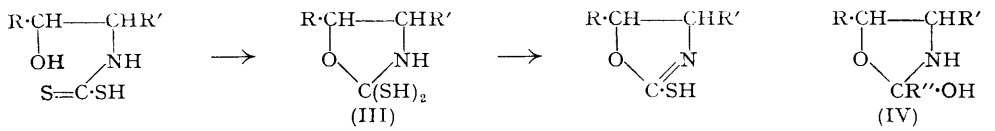
Niederl and Hart (*J. Amer. Chem. Soc.*, 1942, **64**, 2487), and considered to be 2-arylthio-Δ^2-thiazolines.

Δ^2-Thiazolines (cf. II) were prepared from ethanolamine, 2-aminopropan-1-ol, 1-aminopropan-2-ol, and 3-aminobutan-2-ol by conversion into esters (I) of dithiocarbamic acid by carbon disulphide and benzyl chloride or methyl iodide in the presence of triethylamine and pyridine, followed by cyclisation with thionyl chloride (cf. Crawhall and Elliott, *loc. cit.*). This reagent generally gave better results than either phosphorus tribromide or alcoholic hydrogen chloride, although competing reactions were observed in two instances (see below).



(I) (II)

It is noteworthy that, when treated with carbon disulphide and alcoholic alkali, amino-alcohols carrying substituents attached to the same carbon atom as the hydroxyl group are generally converted into 2-mercapto-oxazolines (Bruson and Eastes, *J. Amer. Chem. Soc.*, 1937, **59**, 2011; Hopkins, *Canadian J. Res.*, 1942, **20**, *B*, 268; Maquenne and Roux, *Compt. rend.*, 1902, **134**, 1589; Roux, *Ann. Chim.*, 1904, **1**, 72). Ethanolamine, however, gives 2-mercapto-Δ^2-thiazoline (Knorr and Roessler, *Ber.*, 1903, **36**, 1278). Ettlinger (*J. Amer. Chem. Soc.*, 1950, **72**, 4792) has suggested that the thiazoline is produced by intermediate formation of a xanthate which undergoes internal displacement by the dithiocarbamate ion; the mechanism of this reaction would be analogous to that already postulated for the conversion (I) $\longrightarrow$ (II). Xanthic esters of secondary alcohols (Laakso, *Suomen Kem.*, 1940, **133**, 8; Trieber, *Monatsh.*, 1951, **82**, 53) may be more slowly formed than those from primary alcohols, and 2-mercapto-oxazolines could then be formed by a competing reaction as follows:

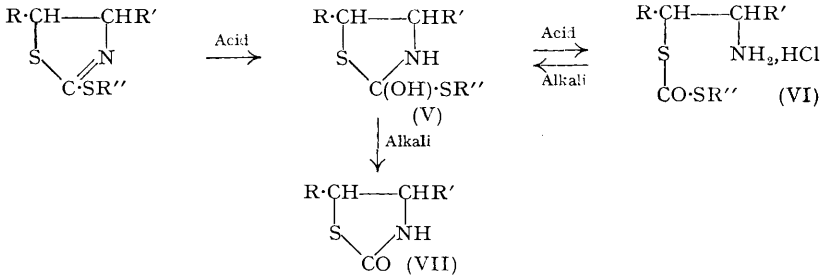


(III) (IV)

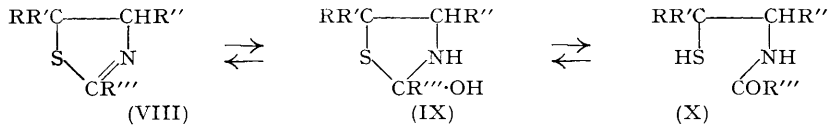
The hypothetical substance (III) closely resembles a compound (IV) first suggested by Bergmann, Brand, and Weinmann (*Z. physiol. Chem.*, 1923, **131**, 1) as the intermediate in the O $\longrightarrow$ N migration of acyl groups in acylated 1 : 2-amino-alcohols. This structure has recently been considered by a number of workers (Phillips and Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 200; Fry, *J. Org. Chem.*, 1950, **15**, 802; Winstein and Boschan, *J. Amer. Chem. Soc.*, 1950, **72**, 4669) and, as Phillips and Baltzly (*loc. cit.*) have pointed out, is probably the intermediate in N $\longrightarrow$ O acyl migration under certain conditions. As a result of the work now described, additional evidence has been obtained that compounds of this structure play an important rôle in acyl migration and related reactions.

