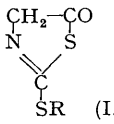
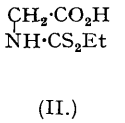
209. *Studies in the Azole Series. Part IV. The Preparation of Some Thiazolones.*

By A. H. Cook, G. Harris, Sir Ian Heilbron, and G. Shaw.

Several α-amino-acids have been converted into *N*-dithiocarbamic esters which have been dehydrated to derivatives of 2-mercaptothiazolone (I; R = H) (Part III, this vol., p. 201), though a comparable *N*-monothiocarbamic ester could not be converted into the corresponding derivative of 2-mercapto-oxazolone. Some reactions of 2-benzylthiothiazolone in particular are described, including attempts to elaborate an analogue of penicillin.

The preparation and properties of 2-mercaptothiazolone (I; R = H) were described in Part III (*loc. cit.*), and the present paper is concerned with some indirect derivatives of this


(I.)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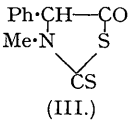
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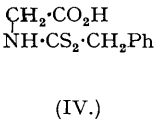
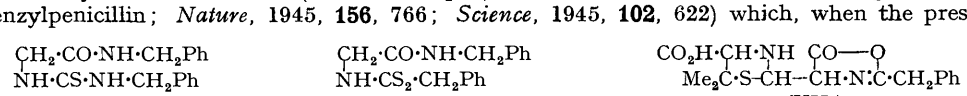

(IV.)

compound where R = a hydrocarbon residue. A search of the literature revealed very few compounds of this kind, and even dithiocarbamic esters of α-amino-acids, which may be expected to yield such thiazolones by dehydration, have rarely been studied. Thus, esters of *N*-dithiocarboxyglycine (*e.g.*, II) have been described (Körner, *Ber.*, 1908, **41**, 1901) and one compound of this kind has been converted into the thiazolone derivative (III) (Fourneau and Vila, *Bull. Soc. chim.*, 1911, **9**, 985).

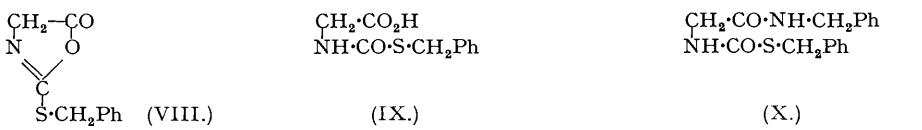
We have now found that the alkali salt of the dithiocarbamic acid resulting from glycine and carbon disulphide readily affords N-*dithiocarbobenzyloxyglycine* (IV) in excellent yield on treatment with benzyl chloride. On treating (IV) with phosphorus tribromide in ether a highly crystalline *hydrobromide* was formed which tended to lose hydrogen bromide in air but there was no doubt from its reactions that it was the salt of 2-benzylthiothiazolone (I; R = CH_2Ph). With diazomethane (cf. Karrer and Widmer, *Helv. Chim. Acta*, 1925, **8**, 203; Karrer and Hussmann, *ibid.*, 1941, **24**, 645) it afforded an unidentified crystalline product which was not the expected free base. When the hydrobromide was shaken with alkali it reverted to compound (IV). With benzylamine in boiling ether it gave benzylamine hydrobromide together with the *bisbenzylamide* (V). On the other hand, the free thiazolone (I; R = CH_2Ph) was obtained by treating the above hydrobromide with aqueous sodium acetate. This compound reacted with benzylamine in the cold to give the *monobenzylamide* (VI).

2-Benzylthiothiazol-5-one (I; R = CH_2Ph) was of interest in relation to penicillin-II (benzylpenicillin; *Nature*, 1945, **156**, 766; *Science*, 1945, **102**, 622) which, when the present



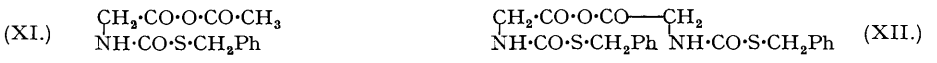
(V.) (VI.) (VII.)

work was carried out, was thought might be (VII). It appeared desirable, therefore, not only to attempt to elaborate (I; R = CH_2Ph) into an analogue of (VII) but also to investigate the corresponding oxazolone (VIII).