The benzylthio- and 2-methylthio-Δ^2-thiazolines, prepared as described above, were all cleaved by hot aqueous acid between the $C_{(2)}$ and the nitrogen atom, yielding derivatives (VI) of dithiolcarbonic acid which were very resistant to further hydrolysis. Purification of the compounds derived from 3-aminobutan-2-ol (cf. VI; R = R′ = Me, R″ = CH_2Ph) and 1-aminopropan-2-ol (cf. VI; R = Me, R′ = H, R″ = CH_2Ph) was complicated by the presence of other substances described below. The basic properties of (VI; R = R′ = H, R″ = CH_2Ph), which can be regarded as representative of this class of compound, were demonstrated by the formation of an acetyl and a formyl derivative. The free bases derived from the hydrochlorides (VI) could not be prepared because in solution above pH 7 immediate liberation of a thiol took place and 2-ketothiazolidine (2-hydroxythiazoline) derivatives (VII) were formed. This reaction could be carried out in the pre-

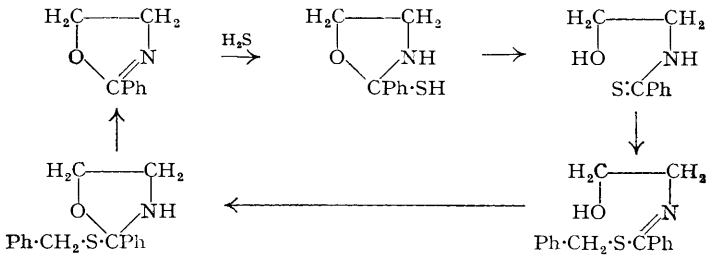
sence of aqueous sodium hydrogen carbonate solution or in a solution of triethylamine in ethanol. These transformations can be explained by the following reaction scheme:



In the 2-alkyl- and 2-aryl-Δ^2-thiazolines on the other hand, the intermediate (IX) is converted into a 2-mercapto-amide under the influence of acid. This shows that the substituent in the 2-position can exert a profound effect on the direction of ring opening. An additional example of ring fission between the sulphur atom and $C_{(2)}$ has been found in this laboratory: 2-phenylthiazoline-4-carboxylic acid (VIII; R = R′ = H, R″ = CO_2H, R‴ = Ph) (Crawhall and Elliott, *loc. cit.*) was rapidly hydrolysed by boiling water, yielding *N*-benzoylcysteine in almost quantitative yield. (This is a convenient method of preparing the rather inaccessible cysteine derivative.) The reversibility of the reaction just described has been demonstrated in derivatives of penicillamine (X; R = R′ = Me, R″ = CO_2H, R‴ = Me or Ph), which are converted by hydrogen chloride in anhydrous solvents into the corresponding thiazolines (Merck and Co. Inc., C.P.S. 237, July 24, 1944); (X; R = R′ = Me, R″ = CO_2H, R‴ = Ph) shows the remarkable property of being cyclised by boiling aqueous hydrochloric acid. These transformations can be interpreted as follows:



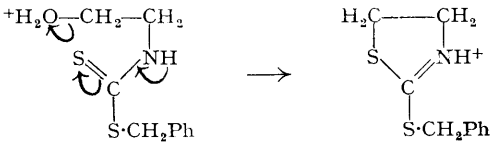
Two reactions of a similar character have been described by Goldberg and Kelly (*J.*, 1948, 1919): 2-phenyl-Δ^2-oxazoline was converted by hydrogen sulphide into *N*-2′-hydroxyethylthiobenzamide and was re-formed when the latter substance was benzylated:



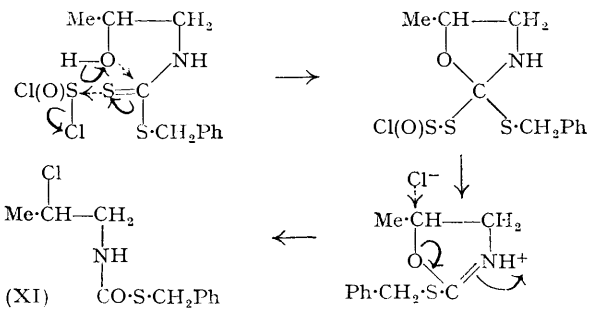
The cyclisation of the thioimidate is analogous to the formation of oxazolines or thiazolines by reaction of 1:2-hydroxy- or 1:2-mercapto-1-amino-compounds with imidic esters (Barber, Gregory, Slack, Stickings, and Woolman, C.P.S. 66, May 24th, 1944; Elliott, *J.*, 1949, 589; Crawhall and Elliott, *loc. cit.*). It will be seen that thiazoline ring formation can take place by two different mechanisms, exemplified by the reactions (I) ⟶ (II) and (X) ⟶ (VIII) or (VI) ⟶ (VII). The essential step in all the above examples, except the reaction (I) ⟶ (II), is the addition of a nucleophilic group to the carbon atom of a carbonyl or thiocarbonyl group. Reactions closely related to these have been described by Davis and Levy (*J.*, 1951, 2419) and Waley and Watson (*Proc. Roy. Soc.*, 1949, *A*, **199**, 499). The first step in the fission of the Δ^2-thiazoline ring is the addition of a hydroxyl group to $C_{(2)}$; the nature of the 2-substituent determines the direction of ring opening. In

the Δ^2-oxazoline series ring fission can occur by a reaction which can be considered as a reversal of the reaction (I) ⟶ (II), namely, nucleophilic attack on $C_{(5)}$ (Fry, *J. Org. Chem.*, 1949, **15**, 438, 802; Winstein and Boschan, *loc. cit.*), but there appear to be no examples of thiazoline ring fission by this mechanism.

Two rather unexpected reactions have been observed during this work. 2-*N*-Dithiocarbobenzyloxyaminoethanol (I; R = R′ = H, R″ = CH_2Ph) on treatment with cold ethanolic hydrogen chloride gave 2-benzylthio-Δ^2-thiazoline (II; R = R′ = H, R″ = CH_2Ph) in excellent yield; from the same reagents in the hot, 2-aminoethyl benzyl dithiolcarbonate hydrochloride (VI; R = R′ = H, R″ = CH_2Ph) was obtained, presumably as a result of cleavage of the thiazoline ring. Cyclisation must have occurred after activation of the hydroxyl group as a hydroxonium ion :



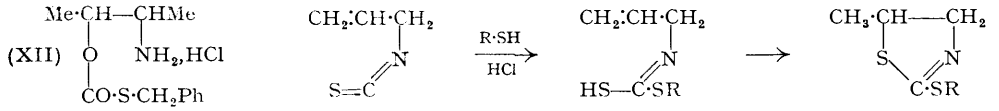
It might have been expected that an oxazoline would have been formed by the alternative mechanism [*e.g.*, (X) ⟶ (VIII)] which operates generally, but not exclusively, when alcoholic hydrogen chloride is used as a reagent on 2-hydroxyalkylamides (Phillips and Baltzly, *loc. cit.*; Welsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3500; Elliott, *Biochem. J.*, 1952, **50**, 542). It is possible that the absence of steric hindrance at the reactive centre encouraged cyclisation by this mechanism. This would explain the fact that the dithiocarbamic esters derived from the substituted ethanolamines gave poor yields of the corresponding thiazolines under the influence of alcoholic hydrogen chloride. In addition to the derivative of dithiolcarbonic acid, already described, a certain amount of 2-chloro-1-thiolcarbobenzyloxyaminopropane (XI) was isolated after treatment of the crude reaction product from (I; R = Me, R′ = H, R″ = CH_2Ph) and thionyl chloride with boiling 6N-hydrochloric acid. It is difficult to visualise the formation of this substance from a thiazoline, and it is concluded that the crude product from the reaction with thionyl chloride contained some oxazoline which was converted into the chloro-compound on treatment with hydrochloric acid. The following reaction scheme, which is in accordance with the above ideas, is suggested :



The possibility that the chloro-compound (XI) was produced directly from the dithiocarbamate is excluded by the fact that the crude product from the thionyl chloride reaction was insoluble in ether whereas (XI) was easily soluble. Unfortunately, all attempts to isolate the oxazoline in a pure state were unavailing. The stability of the chloro-compound towards acid is in keeping with Ehrensvärd's observations (*Nature*, 1947, **159**, 500) on this class of compound. The presence of some oxazoline was also demonstrated in the product resulting from the cyclisation of 3-*N*-dithiocarbobenzyloxyaminobutan-2-ol (I; R = R′ = Me, R″ = CH_2Ph) with thionyl chloride. Samples of the thiazoline (II; R = R′ = Me, R″ = CH_2Ph) which had been distilled only once yielded on hydrolysis with 6N-hydrochloric acid a mixture of 2-amino-1-methyl-*n*-propyl *S*-benzyl thiolcarbonate hydrochloride (XII) and the dithiolcarbonate hydrochloride (VI; R = R′ = Me, R″ = CH_2Ph). The properties of the hydrochloride (XII) were similar to those of the dithiolcarbonic acid

derivatives (VI); it was very resistant to acid hydrolysis and yielded toluene-ω-thiol on treatment with alcoholic triethylamine.

After this work was commenced a publication by Niederl and Hart (*loc. cit.*) came to our notice. As a result of previous researches by Niederl and his collaborators on the condensation of mustard oils with phenols these workers believed that they had obtained arylthio-Δ^2-thiazolines by the condensation of allyl *iso*thiocyanate with thiophenols in the presence of hydrogen chloride:



Niederl and Hart's compounds, however, did not have the properties expected of arylthio-Δ^2-thiazolines; they were stated to be very stable to acid treatment, but were completely hydrolysed in dilute sodium hydrogen carbonate solution, giving a thiophenol and 2-keto-5-methylthiazolidine. These properties were displayed by our dithiolcarbonic acid derivatives (VI), but not by the thiazolines from which they were derived. Niederl and Hart's compounds were thus probably dithiolcarbonic acid derivatives, the more so as the condensation products were dissolved in water and the acid solution evaporated to dryness on the water-bath: our work showed that such treatment would have decomposed the arylthiothiazoline initially formed. Condensation of allyl *iso*thiocyanate with thiophenol under Niederl and Hart's conditions (*loc. cit.*) was therefore repeated, precautions being taken to exclude moisture. After a considerable time a portion of the reaction mixture, which was still liquid, was removed and after a preliminary extraction with ether was treated at once with an excess of sodium picrate. The crystalline picrate so obtained had a melting point different from that of the compound described by Niederl and Hart; it was undoubtedly the picrate of 5-methyl-2-phenylthio-Δ^2-thiazoline which Niederl and Hart believed they had prepared. The free base, obtained from the picrate, was purified by distillation and found to be completely resistant to the action of sodium hydrogen carbonate solution, but it was decomposed by boiling hydrochloric acid, yielding 1-amino-2-propyl *S*-phenyl thiolcarbonate hydrochloride. This substance was found to have the same melting point as the hydrochloride described by Niederl and Hart and was decomposed immediately by sodium hydrogen carbonate solution or by alcoholic triethylamine. In view of our work it is improbable that any of the compounds described by Niederl and Hart were arylthiothiazolines, although thiazolines were produced initially and could have been isolated had these workers been aware of their instability.