(VIII.) (IX.) (X.)

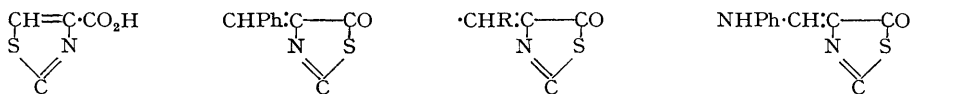
A convenient approach appeared to be *via* the *monothio-ester* (IX) which was obtained in poor yield by oxidising the corresponding dithio-ester with hydrogen peroxide in cold alkali. Attempts to improve this preparation by the interaction of glycine and benzyl chloromonothioformate, Cl·CO·S·CH_2Ph, were unsuccessful. The ester (IX) gave with acetic anhydride in the steam-bath a crystalline compound, $C_{12}H_{13}O_4NS$, which, although it reacted with benzylamine giving the expected *benzylamide* (X), was almost certainly not a derivative of the oxazolone (VIII) but the mixed *anhydride* (XI). When the latter or the ester (IX) was boiled



(XI.) (XII.)

(XIII.) (XIV.)

with acetic anhydride a new crystalline compound, $C_{20}H_{20}O_5N_2S_2$, arose. As the latter gave the same benzylamide (X), it was obviously the *anhydride* (XII). As no better success attended attempts to dehydrate the ester (IX) by means of phosphorus tribromide, attention was redirected to the 2-benzylthiothiazolone series. In the first place attempts were made to apply the relevant reactions to ββ-diethoxyalanine (XIII), treatment of which with carbon disulphide followed by benzyl chloride gave ββ-*diethoxy*-N-*dithiocarbobenzyloxyalanine* (XIV). In attempting to condense the latter compound with ββ-dimethylcysteine (penicillamine) a crystalline acid was formed which, however, was not the anticipated penicillin analogue but gave analytical data corresponding to $C_{11}H_9O_2NS_2$. As the same compound was obtained in the absence of penicillamine, it can only be 2-*benzylthio*-4-*carboxythiazole* (XV) formed by cyclisation. The first indication of a reactive methylene group in a thiazolone (I) was the formation of 2-*ethylthio*-4-*benzylidenethiazolone* (XVI) from the ester (II), benzaldehyde, and acetic anhydride. 2-Ethylthiothiazolone itself (I; R = Et) was formed on treating the ester (II) with acetic anhydride or with phosphorus tribromide, as shown by reaction of the product with benzylamine to give the dibenzylamide (V). Continued work with the ethylthio-derivatives was complicated by the great reactivity of the SEt grouping, attempts to oxidise the ester (II) to the analogue of (IX), for example, failing because of hydrolysis.



(XV.) (XVI.) (XVII.) (XVIII.)

In view of the observed reactivity of the methylene group it was not surprising to find that interaction of 2-benzylthiothiazolone with ethyl orthoformate and acetic anhydride afforded 2-*benzylthio*-4-*ethoxymethylenethiazolone* (XVII; R = OEt), identical with the compound obtained from the derivative (XIV) and acetic anhydride. The compound (XVII; R = OEt) was remarkably reactive. It condensed readily with aniline to give 2-*benzylthio*-4-*anilinomethylenethiazolone* (XVIII), and cold aqueous sodium hydroxide converted it into the corresponding 2-*benzylthio*-4-*hydroxymethylenethiazolone* (XVII; R = OH). Unexpected, however, was the reaction of (XVII; R = OEt) with sulphanilamide, wherein the product was not the expected sulphanilamidomethylenethiazolone for it contained an additional molecule of ethanol.

Acetylsulphanilamide was unaffected under similar conditions, so reaction obviously took place on the nuclear amino-group. As it was shown that ethanol was not introduced during reaction, this product is regarded as the *acyl* compound (XIX). It had no outstanding antibacterial activity.