Experimental

Amino-alcohols.—2-Aminopropan-1-ol, 1-aminopropan-2-ol, and 3-aminobutan-2-ol were prepared from the corresponding nitro-alcohols (Vanderbilt and Haas, *Ind. Eng. Chem.*, 1940, **32**, 34) by hydrogenation at room temperature/100 atm., Adams's platinum oxide catalyst being used. The resulting amino-alcohols were isolated and purified by crystallisation of their oxalates from ethyl alcohol. No attempt was made to separate the diastereoisomeric forms of 3-aminobutan-2-ol.

2-N-*Dithiocarbobenzyloxyaminoethanol.*—To ethanolamine (10·0 g.) in pyridine (30 ml.), triethylamine (1 mol., 16·6 g.) and carbon disulphide (1·1 mols., 13·7 g.) were added with water-cooling. Considerable heat was evolved. The solution was then cooled to 0° and kept at this temperature for 1 hour; benzyl chloride (1 mol., 20·8 g.) was added, and the solution kept at 0° overnight. The solution was then poured into 3N-sulphuric acid (800 ml.) and extracted with ether. The ethereal extract was washed with 3N-sulphuric acid and sodium hydrogen carbonate solution and dried (Na_2SO_4). After evaporation of the ether, light petroleum (100 ml.; b. p. 40—60°) was added to the residual oil, which rapidly crystallised; the solid (33 g., 90%) had m. p. 55°. Repeated recrystallisation from benzene gave pure 2-N-*dithiocarbobenzyloxyaminoethanol*, m. p. 64° (Found: C, 52·8; H, 5·3; N, 6·3. $C_{10}H_{13}ONS_2$ requires C, 52·9; H, 5·7; N, 6·2%).

2-N-*Dithiocarbobenzyloxyaminopropan*-1-*ol.*—2-Aminopropan-1-ol oxalate (m. p. 127—128°; 20 g.) was suspended in pyridine (90 ml.), triethylamine (50 g., 4 mol.) was added, and the mixture vigorously shaken to disperse any large particles. After 1 hour this mixture was

cooled to 0°, and carbon disulphide (2 mols., 19 g.) was added during 15 minutes with shaking, the temperature being kept below 5°. After 2 hours at 0°, benzyl chloride (1 mol., 16 g.) was added, and the mixture left at 0° overnight. The reaction mixture was then treated as above, and the crude product isolated as an oil (26·7 g., 89%).

1-N-*Dithiocarbobenzyloxyaminopropan-2-ol.*—This was prepared in the same manner as its isomer. 1-Amino-2-propan-1-ol oxalate (m. p. 126°; 20 g.) gave 23·5 g. (79%) of 1-N-*dithiocarbobenzyloxyaminopropan-2-ol*, which was an oil (Found: S, 27·0. $C_{11}H_{15}ONS_2$ requires S, 26·6%).

3-N-*Dithiocarbobenzyloxyaminobutan-2-ol.*—This was prepared both from 3-aminobutan-2-ol and from its oxalate (m. p. 164°) in 94% yield. The *product* was an oil (Found: C, 56·6; H, 7·6; N, 5·3. $C_{12}H_{17}ONS_2$ requires C, 56·5; H, 6·7; N, 5·5%).

Cyclisation of the Dithiocarbamates to Δ^2-*Thiazolines.*—*2-Benzylthio-*Δ^2-*thiazoline.* 2-*N*-Dithiocarbobenzyloxyaminoethanol (10 g.) was added during 15 minutes to thionyl chloride (20 ml., purified as described in *Org. Synth.*, Coll. Vol. II, p. 570) cooled in ice, and the reaction mixture kept at 0° for 1 hour. Excess of thionyl chloride was removed under reduced pressure at 35°. Anhydrous ether (50 ml.) was added to the residual oil, which crystallised when scratched, giving 7·59 g. (82%) of solid, m. p. 130°. Recrystallisation from chloroform–light petroleum (b. p. 40—60°) gave pure 2-*benzylthio-*Δ^2-*thiazoline hydrochloride*, m. p. 138° (Found: Cl, 14·6. $C_{10}H_{12}NClS_2$ requires Cl, 14·5%). To prepare the free base, the hydrochloride was covered with a layer of ether, and excess of sodium hydrogen carbonate solution was added. The ethereal layer was dried (Na_2SO_4) and evaporated. The residual oil was distilled, to give 2-*benzylthio-*Δ^2-*thiazoline*, b. p. 130°/0·05 mm., m. p. 47° (Found: N, 6·9; S, 29·9. $C_{10}H_{11}NS_2$ requires N, 6·7; S, 30·7%).

2-*Benzylthio-5-methyl-*Δ^2-*thiazoline.* 1-*N*-Dithiocarbobenzyloxyaminopropan-2-ol (20·7 g.) in anhydrous ether (15 ml.) was added in small portions to purified thionyl chloride (60 ml.) cooled in ice. After 2 hours at 0°, the thionyl chloride was removed under reduced pressure at 30°. The resulting oil, which was completely insoluble in anhydrous ether, was poured into a saturated aqueous solution of sodium hydrogen carbonate, and the free base isolated by ether. The crude product (13·9 g., 73%) was purified by distillation (b. p. 135°/1 mm., 125°/0·5 mm.) or as its *picrate*, m. p. 161° (Found: C, 45·8; H, 3·5; N, 12·4. $C_{17}H_{16}O_7N_4S_2$ requires C, 45·1; H, 3·5; N, 12·4%). Both these methods involved large losses, probably because the crude oil contained compounds other than the thiazoline.

Crude 2-*N*-dithiocarbobenzyloxyaminopropan-1-ol (26·7 g.) was cyclised in a similar fashion, and the crude thiazoline (22 g., 89%) converted by ethereal hydrogen chloride into 2-*benzylthio-4-methyl-*Δ^2-*thiazoline hydrochloride*, m. p. 80° after crystallisation from chloroform–ether (Found: C, 50·7; H, 5·8; N, 5·5. $C_{11}H_{14}NClS_2$ requires C, 50·9; H, 5·4; N, 5·4%).

2-*Benzylthio-4*: 5-*dimethyl-*Δ^2-*thiazoline*, similarly prepared, had b. p. 118°/0·05 mm. (Found: C, 60·6; H, 6·7; N, 5·9. $C_{12}H_{15}NS_2$ requires C, 60·8; H, 6·3; N, 5·9%). The *picrate* had m. p. 128° (Found: N, 12·0. $C_{18}H_{18}O_7N_4S_2$ requires N, 12·0%).

The corresponding 2-methylthio-Δ^2-thiazolines were prepared from 2-*N*-dithiocarbomethoxyaminoethanol and its homologues, which were used in the crude state. 2-Methylthio-Δ^2-thiazoline had b. p. 46°/14 mm. (Gabriel, *Ber.*, 1889, **22**, 1153, gives b. p. 216—217°/760 mm.) (Found: N, 10·5. Calc. for $C_4H_7NS_2$: N, 10·5%). The *picrate* had m. p. 123° (Found: N, 15·5. $C_{10}H_{10}O_7N_4S_2$ requires N, 15·5%). 5-*Methyl-2-methylthio-*Δ^2-*thiazoline picrate* had m. p. 122° (Found: N, 14·5; S, 16·2. $C_{11}H_{12}O_7N_4S_2$ requires N, 14·9; S, 17·0%). The free base has been prepared previously by Hirsch (*Ber.*, 1890, **23**, 967). 4: 5-*Dimethyl-2-methylthio-*Δ^2-*thiazoline picrate* had m. p. 121° (Found: N, 14·6. $C_{12}H_{14}O_7N_4S_2$ requires N, 14·4%).

Alternative Methods of Cyclisation of 2-N-*Dithiocarbobenzyloxyaminoethanol.*—(*a*) 2-*N*-Dithiocarbobenzyloxyaminoethanol (0·5 g.) was heated in a 3N-solution of hydrogen chloride in anhydrous methyl alcohol (6 ml.) at 105° for 6 hours. The solution was then evaporated, leaving a crystalline residue (0·4 g.), m. p. 164°, raised by recrystallisation from acetic acid to 175°. This substance was identical with an authentic specimen of 2-aminoethyl *S*-benzyl thiolcarbonate hydrochloride.

(*b*) 2-*N*-Dithiocarbobenzyloxyaminoethanol (3 g.) was dissolved in anhydrous ethyl alcohol at 0° which had previously been saturated with anhydrous hydrogen chloride. This solution was kept at 0° overnight, and the alcohol distilled off under reduced pressure. A crystalline solid (2·8 g.), m. p. 138°, remained, identical with 2-benzylthiothiazoline hydrochloride prepared by the thionyl chloride cyclisation.

(*c*) 2-*N*-Dithiocarbobenzyloxyaminoethanol (3 g.) was dissolved in anhydrous ether (10 ml.), and phosphorus tribromide (1·1 mols.; 4 g.) was added dropwise. A vigorous reaction occurred with precipitation of a white solid. After 30 minutes the solid was filtered off and dried in a

vacuum-desiccator over sodium hydroxide. The yield was 3·92 g. (theoretical yield for 2-benzylthiothiazoline hydrobromide is only 3·8 g.), m. p. 164° (Found: Br, 25·4. Calc. for $C_{10}H_{12}NBrS_2$: Br, 27·6%). It is probable that the discrepancies in yield and analysis were the result of contamination by phosphorus. The hydrobromide was converted into the hydrochloride, which had m. p. 134°.