(XIX.) $OEt{\cdot}CH{:}C{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2(p)$ with $NH{\cdot}CS{\cdot}S{\cdot}CH_2Ph$ on the C atom

(XX.) $CH(CO_2Et)_2$ with $NH{\cdot}CS_2{\cdot}CH_2Ph$

Most of the reactions so far described were paralleled in other series to establish their general nature and for more specific reasons. Thus the interaction of ethyl aminomalonate, carbon disulphide, alkali, and benzyl chloride gave the *benzyl* N-*dithio*-ester (XX), while interaction of *N*-dithiocarbobenzyloxyglycine and benzaldehyde in acetic anhydride gave 2-*benzylthio*-4-*benzylidenethiazolone* (XVII; R = Ph). Again, *N*-dithiocarbethoxyglycine and acetic anhydride afforded 2-ethylthiothiazolone whereas in presence of ethyl orthoformate it gave the corresponding 4-*ethoxymethylene* compound. Similarly, glycine, carbon disulphide, alkali and ethyl chloroformate gave N-*dithiocarbocarbethoxyglycine* (XXI), which with ethyl orthoformate and acetic anhydride afforded the corresponding 2-*carbethoxythio*-4-*ethoxymethylenethiazolone*.

(XXI.) $CH_2{\cdot}CO_2H$ with $NH{\cdot}CS_2{\cdot}CO_2Et$

(XXII.) $CO_2Me{\cdot}CH{-}{-}NH$ $CO{-}S$ with $Me_2C{\cdot}SH$ $CH{=}C{-}N{=}C{\cdot}SR$

When (XVII; R = OH) and penicillamine methyl ester were brought together in cold ethanol the solution soon ceased to give the ferric chloride and nitroprusside colour reactions of the thiol ester. Although the crystalline product, $C_{17}H_{20}O_3N_2S_2$, gave no catalytic polarographic step, yet anodic oxidation in the polarograph left no doubt that it still contained a thiol grouping. It was therefore formulated as the *penicillenate* analogue (XXII; R = CH_2Ph), a constitution which is confirmed by the similarity of the light absorption of the compound to that of compound (XVII; R = OEt), and by its hydrolysis to the hydroxymethylene derivative (XVII; R = OH) by aqueous sodium hydroxide. The "penicillenate" (XXII) had no antibacterial activity and attempts to complete the thiazolidine ring were unsuccessful. A similar *compound* (XXII; R = Et) was obtained from the appropriate ethoxymethylene compound. Finally, penicillamine itself and the ethoxymethylene compound (XVII; R = OEt) gave the *acid* corresponding to (XXII; **R** = CH_2Ph), which was likewise devoid of biological activity.

Experimental.