2-*Aminoethyl Benzyl Dithiolcarbonate Hydrochloride.*—2-Benzylthiothiazoline hydrochloride (12 g.) was heated under reflux with 6N-hydrochloric acid (120 ml.) for 4 hours, the solution was cooled at 0° for 1 hour, and the crystalline solid (11·35 g.; m. p. 175°) filtered off. Recrystallisation from acetic acid gave pure 2-*aminoethyl benzyl dithiolcarbonate hydrochloride*, m. p. 179° (Found: C, 45·2; H, 5·0; N, 5·4; Cl, 13·7. $C_{10}H_{14}ONClS_2$ requires C, 45·6; H, 5·3; N, 5·3; Cl, 13·5%). The formyl derivative was prepared by the method used by Crawhall and Elliott (*loc. cit.*) for this type of compound and had m. p. 94°.

2-*Acetamidoethyl Benzyl Dithiolcarbonate.*—The foregoing dithiolcarbonate hydrochloride (0·26 g.) was dissolved in acetic anhydride (1·5 ml.), hydrated sodium acetate (1 mol., 0·13 g.) was added, and the solution heated on a steam-bath for 30 minutes, then filtered hot and evaporated under reduced pressure, leaving a clear oil (0·22 g., 83%) which crystallised on addition of light petroleum (b. p. 40—60°). The *acetyl* derivative, recrystallised from ligroin–benzene (9 : 1), had m. p. 83° (Found: C, 53·7; H, 5·5; N, 5·3. $C_{12}H_{15}ONS_2$ requires C, 53·5; H, 5·6; N, 5·2%).

2-*Aminopropyl Benzyl Dithiolcarbonate Hydrochloride.*—Crude 2-benzylthio-4-methylthiazoline (22 g.) was heated under reflux with 6N-hydrochloric acid (200 ml.) for 6 hours. The solution was allowed to cool to room temperature, and the aqueous layer decanted from the lower layer of oil. The acid layer was left overnight at 0°. A white crystalline solid (2·24 g.) appeared. This was the *dithiolcarbonate hydrochloride*, m. p. 122—123° (Found: C, 47·0; H, 5·8; N, 4·8. $C_{11}H_{16}ONClS_2$ requires C, 47·7; H, 5·8; N, 5·0%). The oil resulting from the hydrolysis was added to water (200 ml.), and the solution extracted with ether (200 ml.). The aqueous layer was evaporated to small bulk, yielding an additional crop (12·63 g.) of the dithiolcarbonic acid derivative which had m. p. 122° after two crystallisations from ethyl acetate.

2-*Aminoethyl Methyl Dithiolcarbonate Hydrochloride.*—This was obtained from the hydrolysis of 2-methylthiothiazoline by 6N-hydrochloric acid in the same manner as the corresponding benzyl derivative. Recrystallisation from acetic acid gave the pure *dithiolcarbonate hydrochloride*, m. p. 156° (Found: N, 7·5. $C_4H_{10}ONClS_2$ requires N, 7·5%).

1-*Amino*-2-*propyl Benzyl Dithiolcarbonate Hydrochloride.*—(*a*) 2-Benzylthio-5-methylthiazoline picrate (3·5 g.) was suspended in water (20 ml.), and the free thiazoline liberated by addition of ethanolamine (2 mol., 0·47 g.) and thorough shaking according to the method of Kaye, Kogon, and Burbont (*J. Amer. Chem. Soc.*, 1950, **72**, 5752). The thiazoline was isolated by ether-extraction, evaporation, and extraction from the last traces of picric acid with light petroleum (b. p. 40—60°). The clear oil (1·58 g.) was heated under a reflux condenser with 6N-hydrochloric acid (15 ml.) for 6 hours. After cooling, the solution was made homogeneous by addition of ethyl alcohol to a total volume of 30 ml. An aliquot (1·5 ml.) was directly titrated by iodine solution and gave a very small value, but when another aliquot (1·5 ml.) was first basified with 3N-sodium hydroxide, kept for 2 minutes in a stoppered flask, acidified with concentrated hydrochloric acid, and titrated with iodine, 86% of the theoretical amount was consumed. This iodine consumption was due to the formation of a ketothiazolidine from the dithiolcarbonic acid derivative under the influence of alkali with liberation of toluene-ω-thiol, and shows that at least 86% of the dithiolcarbonate had been formed. The remainder of the alcoholic solution was evaporated to dryness, and the crystalline residue leached with acetone. A further crop of solid was obtained by addition of ether to the acetone washings. The combined solids (1·03 g., 53%) were crystallised from 6N-hydrochloric acid to give a product, m. p. 123°, identical with that described below.

(*b*) Crude 2-benzylthio-5-methylthiazoline (13·92 g.) was heated under reflux with 6N-hydrochloric acid (100 ml.) for 6 hours. After cooling, the acid solution was decanted from the lower layer of oil, which was then dissolved in ether; the solution was dried, and light petroleum added, giving a crystalline solid, m. p. 60—62° (1·0 g.). Crystallisation from light petroleum (b. p. 40—60°) raised the m. p. to 64° (Found: C, 54·8; H, 5·85; N, 5·3; Cl, 14·4; S, 13·7. $C_{11}H_{14}ONClS$ requires C, 54·4; H, 5·75; N, 5·7; Cl, 14·6; S, 13·2%). This compound was formulated as 2-*chloro*-1-*thiolcarbobenzyloxyaminopropane* because it contained non-ionic chlorine and liberated toluene-ω-thiol on treatment with caustic alkali, but gave none with sodium hydrogen carbonate or with an alcoholic solution of triethylamine.

The acid solution was evaporated, and the residual oil dried in a vacuum-desiccator. It was then dissolved in an equal volume of glacial acetic acid, and anhydrous ether added, giving a precipitate of *1-amino-2-propyl benzyl dithiolcarbonate hydrochloride* (3·04 g.), m. p. 123—124°, which had m. p. 124° after crystallisation from 6N-hydrochloric acid (Found: C, 47·6; H, 5·7; N, 5·1. $C_{11}H_{16}ONClS_2$ requires C, 47·7; H, 5·8; N, 5·05%).

2-Amino-1-methylpropyl Benzyl Dithiolcarbonate Hydrochloride.—2-Benzylthio-4 : 5-dimethylthiazoline (3·02 g.) which had been distilled once and was still impure was heated under reflux with 6N-hydrochloric acid (30 ml.) for 6 hours. On cooling, the *dithiolcarbonate hydrochloride* crystallised (0·7 g.), m. p. 170—174°. The acid was evaporated off, the residual oil dissolved in a small volume of ethanol and, on addition of ether, a second crop (0·52 g.), m. p. 159—165°, was obtained. On careful recrystallisation from 6N-hydrochloric acid the m. p. of both crops was raised to 174°. The pure substance crystallised in elongated rectangular plates (Found: C, 49·4; H, 6·8; N, 4·8. $C_{12}H_{18}ONClS_2$ requires C, 49·5; H, 6·2; N, 4·8%). The alcohol–ether filtrate from the above crystallisation was evaporated, leaving a clear oil (1·72 g.). This was dissolved in acetone, and on addition of successive quantities of ether two further crops, m. p. 90—110° (0·68 g.) and m. p. 80—95° (0·21 g.), were obtained. After isolation, this material was insoluble in acetone and was repeatedly crystallised from 6N-hydrochloric acid, forming flat plates, m. p. 140°. This lower-melting material liberated toluene-ω-thiol after treatment with alcoholic triethylamine, contained ionic chlorine, and is formulated as *2-amino-1-methylpropyl S-benzyl thiolcarbonate hydrochloride* (Found: C, 52·4; H, 6·4; N, 4·9; S, 11·7. $C_{12}H_{18}O_2NClS$ requires C, 52·4; H, 6·5; N, 5·1; S, 11·6%).

The refractive indices of the crystals of the two substances were measured by an immersion method using the polarising microscope. The butane-2-thiol derivative had n^{20} 1·56 and 1·70, and the butan-2-ol derivative 1·555 and 1·61. When the latter substance was ground, no particles of n^{20} 1·70 could be found.

Conversion of the Dithiolcarbonates into 2-Ketothiazolidines.—*2-Ketothiazolidine.* 2-Aminoethyl benzyl dithiolcarbonate hydrochloride (1 g.) was suspended in ethyl alcohol (45 ml.) and N-sodium hydroxide (3 mols., 11·4 ml.) was added, giving a total volume of 58 ml., and the mixture was kept in a stoppered flask for 3 hours. A portion (5 ml.) was then acidified with hydrochloric acid, and the liberated toluene-ω-thiol titrated with 0·1N-iodine; 2·7 ml. were required, representing 87% of the theoretical amount. The remaining solution was neutralised with hydrochloric acid, and the solvent distilled off. The residue was thoroughly extracted with ether, and the ethereal extract evaporated to dryness, leaving a crystalline residue; the yield was 0·33 g. (98%), m. p. 47—49°. Recrystallisation from ether gave pure *2-ketothiazolidine*, m. p. 54°, b. p. 160°/20 mm. (Found: C, 34·8; H, 4·7; N, 13·6. C_3H_5ONS requires C, 35·0; H, 4·8; N, 13·6%). This reaction also occurred in the presence of sodium hydrogen carbonate, but for preparative purposes it was more convenient to use sodium hydroxide. The thiazolidine was obtained in a similar way from the corresponding methyl ester hydrochloride.

2-Keto-4-methylthiazolidine, b. p. 165°/10 mm. (Found: C, 41·8; H, 6·2; N, 11·8. C_4H_7ONS requires C, 41·0; H, 6·0; N, 12·0%), and *2-keto-5-methylthiazolidine*, b. p. 140°/10 mm. (Found: C, 41·5; H, 5·8; N, 12·1%), were prepared similarly, except that alcohol instead of ether was used to extract the crude thiazolidines from sodium chloride.