Dithiocarbobenzyloxyglycine and its Reactions.—Glycine (15 g.) in cold water (50 c.c.) containing potassium hydroxide (23·3 g.) was shaken with carbon disulphide (15·2 g.) until a homogeneous solution was obtained (*ca.* 1½ hours), whereupon shaking was resumed (further 1½ hours) with benzyl chloride (25 g.); the white precipitate which soon appeared on adding benzyl chloride eventually redissolved and the clear yellowish solution was acidified to give the crude ester (45 g., m. p. 145—150°). N-*Dithiocarbobenzyloxyglycine* (IV) was purified by solution in aqueous sodium hydrogen carbonate and reprecipitation with acid, and by crystallisation from ether–light petroleum, separating in colourless needles, m. p. 164° (Found: C, 50·2; H, 4·7; N, 5·75; equiv., by titration, 242. $C_{10}H_{11}O_2NS_2$ requires C, 49·8; H, 4·6; N, 5·8%; equiv., 241). The preceding compound (1 g.) in dioxan (10 c.c.) and ether (30 c.c.) was treated with phosphorus tribromide (1·5 g.). After standing overnight the clusters of needles (1·2 g.) were collected and washed with ether; the compound, believed to be 2-*benzylthiothiazolone hydrobromide*, was free from phosphorus but could not be crystallised without decomposition; it had m. p. 96—97° (Found: C, 41·65; H, 3·95; N, 4·9. $C_{10}H_{10}O_2NSBr$ requires C, 41·65; H, 3·5; N, 4·85. $C_{10}H_{10}ONS_2Br$ requires C, 39·4; H, 3·3; N, 4·6%). The hydrobromide (0·24 g.) was triturated with an excess of ethereal diazomethane until solution was complete, and the crystalline *product* obtained on concentration (50 mg.) was recrystallised from chloroform–light petroleum, forming needles, m. p. 144—145° (Found: C, 50·5; H, 4·8; N, 13·3%). The hydrobromide (0·2 g.) was shaken with 1N-potassium hydroxide and the filtrate acidified. *N*-Dithiocarbobenzyloxyglycine was precipitated and identified with authentic material. When the hydrobromide (0·5 g.), benzylamine (1 c.c.), and ether (2 c.c.) were warmed, and the solution added to 2N-hydrochloric acid (25 c.c.) at 0°, a crystalline precipitate was obtained. It was purified by washing with aqueous sodium hydrogen carbonate, water, and ether, and crystallised from ethyl acetate–light petroleum; N-*benzylthiocarbamidoglycine benzylamide* (V) separated in rosettes of needles, m. p. 145—146° (Found: C, 64·85; H, 6·15; N, 13·0. $C_{17}H_{19}ON_3S$ requires C, 65·15; H, 6·1; N, 13·4%). The thiazolone hydrobromide (2·0 g.) was shaken with ether (30 c.c.) and aqueous 10% sodium acetate (50 c.c.). On drying and evaporating the ether layer, 2-*benzylthiothiazolone* (I; R = CH_2Ph) was recovered. It separated from light petroleum in long laths, m. p. 45° (Found: C, 53·9; H, 4·1; N, 6·5. $C_{10}H_9ONS_2$ requires C, 53·8; H, 4·1; N, 6·3%) (yield, 1·0 g.), and was insoluble in aqueous sodium hydrogen carbonate. The thiazolone (0·1 g.) was kept for a few minutes with benzylamine (0·5 g.), and 2N-hydrochloric acid added in excess. N-*Dithiocarbobenzyloxyglycine benzylamide* (VI) (0·13 g.) was collected and recrystallised from ethyl acetate, separating in needles, m. p. 163° (Found: C, 62·1; H, 5·5; N, 8·8. $C_{17}H_{16}ON_2S_2$ requires C, 61·8; H, 5·5; N, 8·5%).

Monothiocarbobenzyloxyglycine and its Reactions.—*N*-Dithiocarbobenzyloxyglycine (5·0 g.) was treated with 1N-potassium hydroxide (62·5 c.c.) and 3% hydrogen peroxide, and the new acid precipitated by

acidification (yield, 1·1 g., m. p. 146—147°). N-*Monothiocarbobenzyloxyglycine* (IX) separated from water in needles, m. p. 146—147° (Found: C, 53·2; H, 4·7; $C_{10}H_{11}O_3NS$ requires C, 53·3; H, 4·9%). The preceding acid (0·2 g.) was heated on the steam-bath for 5 mins. with acetic anhydride (3 c.c.) and excess of reagent removed in a vacuum; the residue crystallised. A little ether-insoluble material was removed and the ether-soluble product crystallised from ethyl acetate containing a little light petroleum; the mixed *anhydride* (XI) separated in colourless needles, m. p. 79° (Found: C, 54·0, 54·15; H, 4·8, 5·2; N, 5·3, 5·2. $C_{12}H_{13}O_4NS$ requires C, 55·95; H, 4·9; N, 5·5%). The compound (0·2 g.), when mixed with benzylamine (0·5 g.), became hot; after 2—3 mins., addition of 2N-hydrochloric acid gave N-*monothiocarbobenzyloxyglycine benzylamide* (X) (0·2 g.), which separated from ethyl acetate–light petroleum in needles, m. p. 153° (Found: C, 65·3; H, 5·9; N, 9·05. $C_{17}H_{18}O_2N_2S$ requires C, 65·0; H, 5·8; N, 8·9%). When the acid (IX) was heated at 100° with acetic anhydride (5—8 parts) and the reagent removed in a vacuum the *anhydride* (XII) was obtained; it separated from ethyl acetate in needles, m. p. 158° (Found: C, 55·5; H, 4·7; N, 6·5. $C_{20}H_{20}O_5N_2S_2$ requires C, 55·5; H, 4·7; N, 6·5).