2-Keto-4 : 5-dimethylthiazolidine.—2-Amino-1-methylpropyl benzyl dithiolcarbonate hydrochloride (2 g.) was shaken in a stoppered flask with N-sodium hydroxide (21 ml., 3 mol.) for 5 minutes, N-hydrochloric acid (24 ml.) was added to the resulting emulsion, and the solution extracted with light petroleum (b. p. 60—80°; 3 × 25 ml.). The aqueous layer was evaporated to dryness under reduced pressure, and the residue extracted with ether (3 × 20 ml.). The extracts were combined and evaporated, and the residual oil was crystallised from ether–light petroleum (b. p. 40—60°). *2-Keto-4 : 5-dimethylthiazolidine* had m. p. 47° (Found: C, 46·4; H, 7·1; N, 10·6; S, 24·6. C_5H_9ONS requires C, 45·8; H, 6·9; N, 10·6; S, 24·5%).

N-Benzoylcysteine.—2-Phenylthiazoline-4-carboxylic acid (2·0 g.) was added to boiling distilled water (100 ml.) under a reflux condenser in an atmosphere of nitrogen. After 15 minutes an aliquot (2·0 ml.) was removed and, after cooling in ice and acidification with dilute hydrochloric acid, was found to consume the amount of iodine expected if complete conversion into *N*-benzoylcysteine had occurred. That the acidification before titration was not responsible for opening the ring was shown by titration of an aliquot which was not acidified. Somewhat more than the theoretical amount was consumed. This is in accordance with Lavine's observation (*J. Biol. Chem.*, 1935, **109**, 141) that titration of cysteine must be conducted in the presence of mineral acid. After cooling of the main solution to 0° overnight, *N*-benzoylcysteine (1·59 g.), m. p. 137° (Fry, *J. Org. Chem.*, 1950, **15**, 439, gives m. p. 136—137°), was filtered off (Found:

N, 6·2. Calc. for $C_{10}H_{11}O_3NS$: N, 6·2%). A second crop (0·32 g.) was obtained by evaporation of the mother-liquors.

Investigation of the Structure of Some Compounds described by Niederl and Hart.—5-Methyl-2-phenylthio-Δ²-thiazoline. Allyl *iso*thiocyanate (9·9 g.) was mixed with thiophenol (1 mol., 11·0 g.) in a crystallising dish in a vacuum-desiccator. The desiccator was evacuated and then filled with anhydrous hydrogen chloride. This process was repeated at intervals of a few days until no more hydrogen chloride appeared to be absorbed. The mixture was then kept in the presence of hydrogen chloride for 2½ months. Even after this time no crystallisation took place. Water was added to a portion of the reaction mixture and after extraction with ether the aqueous layer was treated with a solution of sodium picrate. The precipitate was filtered off, washed with ethanol, and crystallised from ethanol, to give long needles of *5-methyl-2-phenylthio-Δ²-thiazoline picrate*, m. p. 132° (Found : C, 44·2; H, 3·3; N, 12·9. $C_{16}H_{14}O_7N_4S_2$ requires C, 43·8; H, 3·2; N, 12·9%). The picrate was decomposed with ethanolamine in the usual way, to give an oil which was purified by distillation in a short-path vacuum apparatus at 120° (bath-temp.)/0·1 mm., to give pure *5-methyl-2-phenylthio-Δ²-thiazoline* (Found : C, 57·4; H, 5·3; N, 6·9; S, 29·8. $C_{10}H_{11}NS_2$ requires C, 57·4; H, 5·3; N, 6·7; S, 30·7%). The thiazoline gave no thiophenol, as revealed by iodine titration when kept for 1 hour with excess of sodium hydrogen carbonate solution. The pure thiazoline did not give a crystalline hydrochloride.

1-Amino-2-propyl phenyl dithiolcarbonate hydrochloride. (*a*) A portion of the original reaction mixture was boiled with water for 30 minutes and, after cooling, the crystalline precipitate was filtered off and leached with ethanol. Crystallisation from ethanol gave the *dithiolcarbonate hydrochloride*, m. p. 168° (Found : C, 45·6; H, 5·4; N, 5·4. $C_{10}H_{14}ONClS_2$ requires C, 45·7; H, 5·3; N, 5·3%). Niederl and Hart (*loc. cit.*) gave m. p. 171° for the compound which they believed to be 5-methyl-2-phenylthio-Δ²-thiazoline hydrochloride.

(*b*) Pure 5-methyl-2-phenylthio-Δ²-thiazoline was heated under a reflux condenser with 6N-hydrochloric acid for 30 minutes. The solution was evaporated, and the residual oil crystallised by addition of ether to its solution in ethanol. The product had m. p. 166° undepressed on admixture with the previously prepared sample.

The remaining crude reaction mixture, when kept in the presence of moisture, slowly solidified. After 12 months the product was found to be the dithiolcarbonate hydrochloride, m. p. 167°.

Action of alkali. The hydrochloride (0·0252 g.) was suspended in 1% aqueous sodium hydrogen carbonate solution (2 ml.) and the mixture kept for 30 minutes in a stoppered flask. The solution was then acidified with 3N-hydrochloric acid. Titration with iodine revealed that 0·85 mol. of thiophenol had been liberated. A similar result was obtained when the hydrochloride was treated with an alcoholic solution of triethylamine.

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