N-*Dithiocarbobenzyloxy-ββ-diethoxyalanine.*—ββ-Diethoxyalanine (2·12 g.) in water (7 c.c.) containing potassium hydroxide (1·4 g.) was shaken with carbon disulphide (1 g.), and the clear solution further shaken with benzyl chloride (1·5 g.) overnight. Unchanged reagent was extracted with ether and an oil precipitated from the aqueous phase with hydrochloric acid. When this was taken up in benzene, and light petroleum added N-*dithiocarbobenzyloxy-ββ-diethoxyalanine* (XIV) crystallised; it recrystallised from chloroform–light petroleum in needles, m. p. 79° (yield 0·5 g.) (Found: C, 49·85; H, 6·55; N, 4·1. $C_{15}H_{21}O_4NS_2,H_2O$ requires C, 49·85; H, 6·4; N, 3·9%). On one occasion a less soluble unidentified by-product was obtained in small quantity; it crystallised from benzene in needles, m. p. 160° (Found: C, 50·8; H, 5·2%).

The preceding acid (2·5 g.) was treated with excess of ethereal diazomethane. Evaporation of the ether in a vacuum gave a syrup which slowly crystallised. N-*Dithiocarbobenzyloxy-ββ-diethoxyalanine methyl ester* crystallised from ethanol–water in white needles, m. p. 46° (yield 1·5 g.) (Found: C, 54·1; H, 6·5; N, 3·9. $C_{16}H_{23}O_4NS_2$ requires C, 53·75; H, 6·5; N, 3·9%).

The acid (XIV) (0·36 g.), acetic anhydride (3 c.c.), and pyridine (0·2 c.c.) were mixed and heated at 40° for 5 mins. The cooled solution was added to water (10 c.c.) to precipitate a dark oil which crystallised after 24 hours. 2-*Benzylthio-4-carboxythiazole* (XV) crystallised from chloroform–light petroleum in yellow needles, m. p. 187—189° (decomp.) (yield, 0·15 g.) (Found: C, 52·7; H, 3·4; N, 5·7. $C_{11}H_9O_2NS_2$ requires C, 52·6; H, 3·6; N, 5·6%).

Derivatives of 2-*Mercaptothiazolone.*—*N*-Dithiocarbethoxyglycine (2·3 g.), benzaldehyde (1·4 g.) and acetic anhydride (5·0 g.) were heated at 90° for 15 mins., and excess of reagent removed in a vacuum. The residue of 2-*ethylthio-4-benzylidenethiazolone* (XVI) crystallised, and it recrystallised from acetone–water in rhombic plates, m. p. 62—64° (yield, after 3 crystallisations, 1·5 g.) (Found: C, 57·8; H, 4·8; N, 5·75. $C_{12}H_{11}ONS_2$ requires C, 57·8; H, 4·5; N, 5·6%); light absorption (chloroform): max. at 243, 280, 372 mμ; E_1^1 = 350, 310, 1000, respectively. Dithiocarbethoxyglycine (1·0 g.) in ether was kept for 2 days with phosphorus tribromide (1·6 g.), and the oily crystals washed with more ether by decantation. Shaking the crystals with aqueous sodium acetate gave an oil which was taken up in ether and treated directly with benzylamine, whereupon the solvent boiled and ethylthiol was evolved. Very large rhombic plates slowly separated, and more product was obtained on evaporating the filtrate and rubbing the residue with hydrochloric acid. The dibenzylamide (V) crystallised from ethyl acetate–light petroleum, chloroform–light petroleum, or less satisfactorily from acetone–water or methanol–water in plates or rosettes, m. p. 145—146°, identical with the earlier material.

2-Benzylthiothiazolone (VIII) (0·5 g.), ethyl orthoformate (0·5 g.), and acetic anhydride (10 c.c.) were warmed together to 100° for 20 mins., and excess reagent and solvent removed in a vacuum. The dark residual oil was distilled at 50° in a high vacuum and then solidified; it was recrystallised from light petroleum. 2-*Benzylthio-4-ethoxymethylenethiazolone* (XVII; R = OEt) separated in colourless prisms, m. p. 57° (yield, 0·4 g.) (Found: C, 55·9; H, 4·7; N, 5·2. $C_{13}H_{13}O_2NS_2$ requires C, 55·9; H, 4·7; N, 5·0%). The same compound was also obtained as follows: *N*-Dithiocarbobenzyloxy-ββ-diethoxyalanine (0·5 g.) and acetic anhydride (5 c.c.) were heated to 100° for 15 mins., and excess of solvent removed in a vacuum. On refluxing the residue with light petroleum (25 c.c.) and cooling the filtrate, the ethoxymethylene compound (0·2 g.) separated in prisms, m. p. 57°, which did not depress the m. p. of the former product. Light absorption (chloroform): Max. at 241, 260, 328 mμ; E_1^1 = 800, 1000, 1050 respectively.

The ethoxymethylene compound (0·2 g.) was treated with aniline (0·08 g.) in ethanol. Yellow crystals began to be deposited after a few seconds and were collected after 30 mins. 2-*Benzylthio-4-anilinomethylenethiazolone* (XVIII) separated from ethanol in lemon-yellow laths, m. p. 118° (Found: C, 62·5; H, 4·3; N, 8·9. $C_{17}H_{14}ON_2S_2$ requires C, 62·5; H, 4·3; N, 8·6%). The compound (XVIII) (0·2 g.) was shaken with 2N-sodium hydroxide (3 c.c.) at room temperature, and the filtrate was diluted to 10 c.c. and acidified. 2-*Benzylthio-4-hydroxymethylenethiazolone* (XVII; R = OH) (yield, 0·13 g.) separated from aqueous acetone in clusters of small white needles, m. p. 146—147° (decomp.) (Found: C, 52·55; H, 3·7; N, 5·55. $C_{11}H_9O_2NS_2$ requires C, 52·55; H, 3·6; N, 5·55%). The compound (XVII; R = OEt) (0·15 g.) was added to sulphanilamide (0·09 g.) in warm ethanol (5 c.c.). The solution rapidly became yellow and within a few minutes yellow needles separated. The *derivative*, probably (XIX), recrystallised from aqueous acetone, formed yellow needles, m. p. 207—208° (Found: C, 50·55; H, 4·64; N, 8·9. $C_{16}H_{21}O_4N_3S_3$ requires C, 50·55; H, 4·7; N, 9·3%). The same compound resulted from reaction in propanol.

Miscellaneous Reactions.—Ethyl aminomalonate (6 g.) was shaken for 3 hours with carbon disulphide (3 c.c.), and the solution treated with potassium hydroxide (1·6 g.) in water (10 c.c.) and again shaken for 2½ hours with benzyl chloride (4·4 g.). The heavy oil was taken up in ether, freed from acidic impurity, and solvent removed. On standing with light petroleum the oil crystallised. *Ethyl* N-*dithiocarbobenzyloxyaminomalonate* (XX) separated from light petroleum in colourless plates, m. p. 71° (Found: C, 52·8; H, 5·65; N, 4·2. $C_{15}H_{19}O_4NS_2$ requires C, 52·8; H, 5·6; N, 4·1%).

N-Dithiocarbobenzyloxyglycine (2·0 g.), benzaldehyde (0·9 g.), and acetic anhydride (10 c.c.) were heated to 100° for 20 mins. After removal of solvent in a vacuum the residue crystallised completely

and was almost pure (m. p. 120—121°). 2-*Benzylthio*-4-*benzylidenethiazolone* (XVII; R = Ph) separated from chloroform–light petroleum in long pale yellow needles, m. p. 121° (Found : C, 65·2; H, 4·1; N, 4·7. $C_{17}H_{13}ONS_2$ requires C, 65·5; H, 4·2; N, 4·5%).

Glycine (5 g.) in water (6·6 c.c.) and potassium hydroxide (7·7 g.) in water (10 c.c.) were mixed, and the ice-cold solution shaken with carbon disulphide (5·1 g.) until a clear brown solution was obtained. The solution was cooled, stirred, and ethyl chloroformate (7·2 g.) added dropwise. A thick white precipitate soon appeared. The solid was dissolved in water, and the solution acidified, giving a white crystalline precipitate. N-*Dithiocarbocarbethoxyglycine* (XXI) crystallised from ether–light petroleum in white needles, m. p. 125° (yield, 4 g.) (Found : C, 32·6; H, 4·0; N, 6·3. $C_6H_9O_4NS_2$ requires C, 32·2; H, 4·0; N, 6·3%).

The preceding acid (5 g.), ethyl orthoformate (7 c.c.) and acetic anhydride (40 c.c.) were heated on the steam-bath for 30 mins. The solvents were removed in a vacuum to leave a dark oil which crystallised on cooling. 2-*Carbethoxythio*-4-*ethoxymethylenethiazolone* crystallised from petroleum (b. p. 60—80°) as white needles, m. p. 83° (yield, 2 g.) (Found : C, 41·1; H, 4·4. $C_9H_{11}O_4NS_2$ requires C, 41·4; H, 4·2%).

N-Dithiocarbethoxyglycine (9 g.) was heated to 100° for 15 mins. with acetic anhydride (22 c.c.), excess of which was then removed in a vacuum. Residual 2-ethylthiothiazolone distilled as an oil at 40—70° in a high vacuum. When the dithio-acid (2·6 g.), acetic anhydride (4·0 c.c.), and ethyl orthoformate (2·5 g.) were heated to 100° for 20 mins. the solution became purple and the residue, on removal of excess of reactants in a vacuum, crystallised. The coloured impurity was removed by crystallisation from light petroleum (charcoal), 2-*ethylthio*-4-*ethoxymethylenethiazolone* being obtained in colourless plates, m. p. 65—66° (Found : C, 44·4; H, 5·4. $C_8H_{11}O_2NS_2$ requires C, 44·2; H, 5·1%). The ethoxymethylene compound (1 g.) was shaken with potassium hydroxide (10 c.c.) for one hour, and the solution then acidified. 2-*Ethylthio*-4-*hydroxymethylenethiazolone* (yield, 0·7 g.) separated from petroleum (b. p. 60—80°) as white needles, m. p. 100° (Found : C, 38·4; H, 3·9; N, 7·6. $C_6H_7O_2NS_2$ requires C, 38·1; H, 3·7; N, 7·4%).

Penicillenic Acid Analogues, etc.—Penicillamine hydrochloride (0·2 g.), 2-benzylthio-4-ethoxymethylenethiazolone (0·3 g.) and aqueous sodium hydroxide (24·5 c.c.; 0·088N) were shaken together for 4 hours. The reddish solution, which no longer gave thiol colour reactions, was decolorised with charcoal in the cold and acidified with hydrochloric acid (2·0 c.c.; 2N). The solid (0·25 g.) was purified by repeated solution in aqueous sodium hydrogen carbonate and acidification, the penicillenic acid *analogue* forming a solid, m. p. 85° (decomp.) (Found : C, 50·2; H, 3·1; N, 7·0. $C_{16}H_{18}O_3N_2S_3$ requires C, 50·2; H, 4·8; N, 7·3%). Penicillamine methyl ester (0·67 g.) was added to 4-ethoxymethylene-2-benzylthiothiazolone (0·95 g.) in ethanol (4 c.c.). Thiol reactions were no longer given by the solution after a few minutes, and it was evaporated in a vacuum and the gum chromatographed in chloroform on alumina. The pale yellow gum obtained from the filtrate solidified on rubbing with a little methanol to a white powder (yield, 1·0 g., m. p. 108—110°). The *methyl* ester analogue (XXII; R = CH_2Ph) of the above acid separated from aqueous methanol in needles, m. p. 110° (Found : C, 51·55; H, 5·1; N, 6·85. $C_{17}H_{20}O_3N_2S_3$ requires C, 51·5; H, 4·9; N, 7·0%). Light absorption (chloroform) : Max. at 251—256, 281, 359 mμ; E_1^1 = 370, 180, 520, respectively. Similarly, penicillamine methyl ester (1·07 g.) and 4-ethoxymethylene-2-ethylthiothiazolone (1·4 g.) gave the *ethylthio*-ester (XXII; R = Et), which crystallised from petroleum (b. p. 60—80°) in rectangular prisms, m. p. 83° (yield, 1·0 g.) (Found : C, 43·0; H, 5·6; N, 8·4. $C_{12}H_{18}O_3N_2S_3$ requires C, 43·1; H, 5·4; N, 8·4%).

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